

# Research on the Application of Traditional Chinese Medicine in the Prevention and Treatment of Liver Precancerous Lesions

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**Abstract:** Liver cancer is a common clinical malignant tumor, which seriously threatens human health due to its hidden onset, difficult treatment, and poor prognosis. To achieve the "Healthy China 2030" goal, it is particularly important to prevent the occurrence of cancer. Liver precancerous lesions are an important period that needs to be experienced in the evolution of liver cancer, and preventing the formation of precancerous lesions is a key step in the prevention and treatment of liver cancer. Different from Western medicine for the treatment of causes and the characteristics of large side effects of Western medicine, Chinese medicine pays attention to the holistic concept and treatment based on syndrome differentiation, and strives to prevent diseases before they occur, and prevent changes from existing diseases, so it has unique advantages in the treatment of difficult diseases. In recent years, the prevention and treatment of liver precancerous lesions by traditional Chinese medicine has attracted more and more attention. In this paper, by reviewing relevant literature, combing the etiology and pathogenesis of liver precancerous lesions, the application and research of single flavor Chinese medicine, traditional Chinese medicine compound, acupuncture and moxibustion in the prevention and treatment of liver precancerous lesions are summarized as follows.

**Keywords:** Hepatocellular carcinoma; Precancerous lesions of the liver; Traditional Chinese Medicine; Apply; Review

Primary hepatic cell carcinoma (HCC) is a common and poorly prognostic malignant tumor in China, ranking 5th and 2nd among common malignant tumors<sup>[1]</sup>, because of the hidden onset and difficult treatment, seriously threatening people's life and health. Studies have shown a gradual increase in the incidence of liver cancer worldwide<sup>[2]</sup>, and this trend is more pronounced in patients with non-alcoholic steatohepatitis (NASH) and the elderly. Finding effective treatment or preventing the occurrence of liver cancer has become the focus and difficulty of current research. Hepatitis-cirrhosis-liver cancer is recognized as the three-step evolution of hepatitis cancer, and precancerous lesions of liver cancer occur in the process of liver cirrhosis to liver cancer<sup>[3]</sup>, including hepatocellular adenomatous hyperplasia and hepatocellular dysplasia. Liver precancerous lesions can be divided into dysplastic foci (DF) and dysplastic nodules (DN), cirrhosis is closely related to the occurrence of DN, and is divided into low-grade dysplastic nodules (LGDN) and high-grade dysplastic nodules (HGDN) according to the degree of cell dystypia nodules<sup>[4,5]</sup>. Western medicine believes that the etiology of liver precancerous lesions is related to viral hepatitis, metabolism-related fatty liver disease and other carcinogenic factors<sup>[6]</sup>, and clinical evidence can be provided by ultrasound, CT, MRI, and serological examination, and pathological examination is the gold standard for diagnosis<sup>[7]</sup>. Western medicine treatment of liver precancerous lesions is mainly early continuous monitoring of high-risk groups, radiofrequency ablation, surgical resection or liver transplantation. However, surgery and liver transplantation face difficulties such as easy recurrence, lack of donors and high costs, so famous American scholars proposed that cancer prevention is more important than cancer treatment<sup>[8]</sup>, which is in line with the concept of "treating diseases before they occur" in Chinese medicine. TCM's description of similar symptoms of liver cancer can be traced back to the Neijing<sup>[9]</sup>, and has accumulated valuable experience in the development process of thousands of years. Traditional Chinese medicine has been increasingly studied in the prevention and treatment of liver cancer and precancerous lesions due to its advantages of safe curative effect, low price, comprehensive conditioning and small side effects. In recent years, studies have shown that traditional Chinese medicine may prolong or even block the development of precancerous lesions to liver cancer. By

collating and summarizing the relevant literature, the application of traditional Chinese medicine in the prevention and treatment of liver precancerous lesions is summarized as follows.

## 1. The understanding of liver precancerous lesions in TCM theory

### 1.1 Concept

According to the characteristics of the disease, it can be roughly classified as "liver accumulation", "fat qi", "fullness", "flank pain", "jaundice", "mass" and "accumulation"<sup>[9, 10, 11]</sup>, such as "Nanjing·Fifty-six Nan" records: "The accumulation of the liver, known as fat qi, under the left flank, such as covering a cup, there is a head and foot." "Zhubing Yuanhou Lun (Treatise on the Origin of Diseases)" said: "The diagnosis of liver accumulation, the pulse string and thin, the pain under the two flanks... The body has no anointment, likes to turn tendons, the claw nails are black, relieved in the spring and aggravated in the autumn, and its color is blue."<sup>[12]</sup>

### 1.2 Etiology and pathogenesis

The etiology of liver precancerous lesions is divided into internal and external causes<sup>[11,13]</sup>. The internal causes are mainly deficiency of healthy qi, fatigue, internal injury, and emotional failure, resulting in the imbalance of internal organs, qi, blood, yin and yang; The external causes are mainly poison, stasis, phlegm, and dampness. Its pathogenesis<sup>[11,13]</sup> can be summarized as weakness of positive qi and strong evil qi. The body's internal organs are weak, yin and yang are out of harmony, coupled with infection epidemic viruses, cold and evil, dampness and heat, etc., positive and evil qi fighting for a long time, healthy qi deficiency and evil qi remaining, dampness heat and poisonous stasis form each other into cancer. The "Treatise on the Origin of Diseases" says: "Those who accumulate are discordant from yin and yang, weak in their internal organs, suffer from wind and evil, and fight against the qi of their internal organs." Professor Lv Wenliang believed that the main pathological factors of liver cancer and precancerous lesions were "toxicity, deficiency and blood stasis", and concluded that the pathogenesis is "deficiency of healthy qi and mutual connection of poison and stasis"<sup>[14]</sup>. Professor Chang Zhanjie believes that liver precancerous lesions are based on the "deficiency and damage entanglement" of liver cirrhosis, coupled with the results of evil virus invasion, and summarize its pathogenesis as "spleen deficiency, liver damage, poison and stasis intertwined"<sup>[15]</sup>. Professor Li Jingtao believes that "evil poison invasion and blood stasis obstruction" are the key factors causing the disease, and the fundamental cause of the disease lies in "the deficiency of righteous qi and the accumulation of weakness"<sup>[10]</sup>, and advocates the simultaneous treatment of liver and spleen. Wei Ailing summarized the pathogenic evil qi with strong harm as "poison", and "dampness, phlegm, and stasis" as "turbidity", and concluded that "toxic turbidity" is the core etiology of liver precancerous lesions<sup>[16]</sup>, which provides good guidance and enlightenment for follow-up research. Meng Bobo<sup>[17]</sup> concluded that the pathogenesis of liver precancerous lesions can be divided into five categories: "qi stagnation and blood stasis, liver depression and spleen deficiency, damp-heat internal accumulation, toxic and stasis interaction, Yin deficiency of liver and kidney", supplementing the treatment of nourishing yin and benefiting the liver and kidney. According to the above-mentioned doctors' understanding of the etiology and pathogenesis of liver precancerous lesions, the treatment principle of this disease should be mainly based on supporting and detoxifying and removing stasis, harmonizing the liver and spleen, nourishing the liver and benefiting the kidney. In addition, Sun Dongxue<sup>[18]</sup> systematically expounded the application of "the alcohol injury theory" in the prevention and treatment of liver precancerous lesions, which was refreshing. In recent years, some scholars have also explored new ways to prevent and treat liver precancerous lesions from the perspective of intestinal microecology<sup>[19,20]</sup>.

## 2. Research on the application of single Chinese medicine

Through the literature in recent years, it has been found that the treatment of liver precancerous lesions is mainly heat-clearing antidotics, moisture-drying and deworming drugs, tonifying drugs, and Qi-activating drugs. The clinical application and pharmacological research of representative drugs are summarized as follows.

## 2.1 Astragalus

Astragalus, sweet taste, slightly warm, belongs to the spleen and lung meridians. It can strengthen the spleen and tonify, strengthen the surface, lift the yang, diuretic, detoxify and build muscles. The pathogenesis of liver precancerous lesions is mainly due to the deficiency of positive qi, and astragalus is applied to replenish qi and dispel evil. "Zhengzhi Zhunsheng" said: "Astragalus helps true qi, Fangfeng cooperates with astragalus to help true qi." Professor Lv Wenliang commonly used Astragalus, Baizhu and Fangfeng (Yutingfeng powder) to treat chronic liver disease<sup>[21]</sup>. Patients with chronic liver disease have a long course of disease, physical deficiency, and clinical fatigue and weakness. The combination of the three medicines helps the spleen to dissolve phlegm and dampness, support the right qi, replenish the deficiency, and resist the evil outing. Astragalus, white peony and bupleurum can nourish the liver yin and liver body, relieve liver depression, and smooth blood, and have a great effect on cancer fatigue<sup>[22]</sup>. Astragalus is often used in combination with Curcuma Zedoary (E Zhu) to prevent liver cancer. "Bencao Qiuzhen" said: "Curcuma Zedoary specializes in the liver meridian, warm-natured, bitter and spicy in taste, and breaks the blood stasis of liver meridians". It is good at eliminating pain and breaking blood without hurting qi, and is often used to treat liver fibrosis, cirrhosis, liver cancer and other tumors or proliferative diseases<sup>[23]</sup>. Curcuma Zedoary and its extracts have anti-inflammatory, hepatoprotective, and antitumor effects<sup>[24]</sup>. The combination of the two medicines can benefit qi and dissolve stasis, support righteous qi without retaining evil, dissolve stasis without harming healthy qi, and make the lesion disappear invisible. Modern pharmacological studies have shown that astragalus and its extracts are widely used in the prevention and treatment of liver disease, mainly by influencing NF- $\kappa$ B, Wnt/ $\beta$ -catenin, TGF- $\beta$ /Smad, STAT3 and other signaling pathways and inhibiting the expression of related cancer cell proteins<sup>[25,26]</sup>. Recent studies have found that astragalus polysaccharides can inhibit the occurrence and development of non-alcoholic fatty liver disease by regulating the intestinal flora<sup>[27]</sup>, and inhibit the formation of precancerous lesions from the source by regulating the intestinal microbiome and maintaining the balance of the enterohepatic axis<sup>[28]</sup>.

## 2.2 Hawthorn

Hawthorn, sweet taste, slightly warm, belongs to the spleen, stomach and liver meridians, can disperse qi stasis, eliminate food and strengthen the stomach, dissolve turbidity and lower fat. "Compendium of Materia Medica" records: "Hawthorn can transform the diet, eliminate meat accumulation, phlegm drinking and swallowing acid". "Yixue Zhongzhong Canxi Lu" contains: "Hawthorn dispels blood stasis without hurting new blood, opens up depression without hurting healthy qi, and its nature is especially peaceful." Hawthorn can not only produce yin jin to nourish the liver body, but also eliminate stagnation, invigorate qi and blood, consolidate middle-jiao, and regulate the liver and spleen together<sup>[29]</sup>. It is good at promoting the operation of qi and removing blood stasis, making qi stagnation and blood stasis invisible, and can stop bleeding without retaining blood stasis. Professor Guan Youbo's treatment of chronic liver disease emphasizes the joint regulation of the liver, spleen and kidneys, especially medium focus as the key<sup>[30]</sup>, hawthorn supports healthy qi and strengthens the spleen and stomach, which can nourish qi and blood, dissolve phlegm and dampness, and consolidate middle energizer. Clinically, it is often combined with Yanhu Suo and Chuanlian Zi, which can harmonize qi and blood, smooth the liver and relieve pain. The smooth flow of qi and blood prevents cancer poison from invading<sup>[31]</sup>. Modern pharmacological studies suggest that hawthorn total flavonoids can alleviate alcohol-induced liver damage through anti-lipid peroxidation and reduce carbon tetrachloride-induced liver fibrosis by inhibiting  $\alpha$ -SMA and TGF- $\beta$ 1 expression<sup>[32,33]</sup>. Hawthorn can also inhibit the proliferation of hepatoma cells and promote apoptosis of hepatoma cells<sup>[34]</sup>. It can be seen that hawthorn prevents the occurrence of liver precancerous lesions by lowering lipids, protecting liver cells, anti-liver fibrosis and anti-tumor.

## 2.3 Hedyotis diffusa

Hedyotis diffusa, bitter and sweet taste, cold in nature, belongs to the stomach, large intestine, small intestine meridians, can clear heat and detoxification, eliminate carbuncle, dispel dampness. The pathogenesis of liver precancerous lesions is closely related to evil poison and humid heat. Liver disease for a long time, the spleen and stomach are invaded by evil qi, and the function of middle-jiao transport is abnormal, resulting in phlegm dampness and heat. In addition, the deficiency of healthy qi, the dysfunction of the internal organs, resulting in Qi stagnation, phlegm dampness, toxic stasis and stagnation, and finally induce cancer. Clinically, it is often combined with Banzhi Lian to enhance the effect of detoxification and dispelling stasis, which widely used in the treatment of cancer diseases.

Modern pharmacological studies have shown that the anti-tumor effects of *Hedyotis diffusa* mainly include inhibiting the expression of cancer cell genes, promoting apoptosis of cancer cells, and regulating immunity<sup>[35]</sup>, and the anti-tumor effect of combining with Banzhi Lian is better than that of two drugs alone<sup>[36]</sup>.

#### **2.4 *Salvia miltiorrhiza***

Danshen, bitter taste, slightly cold, belongs to the heart and liver meridians, can activate blood and dispel stasis, unblock meridians and relieve pain, cool blood and eliminate carbuncles. Carcinogenesis is due to long-term qi stagnation and liver stasis. Patients with cirrhosis have a dull complexion, sublingual stasis, and often ascites in the later stages. Danshen can generate new blood and promote the operation of qi in the blood. It is widely used in the treatment of various liver diseases by soothing and calming the liver, activating blood and removing stasis, harmonizing qi and blood, expanding liver microvessels, relieving portal vein pressure, improving blood circulation, and restoring liver function<sup>[37]</sup>. Guan Youbo commonly uses Danshen with Zelan to treat cirrhosis with ascites, smoothing the liver and spleen blood network, eliminating diuresis and ascites<sup>[38]</sup>. Modern pharmacological studies have shown that Danshen can treat hepatitis B, liver fibrosis, fatty liver, cirrhosis and liver cancer by anti-virus, influencing signaling pathways, inducing apoptosis of cancer cells, inhibiting tumor angiogenesis and enhancing immunity<sup>[39]</sup>.

#### **2.5 *Scutellaria baicalensis***

Skullcap, bitter taste, cold in nature, belongs to the lungs, gallbladder, spleen, large intestine and small intestine meridians. The work is in clearing heat and dampness, clearing fire and detoxifying, stopping bleeding and preventing miscarriage. The Shennong's Materia Medica records: "It can treat hot and humid jaundice, diarrhea, water and moisture cessation, blood closure and sores." Professor Lv Wenliang<sup>[21]</sup> believes that liver cancer is the result of the long-term effect of toxic stasis. It is easy to accompany phlegm and dampness, and the evil of humidity and heat is not removed, which inhibits the three-jiao machine and leads to imbalance of the environment in the body. Patients with liver cancer often have hypochondriac pain, bad breath, sticky stools and yellow eyes in severe cases. Therefore, Professor Lv often uses Huangqin and Huanglian to clear heat and moisture. The combination of two drugs can remove humid heat and fire poison of the three-jiao, maintain the balance of the internal environment, but attention should be paid to grasping the dosage to avoid consuming yang qi. Huangqin can also contract with Yinchen, Huangqi and other herbs, which can remove dampness and reduce yellow, and dispel evil without harming the right qi. It is known as a traditional Chinese medicine antibiotic. Modern pharmacological studies have shown that the active substance of *Scutellaria baicalensis* can inhibit the replication of hepatitis B virus, and its alkaloids can lower lipids, resist oxidation and protect liver damage, thereby treating hepatitis, liver fibrosis, and preventing the formation of cancer<sup>[40]</sup>.

### **3. Applied research of compounds**

#### **3.1 *Turtle shell decocted pill***

Biejia decoction pill<sup>[41]</sup> was found in Synopsis of Golden Chamber, which was composed of more than two dozen flavors of Chinese medicine. Peng Tao<sup>[42]</sup> divided the medicines into four parts. Chaihu, Guizhi, Banxia, Shaoyao and Huangqin to adjust Shaoyang and Taiyin meridians. Shiwei, Dahuang, Tingli Zi and Tubie Chong to remove water and stasis. Biejia with various insect drugs to fight cancer. E Jiao, Ren Shen, Chaihu, etc. to harmonize qi and blood. This prescription has been widely studied for its remarkable efficacy. Huang Hongna<sup>[43]</sup> experimental research found that this formula can improve the microenvironment of liver cells, inhibit the microangiogenesis of cancer tissues, and prevent the occurrence of precancerous lesions by inhibiting the expression of TGF- $\beta$ 1 pathway, COX-2 and SOD proteins. Chen Weicong<sup>[44]</sup> found that this formula may exert anti-tumor effects by reducing the expression of inflammatory factors and inhibiting the activation of IL-6/STAT3 signaling pathway. In addition, Zhang Wenfu<sup>[45]</sup> concluded that this formula has also achieved remarkable results in the prevention and treatment of fatty liver, chronic hepatitis B and cirrhosis, which indicates that it can be applied to all stages of liver disease to prevent precancerous lesions.

### 3.2 *Yipi Yanggan prescription*

Yipi Yanggan prescription<sup>[46]</sup> is the experience of Professor Chang Zhanjie, a famous Chinese medicine practitioner in Shaanxi Province, which is composed of Dangshen, Baizhu, Baihua Sheshe Cao, Banzhi Lian, Biejia, Yujin, Jianghuang, Shudi Huang and Gouqi. Professor Chang believes that liver disease should be treated together with the liver and spleen, and it is important to strengthen the middle-jiao. Dangshen and Baizhu can replenish qi and strengthen the spleen, consolidate the biochemical source of qi and blood, and support the right qi to dispel evil. Baihua Sheshe Cao and Banzhi Lian can detoxify, remove stasis and fight tumors. Biejia, Yujin and Jianghuang can disperse knots, run qi, relieve depression and activate blood to remove stasis. Shudi Huang and Gouqi can nourish the liver and kidneys, and transport water to moisturize the wood. This prescription has been thoroughly studied in the prevention and treatment of liver cancer prelesions. Liu Yazhu<sup>[47]</sup> found that this formula can inhibit the expression of PCNA and GGT proteins in liver cancerous tissues, and the mechanism may be related to anti-cell abnormal proliferation and antioxidant. Li Jingtao<sup>[48]</sup> found that this formula can reduce the expression levels of inflammatory factors TNF- $\alpha$  and IL-6 in rats, reduce the continuous stimulation of liver cells by the inflammatory microenvironment of the liver, and inhibit cell carcinogenesis.

### 3.3 *Fuzheng Huayu prescription*

Fuzheng Huayu Fang<sup>[49]</sup> is composed of six kinds of traditional Chinese medicines: Danshen, Taoren, Chongcao Junsi, Songhua Fen, Wuwei Zi and Jiaogu Lan. The liver does not like depression, and emotional comfort is a necessary condition for it not to be attacked by diseases. Liver disease for a long time, the body's qi and blood function disorders, easy to produce deficiency and stasis. Jing and Blood are homologous, liver blood insufficiency often involves kidney jing, clinical patients are more likely to see waist and knee soreness, tiredness, dizziness and other symptoms. Danshen and Taoren can activate blood circulation and eliminate stasis. Chongcao Junsi and Wuwei Zi can nourish the kidney and liver. Jiaogu Lan and Songhua Fen can invigorate qi, strengthen spleen to remove dampness, and clear heat and detoxify. The combination of various medicines can replenish the Jing and Blood, restore healthy qi, and clear the poison and dispel evil qi. Modern pharmacological studies<sup>[50]</sup> showed that it significantly reduced the expression of proteins such as  $\alpha$ -SMA, FAP,  $\gamma$ -H2AX and FOXO4 in adjacent tissues, inhibited the activation of hepatic stellate cells, and reduced senescent fibroblasts around tumors. This indicates that this formula can intervene the occurrence of precancerous lesions from the early stage of liver disease.

In addition, the prescription drugs that have been studied more often include Huqi San, Erzhu Jiedu Tang, Qizhu Huaji Fang.

## 4. Applied research on acupuncture

Acupuncture can relieve pain and enhance immunity, and it is easy to operate, safe and inexpensive, with few side effects, and easy to be accepted by patients. The mechanism of disease treatment can be classified into three aspects: "internal disease with external treatment", "Zang-fu meridians", and "Fuzheng Quxie"<sup>[51]</sup>. Moxibustion can replenish healthy qi and solidify the essence. The Neijing records: "If drugs and acupuncture cannot be treated, moxibustion must be used." Studies have shown that moxibustion at acupuncture points such as "Dazhui, Zusan Li, Guanyuan" can enhance immunity and inhibit the proliferation of cancer cells. It has been reported that warm acupuncture can reduce the level of IL-2 receptors, increase the content of free IL-2, and play an anti-cancer effect. Liu Zeyin<sup>[52]</sup> uses acupuncture to treat the pain of advanced liver cancer with significant effect and can enhance immunity. Zhang Le<sup>[53]</sup> experimentally found that moxibustion may exert anti-cancer effects by inhibiting the expression of PCNA, Cyclin D1 and CDK4 proteins in tumor cells. Jia Wenrui<sup>[54]</sup> found that direct moxibustion of "Ganshu point" can reduce the serum AFP content of liver cancer rats, reduce the degree of cell carcinogenesis, and inhibit the expression of Livin factor. At present, there are relatively few studies on the application of acupuncture in the prevention and treatment of liver precancerous lesions, but it deserves more attention because of its unique advantages.

## 5. Summary

Liver precancerous lesions are an important stage in the evolution of cirrhosis into liver cancer.

Early detection and treatment are key to saving patients' lives and improving their quality of life. Some Western scholars have suggested that finding ways to prevent and control cancer may be more valuable than simply curing cancer<sup>[8]</sup>. Whether liver cancer can be effectively avoided, the key is to intervene in time and prevent it in people with cirrhosis or even liver disease at an earlier stage. If the righteous qi is mighty, external evil cannot enter, which can inhibit or delay the occurrence of cancer. As the "Suwen Cifa Lun" says: "If the body is full of righteous qi, then evil cannot be invaded." At present, the research on liver precancerous lesions in traditional Chinese medicine mainly focuses on the influence on signaling pathways and protein expression, and has achieved satisfactory results. Its effects can be summarized as inhibiting the proliferation of cancer cells, promoting apoptosis of diseased cells, promoting precancerous cell differentiation, antioxidant, immunomodulating, and protecting hepatocytes<sup>[55]</sup>. However, the full exploration of its mechanism of action needs further study. Due to the hidden onset of liver cancer, precancerous lesions are not easy to detect, and there is still a lack of clinical-stage research. The human body is a complex whole, the patient's condition is multi-factor, multi-symptomatic entanglement, whether the results of animal experimental research can be well applied to the clinic still need to be observed and explored. However, we believe that with the development of science and technology and the gradual deepening of research, Chinese medicine will definitely be able to better benefit mankind, and cancer will definitely be overcome one day.

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