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Research Progress in Prevention and Cure of Fibrosis by Traditional Chinese Medicine

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Abstract

The development of study on traditional Chinese medicine has seen considerable progress in the prevention and cure of fibrosis by Chinese herbs. Further elucidation on the pathogenesis of fibrosis will be helpful for the study on anti-fibrosis traditional Chinese medicine and medicine selection. Traditional Chinese medicine has the advantage of achieving multiple targets with one dose. And the multiplicity can be enhanced by finding among natural materials activated monomer that has specific pharmacological effect, by elucidating the mechanism of different monomers and effective target positions, and by treating fibrosis according to its multi-facetedness. This paper is a review of major literature produced in the past ten years concerning the anti-fibrosis mechanism of traditional Chinese medicine.

Keywords: Traditional Chinese medicine, Fibrosis, Review

Fibrosis is a slow but dynamic process involving the mutual interaction and mutual regulation of cells, extracellular matrix, cellular factors, and vasoactive substances. Fibrosis may happen in several organs or tissues. The main pathological process of fibrosis includes two aspects: (1) the migration and proliferation of fibroblast in the injury, (2) the accumulation of extracellular matrix. The study on prevention and cure of fibrosis by traditional Chinese medicine in recent ten years is reviewed as follows.

1. The pathological mechanism of visceral fibrosis

1.1 Myocardial fibrosis

Myocardial fibrosis is inevitable when the heart disease comes to its end stage. It symbolizes a crucial change of heart function from compensatory stage to decompensatory stage. Its symptoms often include the proliferation of cardiac fibroblasts, the increase of extracellular matrix, the remarkably increased concentration of extracellular collagen, and the abnormally high level of collagen volume fraction. Myocardial fibrosis is the structural basis for the cirrhosis of injured tissue; it will lead to the decrease of ventricular compliance and influence the systolic and diastolic function of heart. Usually, the accumulation of extracellular matrix will lead to the weakening of electrical coupling between cardiac muscle and the abnormality of E-C coupling of cardiac muscle, and then induce cardiac arrhythmia. The accumulation and reshaping of collagen fiber have close relationship with the diastolic function of heart; It has been widely accepted that myocardial fibrosis and cardiac diastolic dysfunction are among the reasons for heart failure.

1.2 Liver fibrosis

When the hepatic cells putrefy or inflame, connective tissue growth factor will aberrantly increase, which will lead to

proliferation of fibroblasts and the accumulation of extracellular matrix. The imbalance of fibril hyperplasia and fibril decomposition will lead to the connective tissue hyperplasia and deposition in the liver. Liver fibrosis precedes liver cirrhosis pathologically. And the prevention of liver fibrosis is of great significance for the prevention and cure of live cirrhosis. In recent years, drugs for activating blood circulation and removing stasis are used to treat liver cirrhosis, and great achievement has been made in the study on prevention and cure of liver fibrosis by traditional Chinese medicine.

1.3 Pulmonary fibrosis

Pulmonary fibrosis is the short name of diffuse pulmonary fibrosis. There are two kinds of pathogeny-based pulmonary fibrosis: idiopathic pulmonary fibrosis and secondary pulmonary fibrosis, both of which are caused by alveolus inflammation and alveolus structure turbulence. Firstly the pathogenic factors injure the blood vessel endodermis cells and alveolus epithelia, and induce inflammation reaction and immunoreaction. Secondly, various inflammatory cells release cellular factors and inflammatory mediators, expand the tissue injury and induce stroma hyperplasia. Thirdly, fibroblasts, endothelial cells migrate and proliferate, and the metabolism of collagen and extracellular matrix is disturbed, which worsens the injury and hyperplasia, eventually leads to injury of alveolus wall and the dysfunction of capillary vessel.

1.4 Renal fibrosis

Various renal diseases develop to their end stage through renal fibrosis, which is the major pathologic symptom of the diseases turning chronic. Modern medical science has focused on the molecules mechanism of renal interstitial fibrosis and found that the balance between two kinds of molecules plays an important role in the progress of renal interstitial fibrosis. One kind of molecules is the factors that can promote the renal interstitial fibrosis, including transforming growth factor β, connective tissue growth factor, angiotensin Ⅱ, endothelin (ET), platelet-derived growth factors, platelet-derived endothelial growth factor, tissue inhibitor of matrix metal proteinase, plasminogen activator inhibitor, monocyte chemo-attractant protein, etc. The other kind of molecules is the factors that can counteract the renal interstitial fibrosis, including γ-interferon, hepatocyte growth factor (HGF), matrix metal proteinase, relaxin, and so on. The study on renal fibrosis has gone deep into molecular and protein level. The development of modern medical science has enabled traditional Chinese pharmacists to explore more efficacious anti-fibrosis medicines. It is of great significance to combine Chinese traditional medicine and modern medical sciences in the development of anti-fibrosis medicines.

2. Study on the single traditional Chinese medicine and its effective ingredient in anti-fibrosis

2.1 Total saponins of Panax notognseng (PNS)

2.1.1 Prevention and cure of liver fibrosis

To observe the effects of Panax notoginseng saponins (PNS) on liver fibrosis, Yu et al (2005) established a mice liver fibrosis model induced by CCl_4. Yu's research show that PNS could improve liver fibrosis and decrease the level of TNFα, TGF-β, IL-1, and IL-6 in serum. The research indicates that PNS had the effect of anti-liver fibrosis, which might be relevant with the decrease of TNFα, TGF-β, IL-1, and IL-6 level in the serum.

2.1.2 Prevention and cure of pulmonary fibrosis

Quan et al (2005) established a pulmonary rat fibrosis model by bleomycin. Quan's morphological observation shows that PNS and dexamethasone could obviously alleviate inflammation and fibrosis induced by bleomycin. The research also shows that the content of hydroxyproline and expression of TGF-β1 in the lung tissue decrease ($P < 0.01$ and $P < 0.05$ after the use of PNS). Quan et al conclude that that PNS could obviously delay the development of pulmonary fibrosis induced by bleomycin in rats.

2.1.3 Prevention and cure of renal fibrosis

Using the methods of flow cytometry (FCM) and immunofluorescence, Zhang et al (2005) studied the effect of PNS on α-SMA expression of HK-2 cell induced by TGF-β1. Semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) was used to detect the expression of α-SMA. And decreased expression of α-SMA was observed when HK-2 cells were induced by TGF-β1 in 200-800 mg/L PNS groups. The research of Zhang et al shows that PNS could relieve renal interstitial fibrosis by inhibiting trans-differentiation of renal tubular epithelial cells.

2.2 Salviae miltiorrhizae

Song et al (1998) revealed that salviae miltiorrhizae of certain concentration could effectively inhibit the collagen synthesis and the proliferation of fibroblasts.

2.2.1 Prevention and cure of myocardial fibrosis

Sun et al (2003) observed the effect of salviae miltiorrhizae on left ventricular hypertrophy and myocardial fibrosis prevention in spontaneous hypertensive rats.

2.2.2 Prevention and cure of liver fibrosis

Jiang et al (2002) studied the anti-lipid peroxidation effect of salviae miltiorrhizae on mitochondria of hepatic fibrosis in rats. Their results show that salviae miltiorrhizae could effectively inhibit the production of malondialdehyde, a product of peroxidation, and enhance the activity of superoxide dismutase (SOD) in the liver. Zheng et al (2003) found that Tanshensu could inhibit the proliferation of hepatic stellate cells. Their study indicates that salviae miltiorrhizae could reduce the production of extracellular matrix and inhibit the stellate cells from becoming myogenic fibroblasts.

2.2.3 Prevention and cure of pulmonary fibrosis

Wang et al (1994) revealed that sodium tanshionone ⅡA sulfonate could prevent the pulmonary fibrosis by eradicating oxygen free radicals.

2.2.4 Antagonizing renal fibrosis

Zhang et al (1997) showed that salviae miltiorrhizae could inhibit the proliferation of fibroblast and promote the programmed cell death through raising c-myc protein expression in human renal fibroblasts.

2.3 Astragalus and Astragaloside

2.3.1 Prevention and cure of myocardial fibrosis

Zhang et al (2003) treated the murine myocarditis model with 9% astragaloside. Their results showed that 9% astragaloside could improve survival rate, reduce collagen synthesis and cardiac myocytes apoptosis effectively. According to Zhang et al, the anti-apoptotic effect of astragaloside could play an important role in alleviating and reversing myocardial fibrosis.

2.3.2 Prevention and cure of liver fibrosis

Zhou et al (2005) revealed that astragalus had an inhibitive effect on hepatic fibrogenesis and that the mechanism might be associated with its antioxidant activity, decrease of laminin and its inhibition of hepatic stellate cell proliferation. Mou et al (2002) found that astragalus could increase the level of hepatic cell growth factor (HGF), which could reduce the expression of TGF-β1, and accelerate the decomposition of extracellular matrix and counteract fibrosis.

2.4 Matrine

2.4.1 Counteract myocardial fibrosis

Wu et al (2004) found that Matrine could inhibit myocardial fibrosis and collagen synthesis stimulated by angiotensin Ⅱ. They also found that Matrine could counteract myocardial fibrosis by reducing the angiotensin Ⅰ and TGFβ1 expression and increasing the level of MMP13 mRNA expression.

2.4.2 Counteract liver fibrosis

Matrine can inhibit liver inflammation and inhibit the activation of hepatic stellate cells and the proliferation of fibroblasts, so it could counteract the liver fibrosis (Wang and Zhao, 2005).

2.5 Ligustrazine

2.5.1 Counteract myocardial fibrosis

Song et al (1998) found that ligustrazine could effectively inhibit the collagen synthesis and proliferation of fibroblasts. Ren et al (2003) studied the effect of ligustrazine on myocardial fibrosis in rats with pressure overload. Their results showed that collagen volume fraction and myocardial fibrosis decreased significantly. It was indicated that ligustrazine could inhibit the TGF-β/Smads signal pathway, which might be one of the mechanisms to counteract fibrosis. Zhao et al (2006) found that ligustrazine could influence the production of endothelin and nitric oxide (NO) and the balance of both factors. Therefore, ligustrazine plays a role in inhibiting cardiac fibrosis.

2.5.2 Counteract liver fibrosis

Ligustrazine could inhibit the proliferation and activation of hepatic stellate cells in hepatic fibrosis rats induced by CCL_4 (Ji, et al 2003). Dai et al (1999) revealed that therapeutic effect of Ligustrazine on fibrosis might lie in its suppression on pre-collagen Ⅰ mRNA.

2.5.3 Counteract pulmonary fibrosis

Li et al (2007) found that ligustrazine could interfere with the collagen Ⅲ and laminin.

2.5.4 Counteract renal fibrosis

Wang Yaping et al (2004) revealed that ligustrazine could inhibit the transformation of fibroblasts when the kidney was injured, reduce the expression of myofibroblast, and therefore inhibit the process of the formation and development of renal interstitial fibrosis. Sun et al (1995) indicated that ligustrazine could reduce the secretion of IL-6 in mesangial cells, and inhibit the proliferation of mesangial cell and the production of extracellular matrix.

2.6 Cordyceps sinesis Sacc

2.6.1 Counteract liver fibrosis

Cordyceps sinesis Sacc could influence various phases of liver fibrosis, it could prevent hepatitis virus, inhibit the activation of hepatic stellate cells, and inhibit the collagen synthesis and promote collagen decomposition (Wu and Liu, 2001).

2.6.2 Counteract renal fibrosis

Liu et al (1995) treated rats with resection of greater part of kidney and found that the glomerulus cirrhosis, renal tubule shrinking and renal interstitial fibrosis were much less than those of renal failure rats.

2.7 Emodin

2.7.1 Counteract liver fibrosis

Emodin could significantly inhibit the synthesis of hepatic stellate cell collagen, hyaloplasm and laminin, so it could counteract the liver fibrosis (Zhan, et al, 2006)

2.7.2 Counteract renal fibrosis

Wang et al (2002) found that emodin could inhibit the proliferation of human renal fibroblasts and the production of IL-6.

2.8 Ginkgo Biloba leaf

2.8.1 Counteract liver fibrosis

The extract of Ginkgo Biloba leaves has obvious antioxidant and anti-lipid peroxidation effect according to the findings of Liu et al. The researchers asserted that those leaves could markedly improve the activity of SOD and GSH-Px, reduce the content of MDA and counteract the liver fibrosis (Liu et al., 2003)

2.8.2 Counteract pulmonary fibrosis

Ginkgo Biloba leaf preparation has definite effect in treating pulmonary fibrosis, the mechanism might be through inhibiting the activity of NF-kB, decreasing TGF-β mRNA expression and protein, so as to ameliorate the inflammation and fibrosis (Chen et al., 2000).

2.8.3 Counteract renal fibrosis

Tang et al (1998) found that Ginkgo Biloba leaf could ameliorate glomerulus sclerosis and renal tubule-interstitial damage but might not completely prevent the occurrence of this damage.

2.9 Genistein

Gao et al (2001) revealed that genistein could inhibit the proliferation of cardiac fibroblasts and arrest the myocardiac cell progression at G2/M phase and accelerate the cell apoptosis.

2.10 Tetrandrine.

Xu et al (1996) revealed that the proliferation and collagen synthesis in cardiac fibroblast induced by angiotensin Ⅱ might be mediated by angiotensin Ⅱ receptor, and these stimulatory effects could be inhibited by the calcium channel blocker tetrandrine.

2.11 Total flavone of Metasequoia Glyptostroboides

Tian et al (2006) found that flavone of Metasequoia Glyptostroboides could inhibit the proliferation and collagen synthesis of cultured myocardial fibroblast of neonatal mouse induced by insulin-like growth factor 1.

2.12 Salidroside

Wang and Liu (2004) found that salidroside could significantly inhibit HSC proliferation, and inhibit Type Ⅲ collagen, hyaluronic acid and laminin secretion in different degree.

2.13 Rhizome sparganii and radices zedoariae

Luan and Li (2004) revealed that rhizome sparganii and radices zedoariae had immunological regulation function and could counteract hepatic fibrosis.

2.14 Tetrandrine

Tian et al (1997) indicated that tetrandrine could directly inhibit cell proliferation, reduce collagen synthesis and counteract fibrosis. He et al (1995) found that tetrandrine could inhibit directly or indirectly the transcription of collagen gene and thus reduce synthesis of collagen protein. The research teams agreed with each other on tetrandrine's ability to prevent and cure pulmonary fibrosis.

3. Problems and future research

Prevention and cure of fibrosis with traditional Chinese medicine is a valuable and applicable research field. There are many kinds of fibroblasts with different characteristics, but all the fibroblasts have the function of collagen and extracellular matrix synthesis, collagen decomposition, and connective tissue contraction. Fibroblasts are the main places of collagen synthesis, so the study on fibrosis pays much attention to fibroblasts. The influence of drugs, especially the traditional Chinese medicine, on the fibroblast is an important research field. Studies have shown that many traditional Chinese medicines could influence the proliferation, collagen synthesis and DNA synthesis of fibroblasts, but the mechanism is complex. Current studies mainly focus on the function of single traditional Chinese medicine, and drugs for activating blood circulation and removing stasis could significantly inhibit the proliferation and collagen synthesis of fibroblasts. The clinical symptoms of patients are different, so it is inappropriate to treat various kinds of diseases with one medicine. The western medicine has strong side effect, and is expensive, so it is difficult to be popularized. The advantage of traditional Chinese medicine should be thoroughly brought into play, compound medicine should be used to influence the function of fibroblasts and achieve overall regulation and treatment. At present, traditional Chinese medicine has exhibited sound clinical effect in treating fibrosis, but its mechanism is still unclear. Few studies have been devoted to the understanding of the influence of compound traditional Chinese medicine and the combination of traditional Chinese medicine and western medicine on fibroblasts. It is the author's belief that further research will help to clarify how (compound) traditional Chinese medicine can influence fibroblast and that new drugs will be developed. It is also the author's hope that breakthroughs in the prevention of cure of fibrosis can be achieved by combining advantages of traditional Chinese medicine and Western medicine.

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