Review Article

Traditional Chinese medicine, liver fibrosis, intestinal flora: is there any connection?—a narrative review

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Abstract: This paper aims to analyze how intestinal flora regulates liver fibrosis pathogenesis and to evaluate the regulatory effect of traditional Chinese medicine (TCM) on the intestinal flora, providing new insights into liver fibrosis treatment. Destruction of the intestinal microbiome can lead to liver fibrosis development, accelerating the intestinal microbiome's disruption. TCM can effectively regulate the intestinal flora, helping prevent and treat liver fibrosis. This review discusses the mechanisms behind intestinal flora changes in liver fibrosis and how TCM can regulate these changes. We searched PubMed, the Wanfang database, and CNKI for "liver fibrosis", "intestinal microflora", and "intestinal microbiota" and reviewed the retrieved literature. We detail the prevention and treatment options for liver fibrosis though the use of TCM in regulating intestinal flora. We also highlight the influence of the intestinal flora on liver fibrosis and present the research regarding the prevention and treatment of liver fibrosis using TCM. We also describe the effects of TCM on the intestinal flora. TCM can effectively regulate the intestinal flora to prevent and treat liver fibrosis through the liver-intestine axis.

Keywords: Liver fibrosis; intestinal flora; traditional Chinese medicine (TCM); review

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Introduction

Background

The occurrence and development of liver fibrosis (*Figure 1*) occurs in all chronic liver diseases and leads to liver cirrhosis or even liver cancer. The mortality rate of patients with liver cirrhosis is ranked 13th among all chronic diseases, suggesting that this condition has significant effects on quality of life (1). Studies have shown that liver fibrosis and early diagnosed cirrhosis can be reversed, particularly for those who require liver fibrosis treatment (2). Liver fibrosis is caused by excessive deposition of the extracellular matrix components and the disruption of hepatic sinusoidal endothelial cell functions. Hepatic sinusoidal endothelial cells are the gatekeepers of a stable liver environment under physiological conditions. The antifibrotic effects of the sinusoidal endothelial cells prevent Kupffer cell activation and the formation of hepatic stellate cells, enabling hepatic vascular resistance regulation and reducing venous pressure (3). The capillary vascularization of these hepatic sinusoidal endothelial cells in the endothelial basement membrane forms multiple pathological factors and occurs during the early stages of liver fibrosis, thereby altering liver function (4). Disorders of the intestinal flora can also lead to liver disease occurrence and development (5). Notably, the intestine and liver are inseparable from each other

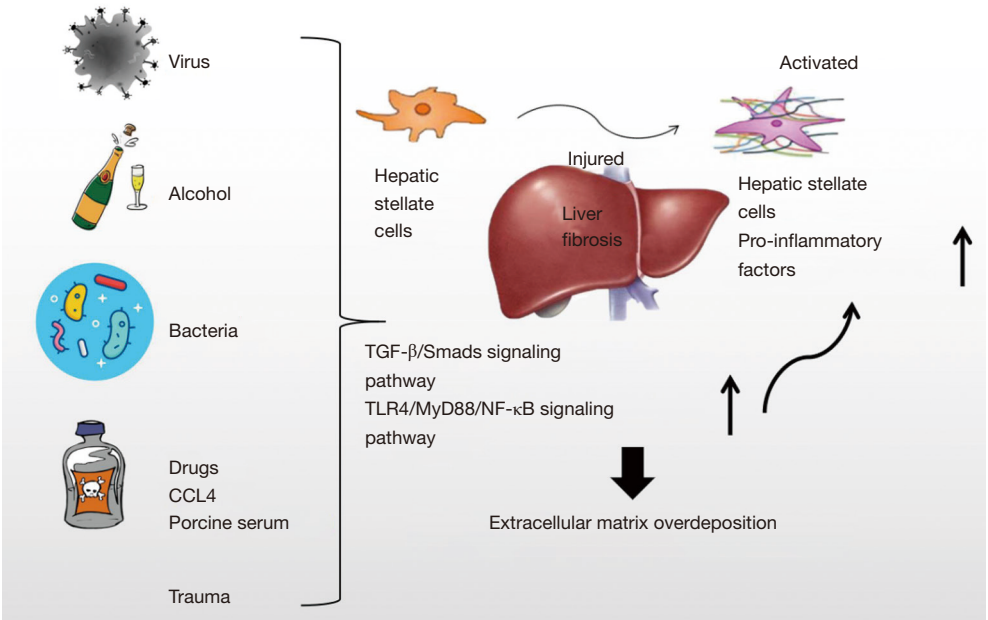

Figure 1 Pathogenesis of liver fibrosis. Induction by viruses, alcohol consumption, bacteria, trauma, and other factor leads to activation of hepatic stellate cells, deposition of the excessive extracellular matrix, and release of inflammatory factors, eventually leading to liver fibrosis.

anatomically, and the intestine supplies 75% of the blood to the hepatic portal vein (6).

Moreover, the intestinal tract and liver functionally interact, and thus homeostasis of the intestinal flora is affected by liver fibrosis (7).

One study showed that liver fibrosis could lead to disorders of the intestinal flora, and NADPH oxidase 4 and RhoA could accelerate the development of liver fibrosis by activating the hepatic stellate cells, leading to dysbacteriosis (8). Under the pathological changes induced by liver fibrosis, an increase in altered Schaedler flora of the intestine accelerates fibrosis progression; this effect can be blocked by inhibiting the altered Schaedler flora and promoting the growth of the specific pathogen-free flora instead (9).

This review discusses the liver fibrosis treatment with traditional Chinese medicine (TCM) and highlights the limitations of current research on preventing liver fibrosis by regulating the intestinal flora via TCM. We also explore new approaches for treating liver diseases by regulating the intestinal flora with TCM to provide a theoretical basis and clinical practice guide.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2129).

Methods

Information on the literature review in this paper is shown in *Table 1*.

TCM regulates intestinal flora

Astragalus

Astragalus polysaccharide an effective extract of *Astragalus membranaceus* (10) and functions as an inflammatory reaction inhibitor by reducing the expression of proinflammatory factors, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α (11). Astragalus polysaccharides can also increase *Lactobacillus* and *Bifidobacterium* production in the intestinal tract and reduce *Salmonella typhi* count, which reduces inflammatory reaction occurrences (12). As a result of this reduction, Astragalus polysaccharides can exert anti-inflammatory effects by regulating the numbers of bacteria (13). Additionally, *A. membranaceus* can alter the intestinal flora's structure and composition and enrich its diversity (14).

Scutellaria baicalensis

Scutellaria baicalensis is a traditional Chinese herbal medicine that has many beneficial effects; it is anti-inflammatory,

Table 1 Sources for this review

1. PubMed: from the establishment of the database to October 2020, we searched for "liver fibrosis", "intestinal microflora", "intestinal microorganisms" and "traditional Chinese medicine"
2. CNKI/Wanfang database: from the establishment of the database to October 2020, we searched for "liver fibrosis", "intestinal flora", and "traditional Chinese medicine"
3. Manual retrieval of references in literature

antibacterial, and has antioxidants properties (15). *S. baicalensis* can effectively promote healthy bacterial growth (*Bifidobacterium* and *Lactobacillus*) in the intestinal tract (16). Notably, *Lactobacillus rhamnosus*, *L. paracasei*, and *L. plantarum* can effectively reduce liver fat percentage and halt the occurrence and/or development of alcoholic liver disease (17). Additionally, *Bifidobacterium* and *L. Rhamnosus* can reduce liver inflammation and block the occurrence of nonalcoholic fatty liver disease (18).

Pueraria lobata

Pueraria lobata comes from the dried roots of leguminous plants and has been shown to have medicinal value. Pueraria polysaccharides are extracted from *P. Lobata* and can be consumed by intestinal microorganisms to benefit metabolism, ultimately affecting the body's physiological function (19,20). After it is fermented and metabolized in the intestinal flora, this TCM can effectively improve drug properties and reduce drug toxicity (21).

P. Lobata reduces the expression of inflammatory factors, such as TNF-α and IL-6. The expression levels of these inflammatory factors after Bifidobacterium fermentation when using *P. Lobata* were shown to be significantly lower than those in *Pueraria* without fermentation (22). Also, in the small intestine and colon of mice fed with a high-fat diet, puerarin, a functional extract of *P. Lobata*, was shown to block the expression of the proinflammatory factors IL-6 and monocyte chemoattractant protein-1 and increase the expression of the anti-inflammatory factor IL-10 (23). Other studies have shown that *Pueraria* can regulate intestinal flora disorder (24) and prevent liver injury by reducing endotoxin contents in the intestinal tract (25).

Monkshood (Fuzi)

The TCM aconite lateral root (Fuzi) has been widely used as an anti-inflammatory drug, analgesic, diuretic, and cardiotonic to treat colds, heart failure, edema, and other diseases (26). This medicine still retains a certain degree of toxicity and can cause toxicity-induced ventricular tachycardia; however, processed aconite's toxicity is significantly reduced (27). Furthermore, experimental studies have confirmed that the content of monoester and diterpenoid alkaloids in processed *Aconitum* is reduced after being metabolized by the intestinal flora, resulting in lower toxicity (28). It has further been shown capable of inhibiting the pathogenicity of harmful bacteria, such as *Staphylococcus aureus* ATCC-25923, and exhibits antitumor effects, including the inhibition of HL-60, SMCC-7721, and SW480 tumor cell growth (29). The metabolism of this TCM after intestinal flora metabolism can be directly analyzed using real-time ionization combined with multistage tandem mass spectrometry, enabling a quantitative analysis (30). Aconite also has inhibitory effects on *Escherichia coli* and *S.* aureus (31,32).

Largehead Atractylodes rhizome

In contrast to Western medicine, TCM places more importance on the whole body as a concept, considering patients as an organic and unified whole; thus, TCM has significant system biology advantages (33). The metabolism of intestinal microorganisms is a key factor affecting the therapeutic effects of TCMs *in vivo* (34).

The TCM, *Atractylodes macrocephala*, has the effect of invigorating the spleen, promoting dampness, and stopping diarrhea; therefore, it is used to treat diarrhea caused by spleen weakness. After treatment with *A. macrocephala*, the pathogenic bacteria, such as *Helicobacter pylori* and *Clostridium*, are significantly reduced. In contrast, beneficial bacteria, such as *Lactobacillus* and Akerman's bacteria, are significantly increased, indicating that *A. macrocephala* promotes probiotic reproduction and maintains the flora's intestinal homeostasis (35).

The therapeutic effects of *A. macrocephala in vivo* are related to the regulation of *E. coli*, *ShigellaI*, and *Alternaria*, and the intestinal flora's homeostasis (36). Also, *A.*

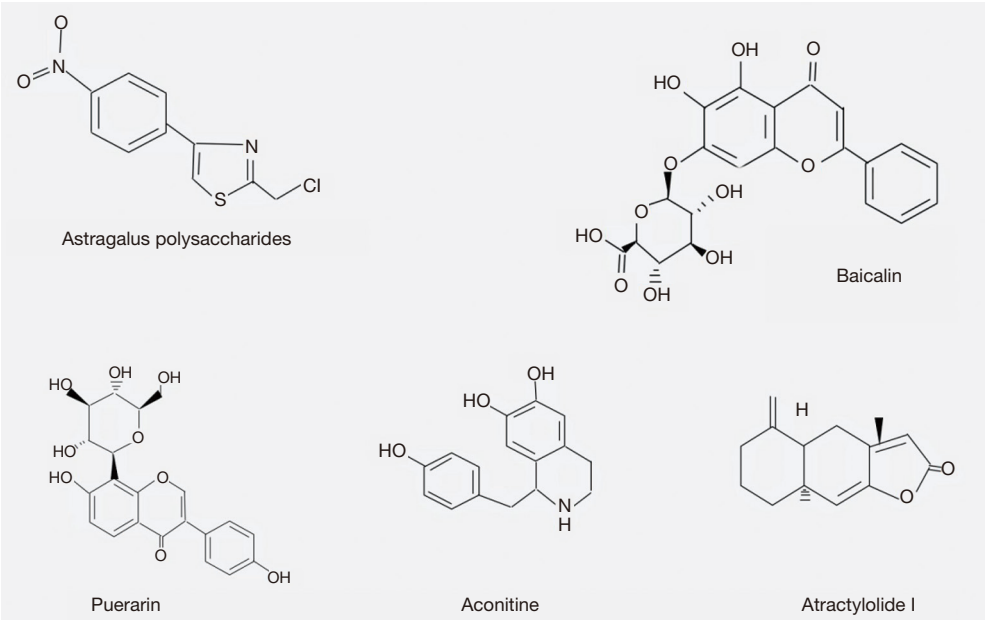

Figure 2 Organic chemical structure of the active fraction of TCM. TCM, traditional Chinese medicine.

macrocephala oil can reduce *H. pylori* biofilm formation, thereby inhibiting the proliferation of *H. pylori* and reducing the expression of the inflammatory factor IL-8 (37). *A. macrocephala* has also been shown to regulate intestinal microorganisms, stabilize the internal environment, and effectively alleviate chronic gastrointestinal diseases (38). *A. macrocephala* polysaccharides can also regulate disorders of the intestinal flora (39), and atractylodin can block *E. coli*, *Bacillus subtilis*, *Candida albicans*, and *S. aureus* activity (40,41).

Summary of the effects of TCMs on the intestinal flora

TCM and their effective compounds (*Figure 2*) have long been used to treat liver fibrosis, showing remarkable curative effects (42). According to existing literature, TCMs can regulate the intestinal flora's homeostasis to prevent the occurrence and development of liver fibrosis. For example, *Schisandra chinensis* can protect the liver and block hepatic fibrosis by regulating intestinal microorganisms and reversing the abnormal bile acid spectrum (43,44).

The liver-intestine axis

There are anatomical and physiological connections between the liver and intestines in the human body (*Figure 3*). The chemical signals that connect these organs make up the liver-intestine axis and include biological processes, such as metabolism and supporting of the internal environment's stability (45). Imbalances in the intestinal flora and hyperproliferation of these microorganisms can lead to the destruction of the intestinal barrier. Because the intestinal flora flows into the liver through the portal vein (46), disruptions of the intestinal flora lead to immune responses in the liver and aggravated liver fibrosis occurrence and development (47). However, homeostasis of the intestinal flora supports the stability of the immune system (48). Notably, the intestinal microflora of rats with hepatic fibrosis was found to be altered (49), and another study showed that dysfunction of the intestinal barrier and flow of intestinal microorganisms into the blood induces inflammatory reactions and eventually leads to liver injury and liver fibrosis (50). These changes also reduce the contents of bacterial metabolites, such as lysozyme and lysophosphatide, which can induce liver fibrosis and inhibit Kupffer cell activation (51).

The liver-intestine axis has a two-way regulation mechanism; that is, liver fibrosis can affect the intestinal microbiome, and the intestinal microbiome can affect liver fibrosis (52). In liver fibrosis caused by chronic hepatitis B, the abundance of the intestinal microbiota decreases, thereby affecting bile acid metabolism (53). Ursolic acid can increase the numbers of *Lactobacillus* and *Bifidobacterium* in the flora, improve bacterial malnutrition, support the

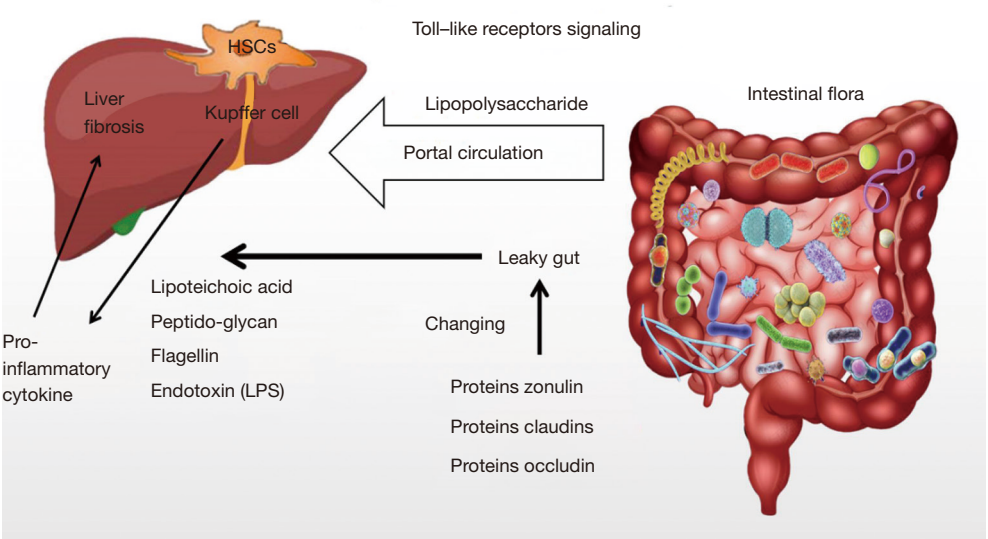

Figure 3 Pathogenic mechanisms of the intestinal flora through the liver-intestine axis. HSCs, hematopoietic stem cells.

stability of the bacterial flora, and inhibit liver fibrosis development (54,55). Moreover, supplementation with the probiotic *L. rhamnosus* was shown to reduce liver inflammation and fibrosis (56), and the composition of the intestinal flora has been associated with inflammation and liver fibrosis (57).

Summary of the liver-intestine axis

A summary of liver-intestine axis studies is shown in *Table 2*. Briefly, because of various stimulating factors, intestinal wall permeability increases, and the bacteria in the intestine enter the liver through portal vein circulation, leading to liver inflammation and subsequent liver fibrosis. The results of these experimental studies (58-67) have shown that TCM extracts can reduce the degree of liver fibrosis by regulating the proportion of intestinal microorganisms, such as *Firmicutes*. Additionally, liver fibrosis affects the homeostasis of intestinal flora (68).

Diagnosis of liver fibrosis in TCM

TCM refers primarily to traditional medicines created by Han people in China, and involves the study of human physiology, pathology, disease diagnosis, prevention, and treatment. Herbal medicine refers to the substances used in the prevention, treatment, and diagnosis of diseases, and the rehabilitation of patients under the guidance of TCM theory. In TCM, several drugs can be combined and decocted into a soup and administered as a prescription. The prescription is typically composed of four parts: "monarch", "minister", "adjuvant", and "envoy" medicine.

Liver fibrosis is interpreted as "chest pain" and "jaundice" in TCM theory. The pathogenesis is typically stagnation of liver qi, blood stasis, and deficiency of liver yin. The pathogenesis of liver fibrosis is most commonly related to dampness, heat, phlegm, toxin, depression, blood stasis, qi deficiency (which acts on the liver meridian), and blood stasis blocking the liver vein (69).

Treatment of liver fibrosis with TCM

TCM is commonly used for the treatment of liver fibrosis (*Figure 4*). Studies have confirmed that *Forsythia suspensa* can reduce liver fibrosis progression through the transforming growth factor TGF-β/Smad signaling pathway and the Toll-like receptor TLR 4/MyD88/nuclear factor NF-κB signaling pathway (70,71). Emodin, an effective rhubarb extract, can block liver fibrosis progression through the TGF-β/Smad signaling pathway (72). Gan Shen Fu Fang can inhibit T6 hepatic stellate cell activation and block hepatic fibrosis (73). TCM has multichannel and multitarget pharmacological effects in the treatment of liver fibrosis.

Additionally, the method of syndrome differentiation and treatment in TCM has multiple advantages (74,75). For example, the Dahuang Zhechong pill can inhibit the development of hepatic fibrosis by deactivating hepatic stellate cells (76). Further, *A. membranaceus* can inhibit

Table 2 Changes in the intestinal flora in patients with liver fibrosis

Study	Induction of liver fibrosis	Changes in the intestinal flora	Research type
Clinical experimental studies			
Schwimmer *et al*., 2019, (58)	High fat diet	*Firmicutes*↑, *Proteobacteria*↑	Cross-sectional
Lee *et al*., 2020, (59)	High fat diet	*Bacteroidetes*↓, *Lachnospiraceae*↓, *Prevotellaceae*↑, *Ruminococcaceae*↑	Cross-sectional
Animal experimental studies			
Naito *et al*., 2020, (60)	High fat diet	*Firmicutes*↑, *Bacteroidetes*↓	Cross-sectional
Zhang *et al*., 2021, (61)	High fat diet	*Bacteroidetes*↓, *Firmicutes*↓	RCT
Li *et al*., 2020, (62)	High fat diet	*Firmicutes*↑, *Bacteroidetes*↓, *Verrucomicrobia*↓, *Cyanobacteria*↓	RCT
Li *et al*., 2021, (63)	CCL4	*Firmicutes*↑, *Bacteroidetes*↓, *Proteobacteria*↑, *Actinobacteria*↑	RCT
Wan *et al*., 2020, (64)	CCL4	*Actinobacteria*↑, *Verrucomicrobia*↑, *Bacteroidetes*↓, *Firmicutes*↓	RCT
Yan *et al*., 2019, (65)	CCL4	*Bacteroidetes*↓, *Firmicutes*↓	RCT
Wan *et al*., 2019, (66)	CCL4	*Firmicutes*↓	RCT
Wu *et al*., 2020, (67)	CCL4	*Proteobacteria*↓, *Bacteroidetes*↓, *Firmicutes*↓, *Prevotella*↑	RCT

The included literature shows that liver fibrosis impacts the homeostasis of intestinal flora (68). RCT, randomized controlled trial; CCL4, carbon tetrachloride.

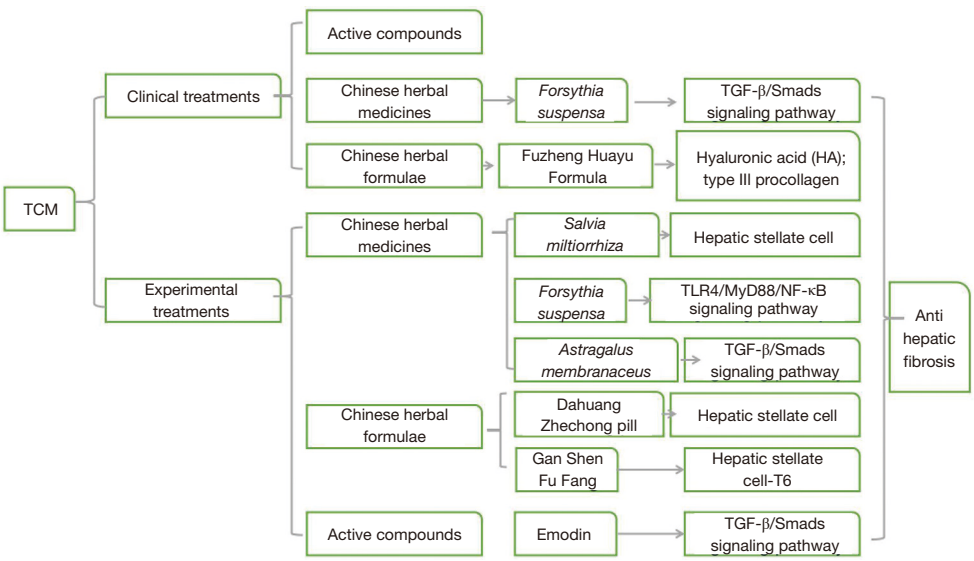

Figure 4 Effects of TCMs on liver fibrosis. The effects of TCM on liver fibrosis are described according to active compounds, Chinese herbal medicines, and Chinese herbal formulae prescription, respectively. TCM, traditional Chinese medicine.

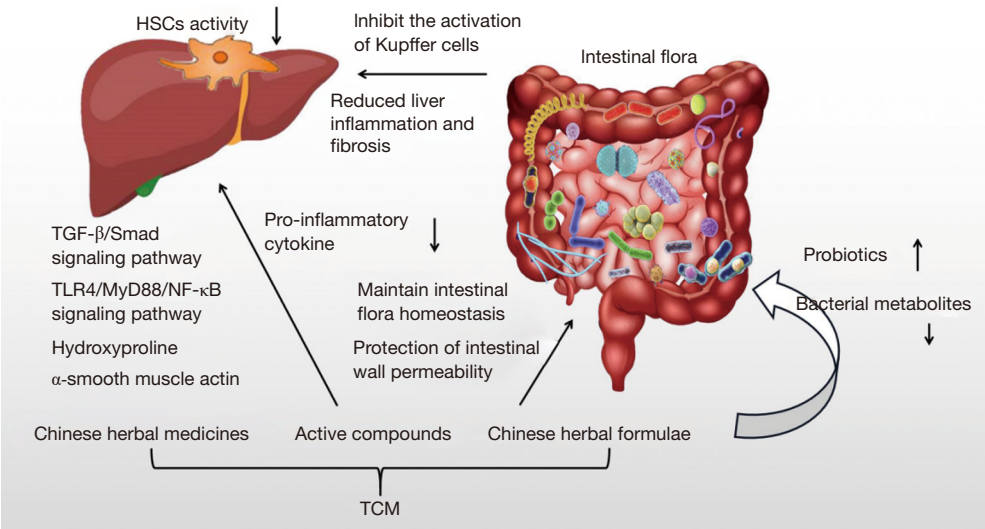

Figure 5 Potential mechanisms through which TCMs mediate the intestinal flora to protect against liver fibrosis. TCM, traditional Chinese medicine; HSCs, hematopoietic stem cells.

hepatic fibrosis by blocking the TGF-β/Smad signaling pathway (77). Also, *Sophora flavescens*, *Ligustrum lucidum*, licorice, *Lonicera japonica* Thunb, and *Salvia miltiorrhiza* Bge are TCMs used to treat liver fibrosis (78-81). Experimental studies have shown that S. *miltiorrhiza* can inhibit hepatic stellate cell activity by enhancing natural killer cell functions to block liver fibrosis (82). Moreover, TCMs can protect the liver and reduce liver fibrosis by improving inflammation and reducing steatosis (83).

Summary of studies of the effects of TCM on liver fibrosis

Researchers have evaluated the effects of active compounds, Chinese herbal medicines, and Chinese herbal formulae on liver fibrosis through animal experiments and clinical studies. TCM has been shown to reduce the secretion of inflammatory factors, regulate the TGF-β/Smad signaling pathway and TLR4/MyD88/NF-κB signaling pathway, inhibit the activation of hepatic stellate cells, and improve liver function, thereby blocking fibrosis and protecting the liver.

Intestinal flora-related mechanisms of TCM against liver fibrosis

TCM can effectively prevent liver fibrosis occurrence and development by regulating intestinal flora, inhibiting the intestinal barrier dysfunction, and reducing inflammatory reactions (84,85). Moreover, the hepatic intestinal axis has been shown to have bidirectional regulatory effects, and TCM has been proven to protect the liver through the liver-intestine axis (86). Notably, changes in intestinal flora can induce the development of liver fibrosis and liver injury. After liver fibrosis, intestinal permeability and the fecal flora change significantly (87). Additionally, increased intestinal bacterial translocation, as a marker of chronic liver disease, can lead to hepatitis and fibrosis (88).

Berberine alters the intestinal flora of *Bacteroides*, xenobiotics, and *Verrucosa* and reduces inflammatory factor expression (89). *Coptis chinensis* can protect against rat liver toxicity induced by cinnabar. These mechanisms may be related to endogenous metabolism, including energy metabolism, amino acid metabolism, and intestinal flora metabolism in rats (90).

Summary of the effects of TCM on liver fibrosis through the liver-intestine axis

Studies of TCMs have evaluated these medicines' ability to protect against liver fibrosis by regulating intestinal microorganisms (*Figure 5*). These findings have supplied insights into novel treatment strategies and approaches for liver fibrosis. For example, the Simiao decoction can reduce inflammatory factor secretion and regulate intestinal flora homeostasis (91). Additionally, a TCM formula was found

to reverse increases in scleroderma and Proteobacteria caused by a high-fat diet, resulting in a decreased scleroderma to *Bacteroides* ratio and an increased abundance of *Bacteroides* (92). Therefore, TCMs can effectively regulate the homeostasis of the intestinal flora, protect the intestinal wall's permeability, increase the contents of probiotics, mediate inflammatory reactions and liver lipid metabolism, block liver fibrosis, and protect the liver.

Conclusions

In this review, we presented findings of earlier studies related to the use of TCMs to regulate intestinal microorganisms and protect against liver fibrosis. However, existing research is not comprehensive, and further studies are needed. Moreover, in future works, it will be necessary to combine the holistic view of the TCM theory and methods of syndrome differentiation and treatment to explore the effects of TCMs on liver fibrosis. Additionally, use nano-imaging technology may be need to track the path of TCMs in the intestines.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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