Research Progress of Traditional Chinese Medicine Based on TGF-β/Smad Signal Pathway in Preventing and Treating Myocardial Fibrosis in Heart Failure

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Abstract: Heart failure is the terminal stage of cardiovascular disease, and its pathological mechanism is ventricular remodeling. Therefore, the fundamental of preventing and treating heart failure is to inhibit ventricular remodeling. The important link of ventricular remodeling is myocardial fibrosis. It can prevent and cure heart failure by inhibiting the occurrence of myocardial fibrosis. By querying relevant domestic and foreign literatures in recent years, it was found that TGF-β/Smad signaling pathway plays an important role in the development of myocardial fibrosis, it may reduce cell damage through anti-inflammatory, antioxidant stress, anti-apoptosis, etc. Maintaining extracellular matrix stability, alleviate the degree of myocardial fibrosis, Chinese medicine in the prevention and treatment of fibrosis has high efficacy, multi-target, improve long-term prognosis and other advantages. To explore a more accurate target drug for preventing and treating myocardial fibrosis in heart failure, reduce the rate of readmission of patients with heart failure, and provide a greater possibility for promoting the prevention and treatment of myocardial fibrosis in heart failure by traditional Chinese medicine.

Keywords: Heart failure, Myocardial fibrosis, TGF-β/Smad, Traditional Chinese medicine, Signal pathway, Summary.

1. Introduction

Heart failure (HF) is due to a variety of reasons caused by changes in the structure or function of the heart, affecting the heart’s systolic and/or diastolic filling capacity, resulting in insufficient blood perfusion of organs and tissues of the body, the body circulation and/or pulmonary circulation stasis, and the clinical manifestations of shortness of breath, limitation of physical activity, fluid retention and other syndrome [1]. HF is the end stage of cardiovascular disease, with a total global prevalence of 1.5-2 per cent according to surveys [1]. Data show that the rate of heart failure among people over 35 years of age in China is 1.3% [2], with the elderly group accounting for a larger proportion of the population, and the rate of serious illness is higher, and some studies have shown that the mortality rate of people aged 65 years and above has a significant correlation with heart failure [3]. The underlying pathological mechanism of HF development is ventricular remodeling [1], and myocardial fibrosis (MF) is the central event of ventricular remodeling, while the TGF-β/Smad signaling pathway is one of the major transcriptional regulatory axes controlling the plasticity of myocardial fibroblasts [4], and it is a key pathway involved in myocardial fibrosis [5]. Therefore, this paper summarizes the modulation of TGF-β/Smad signaling pathway by TCM to prevent and control HF myocardial fibrosis, in order to provide ideas and theoretical basis for the prevention and treatment of HF and the development of TCM.

2. Structure of TGF-β/Smad Signaling Pathway and Activation Activation Pathway

Transforming growth factor-β (TGF-β) consists of a short C-terminal maturation peptide, a long N-segment prophase and signaling peptide. It belongs to the family of regulatory cytokines and is found in insects, mammals and other species. The TGF-β protein family plays a key role in fibroblast activation and extracellular matrix (ECM) production [6] and is a pro-fibrotic mediator.

2.1 Process of TGF-β Activation

Pro-TGF-β peptide (pro-TGF-β) is composed of a latency-associated peptide (LAP) and the mature TGF-β region. In the endoplasmic reticulum, each pro-TGF-β molecule assembles into a dimer through three interchain disulfide bonds, and in the presence of Furin protease the LAP folds to form a labile dimer, RGD [7], which attaches to GARP at the cell surface, mediating direct binding to integrin receptors [8], and releasing the active TGF-β through the twisted folding of the actin cytoskeleton [9]. As in Figure 1.

![Figure 1: TGF-β activation](image-url)

2.2 TGF-β/Smad Signaling Pathway Activation Pathway

Smad proteins are the main effector molecules in the
downstream of the TGF-β/Smad signaling pathway, and a total of 8 types have been identified in the current study, of which those related to myocardial fibrosis in heart failure include receptor-regulated Smad 2 and Smad 3, and co-mediated Smad 4. The TGF-β receptor includes TβRI and TβRII, and activated TGF-β binds to the TβRII on the surface of the cell membrane, attracts TβRI to form a complex, and induces TβRII to phosphorylate and activate TβRI, and then TβRI recruits downstream R-Smads proteins sequentially [10]. βRI to form a complex, which induces TβRII to activate TβRI by phosphorylation, and then TβRI recruits the downstream R-Smads proteins [10] and activates Smad2 and 3 by sequential phosphorylation, which subsequently forms a trimeric complex with TβRI by separating and binding Smad4, which further moves to the nucleus, inducing Smads proteins to aggregate in the nucleus and undergo nuclear translocation in order to regulate related genes such as Type I collagen (Col-I), Type III collagen (Col-III) expression, and participate in the activities of the organism. As shown in Figure 2.

![Figure 2: TGF-β Canonical pathway](image)

There are 2 types of TGF-β/Smad signaling pathways: classical and non-classical pathways, and TGF-β also passes through other non-classical signaling pathways such as PI3K-AKT, MAPKs, RhoA, as well as PP2A in order to modulate the downstream cellular response [11]. The results of the TGF-β signaling pathway are also reliant on the crosstalk of the TGF-β pathway with other signaling pathways, which increases the different complexity and integration in the regulation of cellular responses [12]. The article did not address the non-classical pathway and other pathways, and the specific mechanisms need to be studied in depth.

3. Exploring the Mechanisms of Myocardial Fibrosis in Heart Failure based on the TGF-β/Smad Signaling Pathway

Activated TGF-β can directly down-regulate matrix metalloproteinases and up-regulate matrix metalloproteinase inhibitor levels [13], promote the synthesis of type I procollagen and fibroblasts, cause ECM deposition, and accelerate the fibrosis process. The presence of TGF-β inflammatory factor can be detected in many myocardial fibrosis models, and TGF-β is a contributing factor to myocardial fibrosis [14, 15]. Meanwhile, TGF-β is mainly involved in the regulation of the human immune system and matrix metalloproteinase system in the process of regulating the production and degradation of ECM by the latter. The key pathway involved in myocardial fibrosis is TGF-β1/Smad, a signaling pathway that can mediate myocardial fibrosis by regulating the interactions between members of the Smads protein family [5]. The TGF-β/Smad signaling pathway has been more clearly studied and found to be one of the major transcriptional regulatory axes controlling cardiac fibroblast plasticity [4].

TGF-β isoforms have important roles in the regulation of cardiomyocytes, fibroblasts, immune cells and cardiac repair and remodeling [16]. It has been found [17] that when the myocardium suffers from insufficient oxygen supply, cardiomyocytes synthesize and secrete TGF-β in large quantities, which stimulates alterations in Smads signaling in myocardial fibroblasts and affects collagen production and fibrotic remodeling.

Cardiac vascular endothelial cells themselves are able to synthesize and secrete cytokines such as TGF-β, which can accelerate fibrosis by direct stimulation [18]. In addition, cardiac endothelial cells mainly express TβR type I receptor on their surface, and TβR type I receptor contains seven proteins (ALK1-7), and because different receptor proteins play different roles, the TGF-β signaling pathway has a complex impact on vascular endothelial cell proliferation, migration, and neovascularization [19]. In addition to its role in regulating endothelial cells, TGF-β also has regulatory effects on vascular smooth muscle cells (VSMCs) and pericytes, inducing the differentiation of precursor cells into pericytes and smooth muscle cells. It has been found that the TGF-β signaling pathway can be involved in inducing the differentiation of VSMCs, affecting their specific gene expression including α-SMA, calcium regulatory protein 1, etc. [20] The differentiation of VSMCs controls and affects the diameter of blood vessels, causing hemodynamic changes that ultimately lead to vasconstriction, increase in cardiac output, and cardiac pressure load, inducing cardiac remodeling and HF. In addition, Neverset et al [21] researchers found that T cells are closely related to HF myocardial fibrosis, and activated T cells bind to ventricular myoendothelial cells, infiltrate the left ventricle, induce the development of myocardial fibrosis, and promote heart failure, which led to the speculation that T cells may be the causative agent of heart failure. In addition to this, it has also been reported that dendritic cells, granulocytes and platelet cells are also involved in the regulation of myocardial fibrosis [22].

TGF-β1 promotes myocardial fibrosis formation mainly through the TGF-β1/Smad signaling pathway. One study [23] found that specific deletion of TGF-β1 or Smad3 genes in activated mouse cardiac myofibroblasts attenuated pressure overload-induced cardiac fibrosis.

It is now clear that the TGF-β/Smad signaling pathway is a key pathway in myocardial fibrosis and is closely related to the development of HF. This pathway mainly induces the occurrence of myocardial fibrosis by affecting the function of cardiomyocytes and disrupting the balance of the ECM. It is confirmed that anti-myocardial fibrosis effects can be exerted by regulating this signaling pathway; therefore, targeted intervention of the TGF-β/Smad signaling pathway has become a potential therapeutic idea to fight against HF myocardial fibrosis.
4. Myocardial Fibrosis in Heart Failure Based on Traditional Chinese Medicine Theory

In Chinese medicine theory, there is no "heart failure" disease name, but its main clinical manifestations of the relevant discussion has been early in the "Neijing" in the existence. Such as the "spiritual center - water bloating" cloud: "water began to rise, the eye arena on the slightly swollen, such as the new lying up like, its neck pulse, ..... its water to become." The Suwen - Reverse Tune Theory has the cloud: "Water in the heart, the heart under the firm building, shortness of breath." Recorded the water stops gathering in the heart manifested by shortness of breath, firm construction under the heart, lying down and wheezing and other symptoms, similar to modern medicine left heart failure caused by pulmonary stasis produces dyspnea, sitting up breathing, suffocating and waking up at night and other symptoms. The basic characteristics of heart failure are similar to those of "cardiohydroysis" [24], and nowadays, heart failure and myocardial fibrosis are mostly categorized under the categories of "palpitation", "wheezing", and "cardiohydroysis". Nowadays, heart failure and myocardial fibrosis are mostly categorized as "palpitation", "asthma" and "cardiomyopathy". Wang Yan et al. [25] summarized the research of Professor Chen Bo that the pathogenesis of chronic heart failure in the early stage of this deficiency (qi deficiency and yang deficiency) is the main, the middle stage of yang deficiency and water flooding, qi deficiency and blood stasis, stasis and blood stagnation caused by the late development of qi depletion and yang off, cardiac qi laxity, the treatment of the symptoms and the root cause should be taken into account, in order to benefit qi and warm yang to facilitate the flow of water, blood stasis and circulation, and return to the yang to fix off as a method. Prof. Zhang Junping believed that the main pathogenesis of heart failure is heart yang deficiency and decline, and the treatment is appropriate to warm and pass the heart yang, tonify the middle and nourish the blood, and at the same time to move the qi and diuresis, and advocated that the heart and lungs should be treated together, and according to the seasonal climate change, put forward the therapeutic concepts of nurturing the heart and passing the yang and identifying the evidence in the four times of the year [26]. Zhang Junfang et al [27] believe that heart qi, heart yang deficiency, yang deficiency qi chemistry failure, qi deficiency to promote the power, then qi, blood and fluid operation disorders, resulting in water stasis and water stagnation, water and drink, blood stasis, and so on, each other wrestling for a long time, resulting in the cardiac network into the accumulation of the heart failure, the treatment of qi, blood, water consumption with the same treatment. Based on the combination of literature research and his own experience, Director Li Shaomin proposed that the treatment of heart failure should be based on "tonifying the kidneys and strengthening the heart", believing that the pathogenesis of heart failure is mainly "heart and kidney deficiency, and kidney deficiency is the basis" [28]. Wu Meifang et al. [29] believe that the fundamental pathogenesis of myocardial fibrosis is the deficiency of the underlying symptoms, the body due to the deficiency of qi, the inability to promote the normal transmission of water and liquid, water and liquid stagnation, fluid into phlegm, phlegm paralysis; gas is the mother of the blood, the blood for the gas of the marshal, the blood stopping qi deficiency, the weakness of yang and warming the role of the weakness of the blood coagulation, stasis of blood within the blood, phlegm and stagnation in the cardiac veins. Treatment should be based on benefiting qi and warming yang, activating blood, eliminating phlegm and removing blood stasis. Wei Hong et al [30] that myocardial fibrosis in some aspects of Chinese medicine and "ZhenJiu" similar, in the morphology have shape and the affected area does not move, is part of the cardiovascular disease development to a certain stage of myocardial common fibrosis pathological changes, that the chest paralysis and ZhenJiu formation of the pathological factors have correlation, the ZhenJiu pathological factors and Qi stagnation, phlegm condensation, blood stasis related. It is believed that the pathologic factors of chest paralysis and the formation of zhengyu are correlated, and the pathologic factors of zhengyu are related to qi stagnation, phlegm coagulation and blood stasis. The treatment is similar to that of chest paralysis, which is mainly based on the principles of expelling phlegm and dispersing knots, regulating qi and activating blood. Modern biological studies [31, 32] have shown that phlegm stasis is related to ECM and involved in the formation of myocardial fibrosis. Qi Yifei et al [33] claimed that the main pathogenesis of myocardial fibrosis is positive deficiency and blood stasis, and the treatment should be based on supporting the positive and eliminating blood stasis. Liu Jinying et al [34] believed that myocardial fibrosis is a long time accumulation not eliminated, stasis and toxicity of the internal junction, long-term damage to the blood, blood circulation and detoxification should be through the treatment of myocardial fibrosis. Wang Kang et al [35] believed that the TCM pathogenesis and clinical treatment of myocardial fibrosis were based on the theory of the channels and complexes, and proposed the pathogenesis of "qi deficiency and blood stasis, and the accumulation of complexes and complexes", and formulated an empirical formula to pass the myocardial channels and complexes, which embodied the principle of "searching, picking, dredging, and dredging" of the use of medicines.

In general, heart failure, myocardial fibrosis, the disease mechanism is always the underlying deficiency, which is in line with the theory of Chinese medicine emphasized that "where the evil is, its gas must be deficient", therefore, the treatment is based on replenishing the deficiency and eliminating the real, tonifying the qi and blood yin and yang, so that the qi and blood can run smoothly, and realize the state of yin and yang, yin and yang and the state of self-reconciliation. Heart failure, myocardial fibrosis is from deficiency to reality, mixed process of deficiency and reality, and the late stage of the disease is more blood stasis with water retention, so on the basis of replenishing the deficiency, discretionary addition of eliminating blood stasis and diuresis products.

5. Traditional Chinese Medicine based on TGF-β/Smad Signaling Pathway Against Myocardial Fibrosis in Heart Failure

In recent years, the short-term efficacy of modern medicine in treating HF is remarkable, but it is difficult to reduce the re-hospitalization rate of HF and improve the prognosis, which has become a major bottleneck in the treatment of HF at present [36]. Traditional Chinese medicine (TCM) has
shown many advantages in the prevention and treatment of HF based on holistic regulation and dialectical treatment, for example, TCM compound multi-component, which can play a role through multi-targets and multi-pathways, and can effectively reduce the rate of re-hospitalization of patients with HF, and the efficacy of long-term observation is accurate and has few side effects [37, 38]. TGF-β/Smad signaling pathway, as a key pathway inducing myocardial fibrosis, is of great significance for TCM to intervene and regulate it to fight against myocardial fibrosis and slow down the process of HF. TCM and its extracts exert their antifibrotic effects through different modes of action, which will be described below in terms of oxidative stress, inflammatory response, and apoptosis.

5.1 Suppression of Oxidative Stress

Oxidative stress can directly activate cardiac fibroblast proliferation and differentiation to promote myocardial fibrogenesis [39]. In addition, a study [40] found that oxidative stress can lead to vascular endothelial cell dysfunction, affecting cardiac vascular endothelial cell synthesis and secretion of cytokines, such as TGF-β, which regulate downstream fibrotic pathways. Numerous studies have found that certain traditional Chinese medicines, their extracts, and herbal compounds exert anti-oxidative stress to protect against cardiomyocyte damage, e.g., Pueraia Mirifica [41], Anti Heart Failure Formula [42], and Danhong Injection [43]. The following is a detailed list of TGF-β/Smad-related Chinese medicines and related components.

Rhodiola rosea is a perennial herb of the genus Rhodiola in the family Sedum, which has the efficacy of benefiting qi and activating blood circulation and calming asthma. Modern medical research has found [44] that its main component rhodiola rosea glycosides have anti-inflammatory, antioxidant and cardiovascular protection effects. Chen P et al [45] found that rhodiola rosea glycosides not only inhibit oxidative stress, reduce ECM deposition, and decrease the possibility of fibrosis; they also down-regulate the expression of TGF-β1 and interleukin-1, inhibit the inflammatory response of cardiomyocytes, and weaken the degree of fibrosis. Aloe rhodopisin is a natural anthraquinone derivative and an active ingredient in herbal medicines, such as rhubarb, aloe vera, and thuja, with pharmacological effects such as anti-inflammatory, antioxidant, and neuroprotective effects [46]. In an in vitro study [47], Aloe vera rhodopisin was found to significantly inhibit cardiac oxidative stress by inhibiting hypertrophy and apoptosis in mouse cardiomyocytes, activating the TGF-β/Smad pathway, modulating the expression of myocardial fibrosis-related proteins, and delaying the process of fibrosis. Zhang et al [48] demonstrated that Salvia miltiorrhiza significantly reduced the level of TGF-β1 and the expression of NOX4 mRNA, and increased the level of smad7. NOX4 is a reactive oxygen species-generating oxidase [49], which can regulate the expression of TGF-β [50], proving that Salvia miltiorrhiza significantly alleviated vascular remodeling by inhibiting oxidative stress and the TGF-β/Smad pathway. Lin et al [51] in an in vitro study to alleviate adriamycin-induced cardiomyopathy found that astragaloside IV reduced NOX2, NOX4 expression in cardiomyocytes and inhibited oxidative stress, thereby reducing myocardial fibrosis. Wei et al [52], in observing whether there was a relationship between the cardioprotective effect of astragaloside IV and the regulation of miRNAs, confirmed that astragaloside IV inhibited the activation of the TGF-β/Smad pathway, decreased the expression of a-SMA, and inhibited the occurrence of myocardial fibrosis.

5.2 Suppression of Apoptosis

The Bcl-2 family controls apoptosis by controlling the permeability of the mitochondrial membrane; the anti-apoptotic protein Bcl-2 is present in the outer mitochondrial membrane, and the pro-apoptotic protein Bax may be present in the cytosol, the exact mechanism of which has not been fully elucidated. It has been demonstrated that apoptosis of cardiomyocytes in HF rats showed a positive correlation with the occurrence of myocardial fibrosis [53]. Early studies have demonstrated that TCM plays an important role in inhibiting apoptosis and improving cardiac function [54-56].

Astragalus Ginseng and Yiqi Drops Pill is composed of Astragalus, Panax ginseng, Salvia miltiorrhiza and Descending Fragrance [57], which together exert the efficacy of benefiting qi and activating blood, promoting the circulation of qi, and resolving blood stasis and relieving pain. Modern medicine has found that its pharmacological effects [58] mainly include anti-inflammatory, anti-apoptosis, and inhibition of ventricular remodeling. Astragalus ginseng and yiqi drops can effectively inhibit apoptosis of ventricular myocytes, increase the expression of myocardial fibrosis proteins, and attenuate the degree of myocardial fiber destruction, which improves the cardiac function in mice [59]. Yang Quan et al [60] studied the protective effect of QiShenYiQiDipPill on rats with myocardial ischemia, and found that compared with the model group, the expression of Bax in the treatment group was significantly reduced, and the expression of Bcl-2 was significantly increased, which proved that QiShenYiQiDipPill could reduce apoptosis and alleviate cardiomyocyte injury by down-regulating the expression of pro-apoptotic factor Bax and elevating the expression of anti-apoptotic factor Bcl-2, activating the TGF-β/Smad signaling pathway and inhibiting ventricular remodeling, and improving myocardial fibrosis. Smad signaling pathway, inhibit ventricular remodeling and improve myocardial fibrosis. Liu Zhongyong et al [61] explored the potential mechanism of Zhenwu Tang in the treatment of HF with Wistar heart failure rats, Masson staining showed that the degree of myocardial fibrosis was significantly reduced, and the degree of improvement was positively correlated with the dose; the apoptotic index of cardiomyocytes declined with the increase of the dose, and at the same time, the expression of TGF-β1 was reduced, which proved that Zhenwu Tang could inhibit apoptosis of cardiomyocytes, and reversed the ventricular remodeling. Li et al [62] confirmed that glycyrrhizin significantly inhibited apoptosis, up-regulated TGF-β1, Smad2 expression levels, regulated the activation of TGF-β1/Smad2 signaling pathway, attenuated the degree of myocardial fibrosis, improved cardiac function, and delayed ventricular remodeling in a study of glycyrrhizin's protective mechanism against isoprenaline-induced myocardial fibrosis in mice.

5.3 Reducing the Inflammatory Response
It is well known that the inflammatory response is almost always present in cardiac disease variables. When the myocardium is damaged, inflammatory signaling molecules increase rapidly [63], and when excessive inflammatory response occurs, reparative fibrosis occurs, which eventually causes myocardial remodeling [64]. Modern studies have shown that many traditional Chinese medicines have anti-inflammatory and other effects.

Danshen polyphenolates are a variety of water-soluble substances extracted from Salvia miltiorrhiza, family Labiatae, which can effectively scavenge free radicals and exert their anti-inflammatory effects by decreasing the expression of adhesion factors between endothelial cells [65]. Liang et al [66] found that danshen polyphenolates reduced serum TGF-β1, BNP, IL-6, and CRP concentrations, attenuated inflammatory responses, and inhibited the TGF-β1/Smad2/3 signaling pathway, thereby inhibiting myocardial fibrosis. Study [67] showed that Shengmsan can be used for the treatment of HF and the improvement of cardiac function. Zhao Di et al [68] prepared a rat model of CHF by aortic arch narrowing method, and observed that a small amount of inflammatory cell infiltration in the intima of myocardium in the Shengmsan group, the EF value increased compared with that of the control group, and the compensatory hypertrophy of ventricular muscle was delayed. Masson staining revealed that myocardial fibers in the Shengmsan group did not see any obvious disorders, and there was only a small amount of collagen fiber deposition, the content of collagen I and collagen III was The content of collagen I and collagen III was reduced, and the expression of TGF-β1 and p-Smad3 protein was reduced. Shengweisian may improve the process of heart failure by reducing the inflammatory reaction and participating in the TGF-β1/Smad pathway to inhibit the proliferation of myofibroblasts. Complementing Yang Returning Five Soup, from Wang Qingren’s "Reform and Error in Medical Forests", consists of astragalus, angelica tail, safflower, red peony, chuanxiong rhizoma, and dirong (地龙), which is known for its efficacy in benefiting qi and activating blood circulation, removing blood stasis and opening up the channels. Huang Xianna et al [69] investigated the intervention effect of tonifying Yang and returning five soup on myocardial remodeling in rats with heart failure with abdominal aortic constriction, and observed that the content of HF markers was reduced, and the expression of TGF-β1 and p-Smad2/3 proteins was reduced after applying this formula, which proved that this formula improved the cardiac function and the degree of ventricular myocardial remodeling of rats with heart failure by inhibiting the TGF-β1/Smad pathway. Modern studies [70] have shown that tonifying yang and returning five soups can reduce the expression of inflammatory factors and affect the function of rat myocardial fibroblasts. The study of Chen et al [71] further found that tonifying yang and returning five soups can reduce inflammatory stress in cardiomyocytes, inhibit myocardial TGF-β1, and up-regulate the level of Smad3 phosphorylation, which can significantly reverse myocardial fibrosis. Quercetin is widely found in nature. Jiao Mei et al [72] studied to establish a rat model of chronic heart failure by abdominal aortic narrowing method, confirmed that quercetin was involved in the TGF-β1/Smad3 signaling pathway, and found that quercetin could reduce the expression of TGF-β1, Smad3, collagen I and other related proteins in cardiomyocytes, reduce the inflammatory cell infiltration and collagen fibrillar protein deposition, attenuate inflammatory response, and reduce the degree of fibrosis. In addition to this, it was also found that it could improve the left ventricular ejection fraction of rats and improve the cardiac function of rats with heart failure. Different levels of quercetin can be detected in many traditional Chinese medicines such as astragalus, Hawthorn, etc. In addition, this product can also be detected in fruits, such as red grapes, pomegranate, mango, longan, etc., so it can be consumed appropriately in daily life. Yang et al [73] found that inhibition of Smad3 by Salvia miltiorrhiza and its extracts improved myocardial fibrosis in the study of Salvia miltiorrhiza group, which showed a significant decrease in inflammatory factors IL1 and IL6 and a significant increase in anti-inflammatory cytokine IL10 compared with the model group, and found that it reduced ventricular remodeling and attenuated HF by inhibiting inflammatory responses and Smad3 protein expression and inhibiting the TGF-β1/Smad3 signaling pathway. Gal-3 secreted by macrophages is a major mediator of inflammation and myocardial fibrosis, which can trigger myocardial remodeling and aggravate cardiac function damage [74]. Li QM et al [75] demonstrated that Gal-3, TGF-β and Smad3 protein expression was down-regulated in the Dendroblum group, and Masson staining also confirmed that Dendroblum reduced the degree of myocardial injury, suggesting that it may play an anti-fibrotic role through the activation of the TGF-β1/Smad3 signaling pathway through the anti-inflammatory response. Xu Yini et al [76] found that oxidized Picrasidine inhibited TGF-β1 expression, reduced Smad2 and 3 protein levels, inhibited TGF-β1/Smad signaling pathway, reduced ECM production, and exerted antifibrotic effects when investigating the effects on cardiac fibroblast proliferation and differentiation experiments. Jiang Zhihu et al [77] found that oxidized Picrasidine reduced the expression of pro-inflammatory cytokines and IL-6, inhibited the activation of TGF-β1 and Smad2, and significantly inhibited the TGF-β1/Smad signaling pathway, which attenuated cardiomyocyte injury, reduced inflammatory infiltration, and lowered the occurrence of cardiomyocyte fibrosis.

5.4 Angiotensin II Inhibition

An early study [78] demonstrated that TGF-β1 is an important downstream signaling molecule of angiotensin II (Ang II), and Ang II stimulates the TGF-β/sm signaling pathway, activates receptor-regulated Smad2/3, and induces a downstream pro-fibrotic effect [79], and TCM can inhibit Ang II to exert its anti-fibrotic effect.

Resveratrol is mainly derived from plants such as thuja and mulberry [80], and has been found to have anti-inflammatory, antioxidant, and cardiovascular protective effects in modern medicine [81, 82]. Studies have shown [83] that resveratrol can significantly down-regulate the protein content of AngII-induced TGF-β1, TGF-βRII, and Smad3, and Smad7, and that the anti-fibrotic effects of resveratrol are exerted by inhibition of the AngII, thus affecting the activation of the TGF-β1/Smad signaling pathway. Tan Jianfeng et al [84] demonstrated that ginseng Yangrong Tang significantly down-regulated AngII-induced Smad2/3 protein expression levels, inhibited the TGF-β1/Smad signaling pathway in cardiomyocytes, attenuated cardiomyocyte hypertrophy, and
improved ventricular remodeling. Zhang Yonghua et al [85], in studying the mechanism of Angelica sinensis tonic soup to protect AngII-induced cardiomyocyte hypertrophy, found that the Angelica sinensis tonic soup group significantly down-regulated AngII-induced TGF-β1 and Smad2 expression, inhibited the TGF-β1/Smad2 signaling pathway, improved the degree of cardiomyocyte hypertrophy, and attenuated ventricular remodeling.

Combining traditional Chinese medicine with modern pharmacology to maximize the effect of preventing and treating HF myocardial fibrosis. The above Chinese medicines and main extracts inhibit the expression of TGF-β/Smad signaling pathway related proteins to different degrees through different modes of action, reduce the accumulation of extracellular matrix and maintain the balance of extracellular matrix, thus improving the degree of myocardial fibrosis, reducing myocardial injury and slowing down the process of heart failure. There are many other Chinese medicines that may also be involved in the process of myocardial fibrosis in heart failure by affecting this pathway, and more and more in-depth studies are needed. In conclusion, TCM monomers, combinations and related extracts may modulate the TGF-β/Smad signaling pathway to provide new ideas for combating myocardial fibrosis in heart failure.

6. Summary and Prospects

The above just discussed the prevention and treatment of HF myocardial fibrosis from the TGF-β/Smad classical signaling pathway, which reduces the extracellular matrix collagen fiber deposition and inhibits the differentiation of fibroblasts to myofibroblasts in various ways, reduces the degree of myocardial fibrosis, improves myocardial remodeling, and slows down the process of heart failure. Although there are a lot of experiments using enalapril, pirenidone, ZLY18, etc. to prevent and control myocardial fibrosis by acting on the TGF-β/Smad signaling pathway, all of them are confined to the stage of in vitro animal experiments, and there is no targeted drug for clinical use at present. In order to cope with the many challenges of the aging era, it is urgent to improve the quality of life of heart failure patients and reduce the frequency of rehospitalization to prevent and treat the process of heart failure. Myocardial fibrosis is the pathological basis of heart failure and the key factor causing ventricular remodeling. In response, traditional Chinese medicine has the characteristics of multi-target and multi-pathway integrated intervention, and the anti-myocardial fibrosis effect has been initially shown. Therefore, antifibrosis in TCM is a valuable and promising field. However, due to the large composition of TCM compound drugs and the complexity of the related components, the elucidation of the related compounding mechanism by modern techniques needs further research. It is of great theoretical and clinical significance to strengthen the role and mechanism of TCM in HF myocardial fibrosis. It is believed that with the deepening of the study, the mechanism of the action of Chinese medicine and its combination in intervening HF myocardial fibrosis can be further elucidated at a deeper level, and its therapeutic target can be clarified, which is of great significance for precise clinical application.

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