APM ANNALS OF PALLIATIVE MEDICINE
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Peer Review File

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Reviewer Comments

1. What are the difference of Traditional Chinese medicine (TCM), Chinese herbal medicine and Chinese herbal formula? They should be differentialy used. There were lack of searched keyword such as Chinese herbal medicine, Chinese herbal formula and Chinese herb etc. in this article.
Reply 1: we have modified our text as advised: TCM generally refers to traditional medicines created by the working people of Han nationality in China and 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 in rehabilitation of patients under the guidance of the TCM theory. In TCM, several drugs can be combined and decocted into a soup, which is then administered as a prescription. The prescription is generally composed of four parts, i.e., monarch medicine, minister medicine, adjuvant, and envoy medicine. (see Page 13-14, line 213-220)
Changes in the text: Page 13-14, line 213-220.

2. There are the diagnosis and treatment in TCM, the review should include the two aspects.
Reply 2: we have modified our text as advised: Diagnosis of liver fibrosis in TCM
TCM generally refers to traditional medicines created by the working people of Han nationality in China and 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 in rehabilitation of patients under the guidance of the TCM theory. In TCM, several drugs can be combined and decocted into a soup, which is then administered as a prescription. The prescription is generally composed of four parts, i.e., monarch medicine, minister medicine, 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). (see Page 13-14, line 212-225)
Changes in the text: Page 13-14, line 212-225.

3. The effects of TCM on the liver fibrosis could be divided into clinical and experimental treatments, using tree of active compounds, Chinese herbal medicines and Chinese herbal formulae, respectively.

Reply 3: we have modified our text as advised:

Clinical experimental study

Inducement of liver fibrosis	Changes of intestinal flora	Research type	Study
High fat diet	Firmicutes↑, Proteobacteria↑	Cross-sectional	Jeffrey B. Schwimmer et al., 2019 (58)
High fat diet	Bacteroidetes↓, Lachnospiraceae↓, Prevotellaceae↑, Ruminococcaceae ↑	Cross-sectional	Giljae Lee et al., 2020 (59)

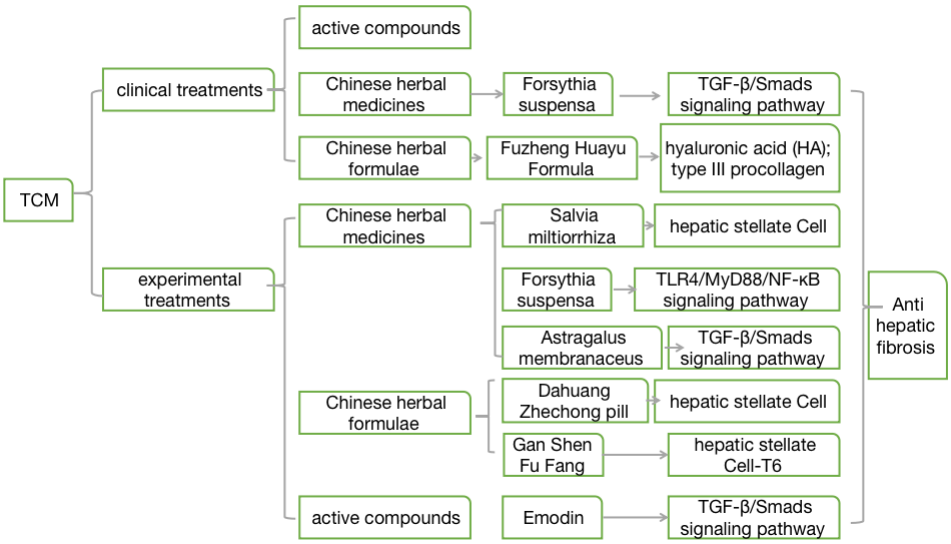
Animal experiment research

Inducement of liver fibrosis	Changes of intestinal flora	Research type	Study
High fat diet	Firmicutes↑，Bacteroidetes↓	Cross-sectional	Yuji Naito et al., 2020 (60)
High fat diet	Bacteroidetes↓,Firmicutes↓	RCT	Xiang Zhang et al., 2019 (61)
High fat diet	Firmicutes↑，Bacteroidetes↓, Verrucomicrobia↓, Cyanobacteria↓	RCT	Ping Li et al., 2020 (62)
CCL4	Firmicutes↑，Bacteroidetes↓,Proteobacteria↑, Actinobacteria↑	RCT	Ming-mei Li et al.，2020 (63)
CCL4	Actinobacteria↑,Verrucomicrobia↑, Bacteroidetes↓, Firmicutes↓	RCT	Sizhe Wan et al., 2020 (64)
CCL4	Bacteroidetes↓, Firmicutes↓	RCT	Zhiqiang Yan et al., 2019 (65)
CCL4	Firmicutes↓	RCT	Si-Zhe Wan et al., 2019 (66)

CCL4	**Proteobacteria↓, Bacteroidetes↓, Firmicutes↓, Prevotella↑**	**RCT**	**Pengfei Wu et al., 2020 (67)**

(see Page 11-13, line 208-209)

Figure 4 Effects of TCMs on liver fibrosis



The effects of TCM on liver fibrosis were described by active compounds, Chinese herbal medicines and Chinese herbal formulae prescription respectively.

(see Page 15, line 245-249)

Changes in the text: Page 11-13, line 208-209; Page 15, line 245-249

4. The structure of the article could be reorganized with different section and independent discussion and conclusion, each section should set up subheadings.

Reply 4: we have modified our text as advised:

Summary of the effects of TCMs on the intestinal flora

TCMs and their effective compounds (Figure 2) have long been used for the treatment of liver fibrosis, showing remarkable curative effects (42). According to existing literature, TCMs can regulate the homeostasis of the intestinal flora 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). (see Page9, line 165-171).

Summary of liver and intestine axis

A summary of studies of the liver/gut axis 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 experimental studies (58–67) have shown that TCM extracts can reduce the degree of liver fibrosis by

regulating the proportions of intestinal microorganisms, such as Firmicutes. Additionally, liver fibrosis affects the homeostasis of intestinal flora (68).(see Page 11, line 200-207).

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. TCMs have been shown to reduce the secretion of inflammatory factors, regulate the TGF-β/Smad signalling pathway and TLR4/MyD88/NF-κB signalling pathway, inhibit the activation of hepatic stellate cells, and improve liver function, thereby blocking fibrosis and protecting the liver.(see Page 15-16, line 250-256).

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

Studies of TCMs have evaluated the ability of these medicines to protect against liver fibrosis by regulating intestinal microorganisms (Figure 5). These findings have provided insights into novel treatment strategies and approaches for liver fibrosis. For example, the Simiao decoction can reduce the secretion of inflammatory factors and regulate the homeostasis of the intestinal flora (91). Additionally, a TCM formula was found to reverse increases in Scleroderma and Proteobacteria caused by a high-fat diet, resulted 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 permeability of the intestinal wall, increase the contents of probiotics, mediate inflammatory reactions and liver lipid metabolism, block liver fibrosis, and protect the liver. (see Page 16-17, line 272-283).

Changes in the text: see Page 9, line 165-171; see Page 11, line 200-207; see Page 15-16, line 250-256; Page 16-17, line 272-283.

5. The potential intestinal flora-related mechanisms of TCM against liver fibrosis should be further summarized and graphed.

Reply 5: we have modified our text as advised: Intestinal flora-related mechanisms of TCM against liver fibrosis

Changes in the text: TCM can effectively prevent the occurrence and development of liver fibrosis through regulation of the intestinal flora, inhibition of intestinal barrier dysfunction, and reduction of inflammatory reactions (84,85). Moreover, the hepatic intestinal axis has been shown to have bidirectional regulatory effects, and TCM has been demonstrated to protect the liver through the liver/gut axis (86). Notably, changes in intestinal flora can induce the development of liver fibrosis and liver injury. After liver fibrosis, intestinal permeability and the faecal 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 the expression of inflammatory factors (89). Coptis chinensis can protect against rat liver toxicity induced by cinnabar. This mechanism may be related to endogenous metabolism, including energy metabolism, amino acid metabolism, and intestinal flora metabolism, in rats (90). (see Page 16, line 257-271).

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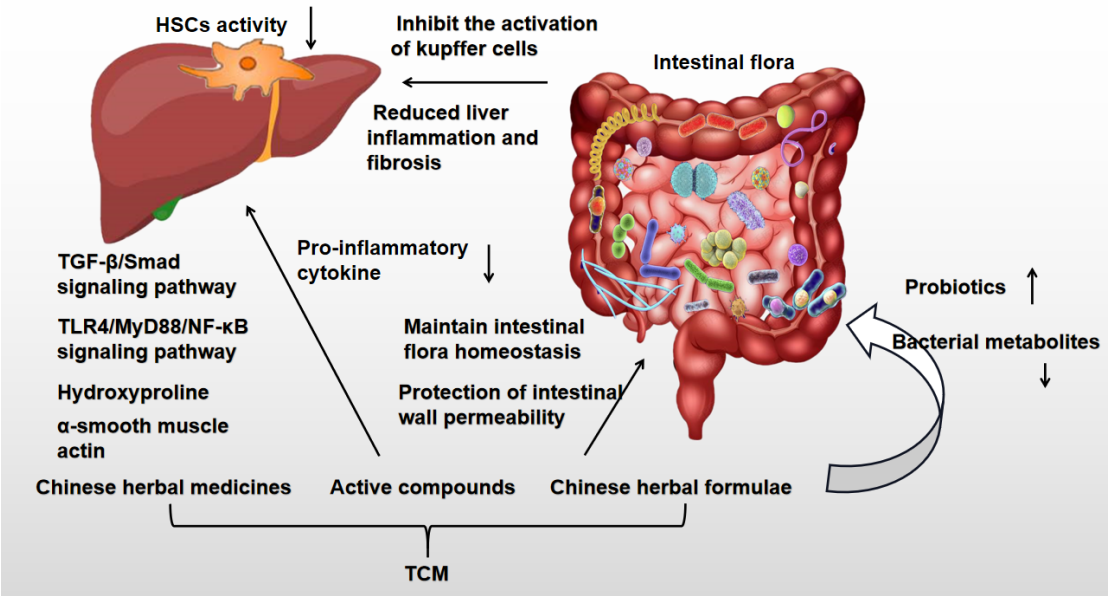
Figure 5 Potential mechanisms through which TCMs mediate the intestinal flora to protect against liver fibrosis.



(see Page 17, line 284-286).