DOI: 10.53469/jcmp.2026.08(03).18

# A Study on the Medicinal Patterns of Traditional Chinese Medicine in Treating Liver Fibrosis

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**Abstract:** ***Liver fibrosis represents a pivotal stage in the progression of chronic liver disease towards cirrhosis, exhibiting reversibility and thus underscoring the critical importance of early intervention. Presently, Western medicine lacks specific anti-fibrotic agents, whereas traditional Chinese medicine demonstrates unique advantages in preventing and treating liver fibrosis. This study employed data mining on 147 patented TCM compound formulas to analyse their prescribing patterns, including drug frequency, properties, meridian tropism, and combination formulations. High-frequency herbs predominantly comprised Astragalus membranaceus, Salvia miltiorrhiza, Carapax Testudinis, and Angelica sinensis, exhibiting predominantly cold, warm, or neutral natures. Their tastes were chiefly bitter, sweet, or pungent, with primary meridian tropism towards the liver and spleen channels. Blood-activating and stasis-resolving agents, alongside tonic herbs, form the therapeutic core, supplemented by heat-clearing, dampness-draining, and qi-regulating substances. Cluster analysis further identified multiple core drug combinations, whose mechanisms of action were explored through network pharmacology. These findings provide theoretical foundations for TCM treatment of liver fibrosis, while also offering guidance for novel drug development and optimisation of clinical prescribing.***

**Keywords:** Liver fibrosis, Traditional Chinese Medicine, Medication regimen**.**

## 1. Research Background

Liver fibrosis is the most common chronic disease of the digestive system encountered clinically. It represents the liver's reparative response to various chronic insults, typically manifesting as abnormal proliferation of fibrous connective tissue within the liver. This process generally occurs following hepatic cell necrosis and inflammatory stimulation, leading to the replacement of normal liver tissue with scar tissue. The causes of liver fibrosis are diverse, primarily including viral hepatitis, alcoholic liver disease, fatty liver disease, drug or chemical toxins, cholestasis, parasitic infections, and genetic or metabolic disorders. Under these influences, the liver undergoes repeated inflammatory damage, triggering its self-repair mechanisms that produce excessive fibrotic material. This material accumulates within the liver, progressively segmenting it into numerous small nodules. This obstructs the functioning of hepatic ducts and ultimately impairs liver function. Liver fibrosis typically presents no obvious clinical symptoms in its early stages. As the condition progresses, symptoms such as fatigue, loss of appetite, indigestion, and bleeding may manifest in the middle and late stages. Diagnosis of liver fibrosis is primarily confirmed through histopathological examination of liver tissue, graded from stage 0 to stage 4. Serological markers such as PCIII, LN, and IV-C may also be utilised, as these indicators reflect the extent and activity of fibrosis, aiding in early diagnosis and disease assessment. China faces a significant burden as a country with a high prevalence of viral hepatitis, with over 500,000 annual deaths attributable to liver fibrosis, cirrhosis, and hepatocellular carcinoma. In recent years, the number of chronic liver disease patients in China has increased annually, imposing a substantial economic burden on healthcare systems. Concurrently, improvements in lifestyle have led to an upward trend in diseases primarily characterised by liver fibrosis, with alcoholic liver disease being particularly prominent [1]. Internationally, Western medical approaches to treating liver fibrosis primarily involve controlling causative factors, reducing extracellular matrix formation, diminishing or inhibiting hepatic stellate cell activation, and promoting fibrotic tissue degradation. In China, the use of traditional Chinese medicine has demonstrated significant efficacy in preventing and treating liver fibrosis [2,3]. Consequently, the management of liver fibrosis remains a focal point within the medical community. Currently, no specific drugs exist for the clinical treatment of liver fibrosis. Management primarily targets the underlying causes, such as lifestyle modifications, alcohol abstinence, and antiviral medications. However, these interventions yield suboptimal outcomes for patients with advanced fibrosis and cannot fundamentally reverse the condition. Liver transplantation remains the ultimate and sole treatment option for end-stage fibrosis, yet it is severely constrained by donor shortages. Consequently, the development of anti-fibrotic drugs is urgently required [4]. The pathogenesis of liver fibrosis remains incompletely elucidated. Nevertheless, the vast majority of scholars concur that early detection and timely intervention can effectively reduce mortality rates among cirrhosis patients and improve prognosis. Conventional Western medications, however, are often restricted in clinical application due to their numerous adverse reactions and high cost. In recent years, numerous scholars both domestically and internationally have observed that TCM exhibits fewer adverse reactions, lower cost, and significant efficacy in treating liver fibrosis. Consequently, research into the pharmacological patterns of TCM for liver fibrosis treatment holds significant practical relevance and urgency. This study aims to provide new theoretical foundations and experimental guidance for TCM treatment of liver fibrosis, while also offering valuable reference for the modernisation and clinical application of traditional Chinese medicines.

## 2. Research Significance

Through data mining of patented Chinese herbal formulae for treating liver fibrosis, this study explores their pharmacological patterns. Employing network pharmacology methods, it investigates the mechanisms by which core high-frequency drug pairs exert therapeutic effects on liver fibrosis, aiming to provide insights for novel drug development and clinical applications in this field [5]. This manifests primarily in the following aspects: (1) Enhancing therapeutic efficacy and guiding clinical prescribing: By studying medication patterns in liver fibrosis treatment, we can identify which drugs prove more effective during therapy. This guides clinicians in selecting and administering medications more rationally, thereby improving treatment outcomes. Optimising treatment regimens: Understanding the mechanisms of action and efficacy characteristics of different drugs facilitates the formulation of personalised treatment plans, allowing adjustments and optimisation according to individual patients' conditions and needs. (2) Advancing drug development and identifying novel therapeutic targets: Investigating medication patterns in liver fibrosis may reveal key molecular mechanisms underlying disease onset and progression, thereby providing targets for novel drug discovery. Promoting pharmaceutical innovation: Evaluating and analysing the efficacy of existing drugs can identify their limitations, subsequently driving improvements and innovations in pharmaceuticals. (3) Enhancing Medical Standards and Clinician Competence: By studying and mastering the patterns of drug use in liver fibrosis, clinicians can elevate their diagnostic and therapeutic capabilities, enabling more accurate disease assessment and treatment planning. Fostering academic exchange: Research findings on liver fibrosis medication patterns stimulate scholarly discourse within the medical community, driving collaborative advancement in related fields. (4) Improving patient prognosis and slowing disease progression: Effective drug therapy can delay the progression of liver fibrosis, reduce the incidence of complications, and enhance patients' quality of life. Reducing mortality: Through rational drug treatment, mortality rates among liver fibrosis patients can be lowered, thereby extending survival time.

## 3. Current State of Research

This study extensively collected information on traditional Chinese medicine formulas for treating liver fibrosis from authoritative databases such as China National Knowledge Infrastructure (CNKI). This information encompassed formula composition, dosage, and administration methods. Through advanced searches on CNKI using the keywords 'traditional Chinese medicine' and 'liver fibrosis', relevant literature was retrieved. Inclusion criteria were: studies employing traditional Chinese medicine or integrated Chinese-Western medicine approaches for treating liver fibrosis, encompassing clinical trials, summaries of renowned physicians' experiences, and case reports. Formulas documented in the literature must possess clearly defined drug compositions, detailed dosages, and be administered orally [6]. The search yielded 147 formulas. Subsequently, data standardisation and database construction were undertaken. Patent compound formulas meeting inclusion criteria were standardised according to the Chinese Materia Medica for herbal nomenclature. Formulas not listed in the Chinese Materia Medica were referenced against the Chinese Medicine Intelligence Network (https://db.yaozh.com/) or retained their original names [4]. Data import and verification were subsequently conducted, utilising the Traditional Chinese Medicine Inheritance Support System software for processing and analysis. This involved statistical evaluation of fundamental attributes such as frequency of use, medicinal properties, taste, and meridian tropism within the formulas, alongside analysis of drug combination patterns and association rules. Concurrently, cluster analysis identified core drug combinations, which served as the basis for proposing novel prescription strategies.

Following rigorous screening and meticulous analysis, 147 formulas associated with liver fibrosis were identified, involving 431 Chinese medicinal substances with a total of 1,386 usage instances. Among these, 34 medicinal substances were used ≥10 times. Further analysis of these 431 herbs revealed their primary natures as cold, warm, or neutral, with no hot-natured herbs. Their tastes predominantly exhibited bitter, sweet, and pungent qualities. Meridian affinity analysis indicated primary affiliation with the Liver and Spleen meridians, followed by the Heart and Spleen meridians. Analysis of formulation patterns across these 147 prescriptions, ranked by frequency of drug combinations from highest to lowest, yielded 25 commonly used combinations involving 11 frequently employed herbs. Concurrently, cluster analysis identified multiple core drug combinations and novel prescription strategies. These core combinations may provide valuable reference and support for future clinical applications and research.

## 4. Commentary

Liver fibrosis is a chronic liver disease that serves as a precursor to cirrhosis and represents the only reversible treatment opportunity prior to cirrhosis development. Modern medical understanding attributes the primary causes of liver fibrosis to multiple injurious factors including hepatitis viruses (predominantly hepatitis B and C), alcohol, lipid metabolism disorders, toxins, medications, cholestasis, autoimmune factors, and genetics. Under prolonged, chronic stimulation from one or more of these factors, the liver undergoes chronic inflammatory changes. Continuous necrosis and apoptosis of hepatic parenchymal cells subsequently trigger the fibrotic process [7]. The pathogenesis of hepatic fibrosis primarily involves hepatic-renal dysfunction, qi stagnation with blood stasis, and obstruction of hepatic collaterals. The principal pathological factors are liver qi stagnation, blood stasis, and damp-heat. Patients with liver fibrosis may initially present without pronounced symptoms. As the condition progresses, digestive system symptoms such as fatigue, loss of appetite, nausea, and vomiting may emerge, alongside abdominal distension, constipation, or diarrhoea. Severe cases may exhibit a tendency towards haemorrhage. Chen Guoliang posits that liver fibrosis constitutes a progressive pathological process. It commences with exposure to pathogenic damp-heat toxins; prolonged retention of these pathogens penetrates inward, leading to qi stagnation, impaired spleen function, impaired blood circulation, and stasis accumulation. This dynamic evolution progresses from excess to deficiency, from the exterior to the interior, and from the qi aspect to the blood aspect. The primary TCM syndromes are Liver Qi Stagnation

with Spleen Deficiency, Spleen Deficiency with Damp-Heat, and patterns of mutual entanglement of stasis and heat. Treatment adheres to the principles of 'expelling pathogenic factors' and 'strengthening the body's inherent vitality.' Depending on the stage of the pathological process, it is essential to fully consider the three factors (pathogen, constitution, environment) and integrate the disease pattern with the syndrome. Building upon the fundamental therapeutic methods of nourishing yin, invigorating blood, and resolving stasis, one should flexibly employ methods such as clearing heat and draining dampness, soothing the liver and strengthening the spleen, tonifying qi and nourishing yin, tonifying the liver and kidneys, and invigorating blood and resolving stasis [8].

Secondly, adjunctive therapies such as heat-clearing agents, surface-relieving agents, haemostatic agents, digestive - promoting agents, purgatives, and diuretic – dampness - draining agents enhance overall therapeutic efficacy through approaches like clearing heat and draining dampness, fortifying the spleen, and nourishing blood. Heat-clearing herbs such as Scutellaria baicalensis and Forsythia suspensa effectively mitigate hepatic inflammatory responses. Diuretic and dampness-draining agents like Poria cocos and Alisma orientale assist in expelling internal dampness, thereby alleviating hepatic burden. Within TCM theory, the liver corresponds to wood and the spleen to earth, with wood overcoming earth. The liver governs free flow, regulating the unimpeded circulation of qi throughout the body; the spleen governs transformation and transport, converting food into the refined substances required by the body. The spleen and stomach constitute the foundation of acquired constitution, while the kidneys represent the root of innate constitution. Dysfunction in the spleen and stomach impairs the normal operation of the kidneys and other organs, thereby precipitating various diseases. Should the liver fail in its dispersing function, leading to stagnant qi movement, this disrupts the spleen's transformative capacity. This imbalance in the spleen and stomach's ascending and descending functions manifests as loss of appetite, abdominal distension, and diarrhoea. Conversely, if spleen qi is deficient and fails to properly transform and transport food and fluids, the liver becomes inadequately nourished, leading to stagnation of liver qi. Zhang Zhongjing elucidates in the Golden Cabinet Essential Prescriptions: "Upon observing liver disease, one recognises that the liver transmits to the spleen; one should first fortify the spleen... Mediocre practitioners, unaware of this transmission, upon seeing liver disease, fail to understand the need to fortify the spleen, treating only the liver... Therefore, by fortifying the spleen, the liver will naturally recover. This is the essential principle of treating liver disorders by supplementing the spleen.' This not only emphasises the importance of considering the spleen when treating liver disease but also identifies 'fortifying the spleen" as the key to treatment. By strengthening the spleen, its transporting and transforming functions are enhanced, ensuring a sufficient source for the generation of qi and blood. This nourishes the liver wood, thereby restoring the liver's normal dispersing function. Moreover, Zhang Zhongjing's theory reminds practitioners to adopt a holistic perspective in disease management. Treatment should not be confined to the affected organ but must consider the mutual influence between organs, implementing corresponding preventive measures. This therapeutic philosophy, rooted in a holistic approach and integrating prevention with treatment, holds significant reference value for modern medicine as well.

Moreover, contemporary pharmacological research has revealed that traditional Chinese medicines exhibit potent antiviral properties, immune-modulating effects, and hepatoprotective capabilities, demonstrating distinct advantages in treating liver fibrosis. Analysis of the extracted results indicates that the 21 herbal medicines identified in the treatment regimen precisely correspond to the top 21 most frequently used herbs, suggesting these 21 formulations constitute the core therapeutic agents for liver fibrosis [9]. Concurrently, the therapeutic effects of certain active constituents in traditional Chinese medicines on liver fibrosis have been substantiated, providing scientific rationale for their application. For instance, peach kernel preparations can reduce hyaluronidase (HA) and laminin (LN) levels, increase serum albumin, and enhance cellular immunity. Cordyceps sinensis preparations inhibit the deposition of total collagen, type I collagen, and type III collagen in the liver. Stephania tetrandra extract reduces serum type III procollagen peptides and hyaluronic acid (HA), thereby alleviating the severity of liver fibrosis. Colchicine, meanwhile, decreases collagen synthesis and halts the progression of liver cirrhosis.

Based on the core drug combinations and novel prescription strategies derived from cluster analysis, we propose the following novel therapeutic approaches for liver fibrosis: Firstly, prioritise the application of blood-activating and stasis-resolving agents to mitigate fibrosis severity by enhancing hepatic microcirculation. Secondly, reinforce the formulation of qi-regulating herbs to alleviate symptoms of hepatic qi stagnation and blood stasis through modulating liver qi function. Thirdly, integrating methods such as clearing heat and draining dampness, fortifying the spleen and nourishing blood, to comprehensively regulate liver function and promote recovery and improvement of the condition. Concurrently, further investigation is required into the pharmacological mechanisms and target sites of Chinese herbal medicine in treating liver fibrosis, providing more scientific and precise evidence for its clinical application. Although the pathogenesis of liver fibrosis is complex and diverse, with variable disease progression, timely detection and appropriate effective treatment can not only halt further fibrosis progression and prevent the adverse outcome of cirrhosis, but may even reverse fibrosis [6].

## 5. Summary

In summary, traditional Chinese medicine possesses unique advantages in treating liver fibrosis. Through rational medication protocols and formulation methods, it can effectively improve patient conditions and enhance quality of life. With ongoing research, traditional Chinese medicine is expected to play an increasingly significant role in the prevention and treatment of liver fibrosis.

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