

# *Progress in the Clinical Application of Traditional Chinese Medicine in Treating Hepatic Fibrosis*

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**Abstract:** Liver fibrosis is a kind of chronic disease process, is a common characteristic of many kinds of chronic liver diseases, If not alleviated and treated as soon as possible, it may deteriorate to cirrhosis or even liver cancer, which seriously reduces the quality of life of patients and endangers their life and health. Western medicine in the treatment of liver fibrosis has not yet clear drugs, but the clinical has proved that traditional Chinese medicine in the treatment of liver fibrosis has a good effect. Through the combination of a variety of traditional Chinese medicine, TCM exerts its multi-target and multi-mechanism therapeutic effect, reduces the side effects of drugs, and has some advantages in the prevention and treatment of liver fibrosis. The TCM dialectics of liver fibrosis are mainly divided into dampness and heat of liver and gallbladder, blockage of blood, Yin deficiency of liver and kidney, liver depression and spleen deficiency. It follows the treatment methods of clearing heat and detoxifying, promoting blood circulation and removing stasis, and fuzheng and tonifying deficiency. The liver fibrosis was delayed and treated by the use of Chinese medicine compound, Chinese medicine monomer, acupuncture, acupoint application, acupoint injection, ear point pressure and other methods. Based on the analysis and summary of the literatures related to liver fibrosis in recent years, this paper summarizes the anti-liver fibrosis of traditional Chinese medicine, in order to provide reference for the clinical treatment of liver fibrosis.

## 1. Introduction

Hepatic fibrosis is a pathological change of the liver, which occurs in the process of alcoholic hepatitis, viral hepatitis, drug-induced liver injury, cholestasis and other chronic liver diseases. Due to various pathogenic factors, liver cell injury, chronic inflammation continuous accumulation, and excessive proliferation and deposition of Extracellularmatrix (ECM). Lead to abnormal hyperplasia of hepatic connective tissue. Because after the destruction of liver cells, they will regenerate and rebuild, but the new structure that has been repeatedly regenerated no longer has the same structure and function as normal liver, and the structure is disorganized and similar to scar. This reversible wound healing reaction of liver tissue is called liver fibrosis (HF). Without timely intervention, liver

cirrhosis will gradually form. Even liver cancer, liver failure. (Figure 1) Therefore, early detection, early treatment, and timely reversal of liver fibrosis is an effective means to treat liver disease and improve the quality of life of patients. Due to the complex etiology and pathogenesis of liver fibrosis, there is no specific clinical drug with clear curative effect at present, and a large number of literatures and studies have shown that traditional Chinese medicine has clear advantages in the field of anti-liver fibrosis.

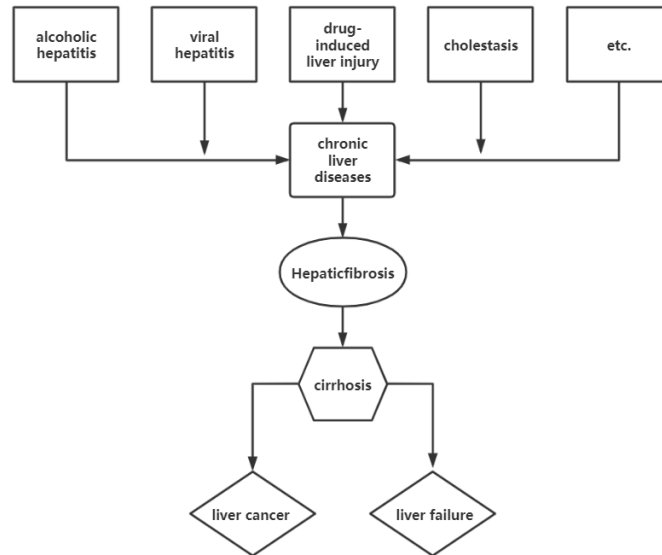


Figure 1: Progress map of liver fibrosis

## 2. Etiology and Pathogenesis of Liver Fibrosis

Liver, body Yin and Yang, the main drainage, the main storage of blood. The body feels the external evil, mainly dampness-heat epidemic poison, which invades the liver, damages the liver cells and tissues, affects the liver function, makes the liver lose in the drainage, the blood storage function is abnormal, and then qi stagnation and blood stasis. Stagnation and heat, dampness-heat obstructing phlegm, liver fire invade the spleen, dampness-heat trapped the spleen, spleen transport function disorder, this is the standard; And the body of the lack of positive qi is this deficiency. The five viscera are integrated, the liver and spleen are damaged, and the kidney is involved for a long time, which eventually leads to the deficiency of the liver and kidney, and intermingled deficiency and excess. (Figure 2) The pathological properties of liver fibrosis are nothing more than the deficiency in essence and excess in superficiality. Dampness-heat evil poison is the main pathogenic factor of liver fibrosis, liver depression and spleen deficiency, dampness-heat stasis is its formation and development process, and blood stasis is an important link of pathological products and pathogenesis of disease. Traditional Chinese medicine believes that liver fibrosis is the result of qi stagnation and blood stasis, phlegm turbidity blocking, and evil invasion of liver, spleen and kidney under the combined action of multiple factors such as emotion and diet. (Figure 3) The main pathogenesis is positive deficiency and evil accumulation. Professor Hu Shiping believed that obstruction of evil toxins was the main pathogenesis of liver fibrosis, with dampness-heat epidemic toxicity and qi stagnation and blood stasis predominating in the early stage and liver depression and spleen deficiency in the late stage [1]. Professor Chen Guoliang believed that the deficiency of the original is actually the basic pathogenesis of liver fibrosis. The deficiency of the original refers to the deficiency of the liver, spleen, kidney and qi and blood, with spleen deficiency being the most common. Standard reality refers to dampness-heat epidemic toxin interjunction, remaining in the

blood, blood stasis. The pathogenesis of liver fibrosis is dynamic, from dampness-heat toxicity to blood stasis and then deficiency [2].

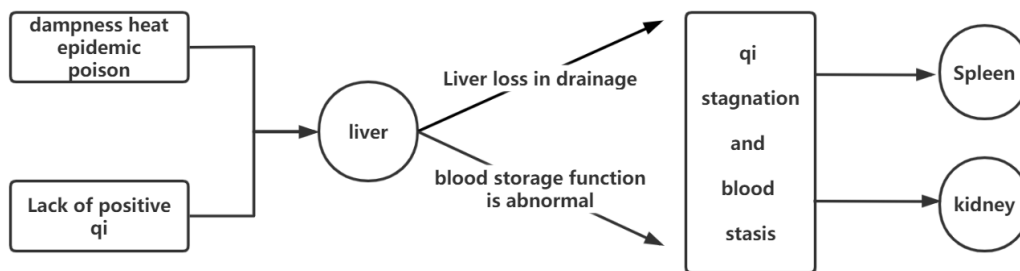


Figure 2: Pathogenesis of liver fibrosis

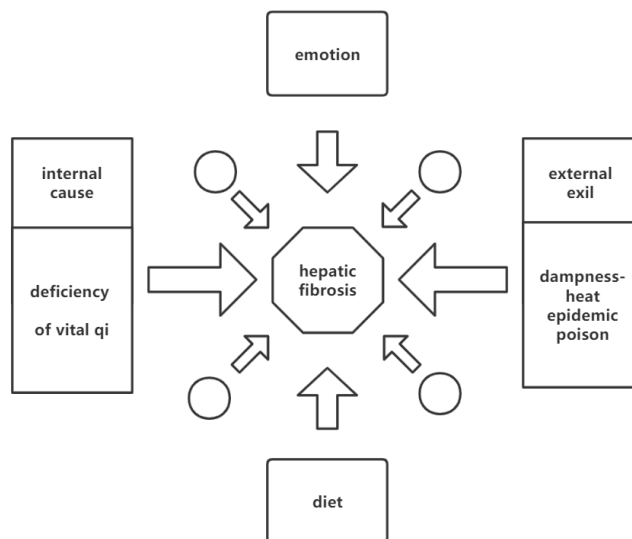


Figure 3: Etiology of liver fibrosis

### 3. TCM Syndrome Type of Liver Fibrosis

Throughout traditional Chinese medicine literature, there is no clear concept of liver fibrosis. From main manifestations and signs, liver fibrosis can be divided into "accumulation", "hypochondriac pain", "distention", etc. The etiology of liver fibrosis is various and the pathological mechanism is complex. Traditional Chinese medicine believes that the basic syndromes of liver fibrosis are deficiency of Qi and Yin, blockage of collages by blood stasis. According to different stages of the disease and individual differences, there will also be syndromes such as dampness-heat accumulation, liver depression and spleen deficiency. According to the Diagnosis and Treatment Guide of Integrated Chinese and Western Medicine for Liver Fibrosis (2019 Edition) [3], TCM can be divided into basic and general syndromes. The former is deficiency and accumulation, positive deficiency and stasis, while the general syndromes are dampness-heat of liver and gallbladder, deficiency of liver and kidney Yin and deficiency of liver and spleen. The fundamental cause of chronic hepatitis B (CHB) liver fibrosis is Yang deficiency syndrome, for a long time, liver veins will be damaged, resulting in Qi and blood stasis. Dampness and heat of liver and gallbladder are two manifestations of liver qi stagnation. Zhu Peiguo [4] pointed out that the liver and blood stasis

syndrome, liver depression and spleen deficiency syndrome, Yin deficiency and internal heat syndrome, spleen and kidney Yang deficiency syndrome of five major syndrome, mainly liver depression and spleen deficiency syndrome. Mild liver fibrosis is mainly manifested by liver qi stagnation and internal stagnation of water and dampness, moderate liver fibrosis is manifested by dampness-heat accumulation and internal stagnation of blood stasis, and severe liver fibrosis is manifested by deficiency of liver and kidney Yin and deficiency of spleen and kidney Yang. (Figure 4)

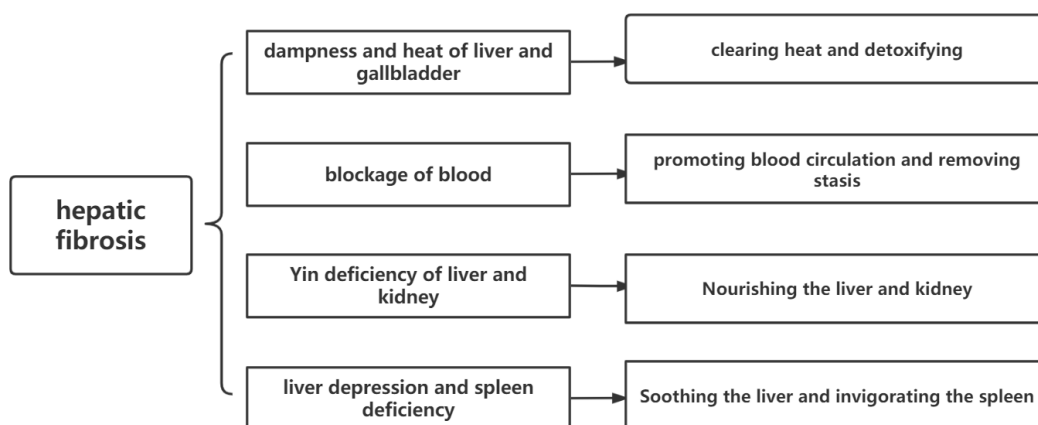


Figure 4: TCM syndrome types of liver fibrosis

## 4. TCM Treatment of Liver Fibrosis

### 4.1. Chinese Herbal Compound

A large number of literatures and studies have shown that Jingfang or compound with the effects of promoting blood circulation, removing blood stasis and invigorating qi can effectively intervene in liver fibrosis, reduce liver fibrosis indicators, improve patients' clinical symptoms and signs, improve liver function, and thus play an anti-liver fibrosis role.

Biejiajian pills can inhibit mononuclear infiltration, reduce the secretion of mononuclear cell-related pro-inflammatory and pro-fibrotic cytokines, and thus relieve liver fibrosis, and can be used for clinical prevention and treatment of liver fibrosis [5]. Yiqi Huayu Rougan formula may alleviate CCL4-induced rat liver fibrosis by regulating the activity of NLRP3 inflammasome signaling pathway, so as to reduce the degree of liver injury and inflammation [6]. Entecavir combined with Compound Biejia Ruangan Tablets can be used to treat hepatitis B cirrhosis, inhibit hepatitis B virus replication and liver fibrosis hyperplasia, and play a role in reducing clinical indicators of hepatitis B virus and promoting liver function reconstruction [7]. Studies have shown that Fuzhenghuayu capsule can reduce collagen fiber deposition in liver tissue, reduce the number of inflammatory lesions in liver tissue, reduce Hyp content, serum ALT, AST and other levels in mouse liver tissue, and effectively treat non-alcoholic fatty liver fibrosis [8]. Rhubarb insect pill can reverse the expression level of ASIC1a/VEGF protein in liver tissue, reduce the liver fibrosis markers  $\alpha$ -SMA and colligation-I, and improve liver fibrosis [9]. Fuganhuaaxian decoction can inhibit the activation of MAPK signaling pathway and down-regulate the protein expression of p-JNK, p-ERK and p-p38, thus alleviating liver injury, protecting liver cells and alleviating liver fibrosis [10]. Jiawei Sini Decoction can reduce serum ALT, AST, ALP and GGT in experimental rats, promote liver protein synthesis, reduce liver injury, improve liver function and treat liver fibrosis [11]. Guizhi Fuling Pill can inhibit the proliferation and invasion of HSC-T6 induced by

TGF- $\beta$ 1, down-regulate the expression of TGF- $\beta$ 1/Smad2 signaling pathway, inhibit the activation of HSCs, reduce ECM generation and accelerate its degradation, and reverse liver fibrosis [12].

In addition, Yupingfeng Powder, Anluo Huaxian pills, Qianggan Capsules (pills), Amfat, Ganxinling, Ganshuang granules, minor bupleurum decoction, Fugan pills and matrine capsules can improve liver fibrosis and liver function to varying degrees [3].

#### 4.2. TCM Monomer

Through the objective regulation of phosphatidyl inositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, Chinese herbal monomer has successfully inhibited the hepatic stellate cells, HSCs) activation and proliferation, accelerate HSCs apoptosis, reduce ECM deposition, accelerate hepatocyte autophagy, and antioxidant to achieve anti-hepatic fibrosis effect.

The anti-hepatic fibrosis mechanism of gardeniin is mainly through regulating TGF- $\beta$ 1/Smad signaling pathway, down-regulating the expression of TGF- $\beta$ 1 and inhibiting the activation and proliferation of HSCs, thus improving rat hepatic fibrosis [13]. Saikosaponin D can reduce the release of inflammatory factors in the liver of rats with immune liver fibrosis, reduce the levels of ALT and AST in the serum of rats to improve liver fibrosis and alleviate liver damage [14]. Astragalus membranaceus can regulate the expression of related proteins in the upstream and downstream of p38MAPK signaling pathway in the liver of rats with liver fibrosis, inhibit fibrosis-causing inflammation, and partially reverse liver fibrosis [15]. Querpectin can reduce the levels of inflammatory factors, serum ALT/AST levels, liver/body weight ratio and histopathological lesions, as well as protect hepatocytes and inhibit liver fibrosis [16]. Curcumin can reduce the expression of TGF- $\beta$ 1 and Smad2/3 protein by inhibiting TGF- $\beta$ 1/Smad signaling pathway, thereby improving liver function and achieving the efficacy of anti-liver fibrosis [17]. Arbutin can inhibit the activation of HSCs by regulating p-Akt/Akt and Smad3 signaling pathway, and alleviate liver damage induced by carbon tetrachloride (CCl<sub>4</sub>) and biliary ligation (BDL), thus reducing liver fibrosis [18]. Artesunate can reduce fibrous tissue hyperplasia, inflammatory cell infiltration, improve liver tissue structure, and improve liver fibrosis. This is mainly accomplished by inducing HSC wire mesh through up-regulation of oncosuppressor gene P53 protein [19].

#### 4.3. Other Therapies

Acupuncture and moxibustion therapy, acupoint application, acupoint injection, ear point pressure bean and other external treatment can effectively stimulate the meridians and acupoints on the body surface, in order to play the role of clearing heat and dampness, promoting blood circulation and removing blood stasis, nourishing qi and Yin, nourishing the positive and benefiting the deficiency, so as to achieve the adjustment of Yin and Yang, adjust the function of qi and blood in the zang fu organs.

Both electric acupuncture and medicinal vesiculation can reduce the deposition of liver fiber connective tissue, improve liver function and reduce the degree of liver fibrosis in carbon tetrachloride liver fibrosis model rats to varying degrees, and medicinal vesiculation is superior to electric acupuncture. Studies have found that electric acupuncture on Zusanli and liver acupoints can reduce the levels of ALT and AST in serum and reduce the score of liver fibrosis through the mechanism of reducing TGF- $\beta$ 1 in liver tissue and up-regulating the level of RLX [20]. Xiangdan injection at bilateral Zusanli point can protect liver tissue, slow down the degree of liver fibrosis and improve liver function of cirrhosis, and the effect of point injection combined with western medicine intravenous drops is more obvious [21]. Studies have proved that the effect of acupoint application of diamine glycyrrhizinate enteric-coated capsules combined with Buganshen paste recipe on inhibiting inflammatory response, reducing hepatocyte apoptosis and treating liver

fibrosis is better than that of the control group using diamine glycyrrhizinate enteric-coated capsules alone [22].(Figure 5)

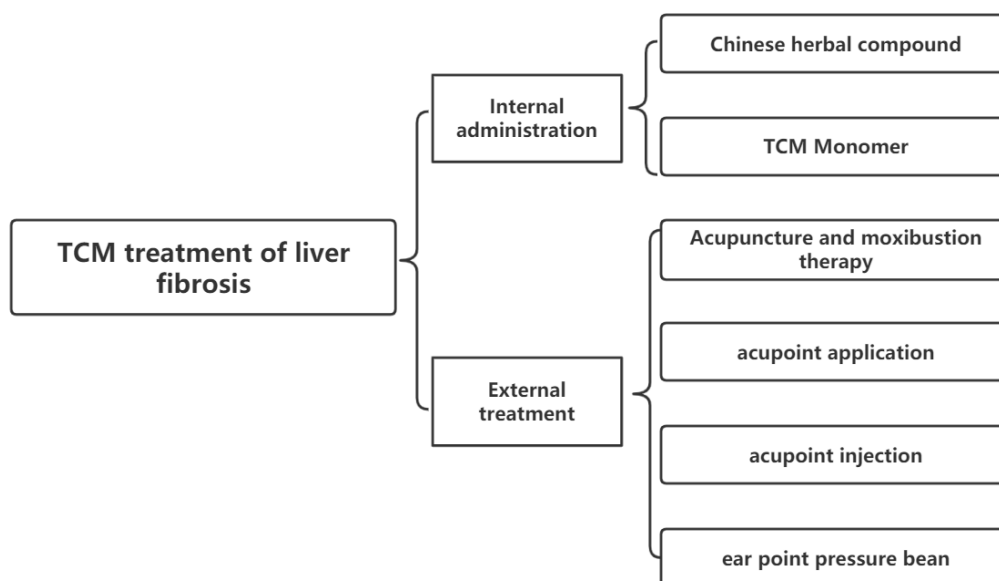


Figure 5: TCM treatment of liver fibrosis

## 5. Discussion

With the development of modern society and the change of people's living habits and diet structure, the number of people suffering from obesity and diabetes has increased significantly, and the prevalence of non-alcoholic fatty liver disease (NAFLD) has also increased significantly. If the liver fibrosis is not early intervention treatment, abhorrent cirrhosis, even liver cancer. And liver fibrosis is a necessary process of cirrhosis. How to delay, treat and even reverse hepatic fibrosis has become a hot research topic in recent years. Following the therapeutic principles of clearing heat and detoxifying, promoting blood circulation and removing stasis, and reinforcing deficiency, TCM can play the role of anti-inflammatory and antioxidant, inhibiting signal pathway and promoting apoptosis of hepatic stellate cells by means of TCM compound, single drug and active ingredient in multiple targets and multiple ways, so as to effectively improve hepatic fibrosis. It is often used in combination with western medicine, which can better treat liver fibrosis and reduce the occurrence of complications. However, there are many pathogenic factors and complex mechanisms of liver fibrosis, and no mature prevention and treatment system has been formed in clinical practice. Studies on the mechanism of TCM anti-liver fibrosis are still not perfect, and a large number of more standardized clinical studies are still needed.

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