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• Review

Traditional Chinese medicine for treatment of liver diseases: progress, challenges and opportunities

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ABSTRACT: Traditional Chinese medicine (TCM) is commonly used in treating liver diseases worldwide, especially in China. The advantages of using TCM for treatment of liver diseases include: protecting hepatocytes, inhibiting hepatic inflammation and antifibrosis in the liver. In this article, we introduce TCM herbal preparations from the Chinese materia medica (such as Fuzheng Huayu) that are typically used for the treatment of liver diseases. Literature surrounding the mechanisms of TCM therapy for treatment of liver diseases is presented and discussed. We propose that side effects of herbal compounds are often under-appreciated, and that more care should be taken in the prescription of potentially hepatotoxic medicines. Further, to deepen the understanding of TCM mechanisms, new techniques and methodologies must be developed. Future studies will lead to the enhancement of clinical outcomes of TCM. As complementary and alternative therapies, TCMs will play an expanding role in the future of liver disease treatment.

KEYWORDS: medicine, Chinese traditional; drugs, Chinese herbal; liver diseases (TCM); liver cirrhosis; hepatoprotective drugs; hepatotoxicity; reviews

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1 Introduction

In China, traditional Chinese medicine (TCM), especially traditional Chinese patent medicine, has been, and continues to be widely used to treat various diseases. Even during the severe acute respiratory syndrome (SARS) outbreak in 2003, TCM, combined with Western medicines were used to control and eventually halt the spread of the disease. Compared with Western medicine alone, patients receiving treatment with Western medicine and TCM had reduced hospital stays, pneumonia duration and mortality. Early

TCM treatment can also decrease glucocorticoid dosage needed in the treatment of SARS^[1]. Before Western medicine was introduced into China, the Chinese health care system mainly depended on TCM. Although TCM does not treat specific conditions, it treats patterns of illness such as those associated with infectious diseases^[2–4], cardiovascular and cerebrovascular diseases^[5–11], respiratory diseases^[12–14], digestive diseases^[14–16], urinary diseases^[17–19], reproductive diseases^[20] and blood system diseases^[21], as well as fractures^[22], trauma^[23], ear, nose and throat diseases^[24,25], skin diseases^[26] and mental disorders^[27]. TCM can improve the clinical symptoms, reverse some pathological changes and restore

the body's normal physiological function. Since Western medicine was introduced into China in the 16th century CE, most diseases listed above are treated mainly with Western medicinal interventions. Gradually, TCM has become an alternative medicine rather than mainstream medicine. Even so, TCM therapy still has its advantages in some medical fields where Western medicine has not been as effective, such as in liver diseases. This review will introduce TCM in the treatment of liver diseases.

2 TCM therapy has advantages in liver diseases

Liver diseases are mainly classified into viral hepatitis, nonalcoholic fatty liver, alcoholic liver disease, autoimmune liver disease, schistosomiasis liver disease, drug-induced liver injury, hereditary liver disease, liver cirrhosis due to various causes and diverse liver tumors. TCM is widely applied in the treatment of liver diseases in China by both Chinese medicine doctors and Western medicine doctors because its ability to protect hepatocytes, inhibit hepatic inflammation and reduce fibrosis in the liver. In recent years, the application of TCM in liver cancer treatment has been increasingly widespread^[28,29]. It has been confirmed that TCM can not only reduce the toxic side effects of chemotherapy or radiotherapy, but also inhibit tumor growth and increase survival of patients with tumors^[30]. Although TCM has many uses in treating liver diseases, it cannot replace other treatment methods such as antiviral drugs, hormones, schistosomicide, surgical operation and transplantation.

TCM can be applied to treat diseases in one of the two ways: treatment based on *disease differentiation* or *syndrome differentiation*^[31]. For the disease differentiation approach, Western medicine methods are typically employed to diagnose specific liver diseases. Subsequently the appropriate TCM formula or patent drug is selected to treat the disease according to TCM's characteristics and advantages. The evaluation of the curative effect is based on the recovery of liver function or improvement in pathological changes. In the *syndrome differentiation* approach, TCM diagnosis of a patient's symptoms and signs is used to determine to which syndromes the patient belongs. The appropriate TCM formula or patent drug is then chosen to treat that TCM syndrome. The evaluation of the curative effect depends on the relief or elimination of the symptoms and signs. It is believed that the combination of two kinds of therapies can obtain greater curative effects for liver diseases^[32].

3 Chinese materia medica is frequently used to treat liver diseases

In acute stage of liver diseases, liver inflammation is prominent. Materials listed in the Chinese materia medica,

especially those for heat-clearing and detoxifying, are often applied to protect the liver, inhibit inflammation, decrease activity of serum transaminase and reduce serum bilirubin^[32]. Meanwhile according to the symptoms and signs of each patient, a matching therapy, such as adjusting yin and yang, invigorating qi and blood, soothing the liver, regulating qi, clearing heat and removing dampness, is also applied.

In the chronic stage of liver diseases, the symptoms of the disease are more complicated. Treating the source of the disease (*i.e.*, the virus) is one important and necessary approach. Western medicine does well in inhibiting the viruses that cause hepatitis B (HBV) and hepatitis C (HCV). TCM has little effect in inhibiting the virus, but works well to protect liver function, inhibit inflammation, decrease activity of serum transaminase, reduce serum bilirubin, lower lipid levels^[33], promote diuresis^[34] and relax the bowels^[35]. Depending on the stage of liver disease progression, or different syndrome classifications, TCM can be used to adjust yin and yang, invigorate qi and blood, soothe liver, regulate qi, clear heat and remove dampness^[36-38]. Zhang *et al*^[39] summarized and provided a critical meta-analysis of randomized controlled trials (RCTs) of TCM formulations for the treatment of chronic hepatitis B (CHB) that were reported in China from 1998 to 2008. The results showed that (i) TCMs (TCM formulations alone or in combination with interferon (IFN) or lamivudine (LAM)) had a greater beneficial effect than IFN ($P=0.0003$) and slightly better effect than LAM ($P=0.01$) on normalization of serum alanine aminotransferase; (ii) TCMs had a similar beneficial effect on antiviral activity when used in conjunction with IFN or LAM for CHB, which was evidenced by the reduction of serum HBeAg and HBV DNA; (iii) Treatment with TCMs in conjunction with IFN or LAM resulted in improved liver function.

When the liver tissue is damaged, its repair is accompanied by the formation of an extracellular matrix, also known as fibrosis. Fibrosis is the common pathological process of many liver diseases, and is also reversible. Antifibrotic effects are an important component in the treatment of various chronic liver diseases^[40]. One famous hepatologist, Professor Hans Popper, once said, "Anyone who can stop or delay liver fibrosis would be able to cure most chronic liver diseases"^[41]. The focus of Western medicine scientific and medical research has been on discovering targets for antifibrotic therapy, and developing customized multi-drug regimens^[42].

According to the TCM theory, diseases of liver Zang will transmit to the spleen Zang, thus in the course of treatment, the spleen Zang should be strengthened before it is impaired. If the liver disease has been long-standing, kidney yin should be evaluated during the treatment because the liver Zang and kidney Zang are derived from the same source. In clinical practice, symptoms and signs of spleen-qi deficiency

are frequently seen in patients with liver diseases. They always complain of fatigue, pain or weakness in the legs, abdominal fullness, right upper quadrant discomfort or pain, loose stool, pale tongue or swollen tongue (teeth-marked tongue) with whitish fur and weak pulse. Patients with chronic liver disease additionally present symptoms and signs of kidney-yin deficiency, such as dry mouth, internal-heat, red (or red and dry) and uncoated tongue, and weak pulse.

According to the theory of syndrome differentiation therapy, methods of invigorating spleen-qi and nourishing

kidney-yin should be used to treat liver diseases. In TCM, the pathogenesis of liver diseases does not necessarily relate to the liver Zang, it can also be related to the spleen and kidney. Table 1 shows TCM functions matched with herbs and dosages commonly used in the treatment of liver diseases. Herbs with different functions are selected according to syndrome differentiation. Dosages within the recommended range are determined by the severity of the symptoms and signs.

Several patent drugs (Chinese herbal formulas) for treatment

Table 1 Different functions of herbs commonly used for treating liver diseases and their dosage

Function	Herb	Latin name	Dosage (g)
Heat-clearing and detoxifying	Tianjihuang	<i>Hyperici Japonici</i>	15–30
	Yinchen	<i>Artemisia capillaris</i>	15–30
	Baihuasheshecao	<i>Hedyotis diffusa</i>	15–30
Reducing bilirubin	Chishao	<i>Paeonia lactiflora</i>	30
	Jinqiancao	<i>Lysimachia christinae</i>	15
	Aidicha	<i>Ardisia japonica</i>	15
	Yumixu	<i>Zea mays</i>	15
	Chaihu	<i>Bupleurum chenense</i>	10
Soothing liver and regulating qi	Yujin	<i>Curcuma wenyujin</i>	10
	Xiangfu	<i>Cyperus rotundus</i>	10
	Laiфуzi	<i>Raphanus sativus</i>	15
	Shengshanzha	<i>Crataegus pinnatifida</i>	15–30
Reducing lipid	Zexie	<i>Alisma orientale</i>	15
	Juemingzi	<i>Cassia obtusifolia</i>	15
	Pianjianghuang	<i>Curcuma wenyujin</i>	15
	Huzhang	<i>Polygonum cuspidatum</i>	15
	Heye	<i>Nelumbo nucifera Gaertn</i>	10–15
	Fuling	<i>Poria cocos</i>	15–30
	Zhuling	<i>Polyporus umbellatus</i>	15–30
Promoting diuresis	Zexie	<i>Alisma orientale</i>	15
	Cheqiangzi	<i>Plantago asiatica</i>	15
	Hulu	<i>Lagenaria siceraria</i>	15–30
	Banbianlian	<i>Lobelia chinensis Lour</i>	15
	Aidicha	<i>Ardisia japonica</i>	15
	Qumai	<i>Dianthus superbis L.</i>	15
	Dangshen	<i>Codonopsis pilosula</i>	10
	Baizhu	<i>Atractylodes macrocephala Koidz.</i>	10
Invigorating spleen-qi (Sijunzi Tang)	Huangqi	<i>Astragalus membranaceus</i>	20
	Fuling	<i>Poria cocos</i>	10
	Yujin	<i>Curcuma kwangsiensis</i>	10
	Gancao	<i>Glycyrrhiza uralensis Fisch.</i>	10
	Shashen	<i>Adenophora stricta Mip.</i>	15
	Dihuang	<i>Rehmannia glutinosa</i>	15
	Maidong	<i>Ophiopogon japonicus</i>	15
	Gouqizi	<i>Lycium barbarum L.</i>	15
	Danggui	<i>Angelica sinensis</i>	10
	Shihu	<i>Dendrobium nobile Lindl</i>	10–15
Nourishing kidney-yin (Yiguanjian Recipe)	Chuanlianzi	<i>Melia toosendan Sieb</i>	10

of fibrosis have obtained certificates from the State Food and Drug Administration in China (e.g., Fuzheng Huayu Capsule/Tablet (FZHYC), compound Biejia Ruangan Troche, Anluo Huaxian Pill and Qianggan Capsule). Among them, FZHYC has been studied intensively. Fuzheng means supporting the healthy energy and Huayu means dispersing blood stasis. FZHYC is composed of Danshen (*Salvia miltiorrhiza*), Dongchong Xiacao (*Cordyceps sinensis* Sacc), Taoren (*Prunus persica*), Jiaogulan (*Gynostemmis pentaphylli*), Songhuafen (*Pinus armandii* Franch) and Wuweizi (*Schisandra chinensis*). It has been used in clinics for more than 10 years, with no reports of serious side effects.

Clinical observations showed that FZHYC can effectively improve liver function and decrease the expression of fibrosis biomarkers such as serum hyaluronic acid, collagen type IV, procollagen type III and laminin, in chronic liver disease patients with fibrosis or cirrhosis^[43,44]. FZHYC can also regulate immune function^[45], balance amino acid^[46] and endocrine^[47] metabolism and reduce portal hypertension^[48].

The results of several multicenter RCTs have confirmed that TCM can reverse liver fibrosis^[49-51]. FZHYC was used to treat liver fibrosis in patients with CHB for six months. Fifty patients in the trial group were treated with FZHYC. A control group of 43 patients was treated with Heluo Shugan Capsule, another Chinese patent medicine. All patients received liver biopsies pre- and post-treatment. Pathology results showed that in the treatment group, the stage of fibrosis was decreased by one or more in 52% of the patients; the remaining 48% of the patients in the trial group had no changes. However, in the control group only 23.3% patients had a decrease in fibrosis stage, 55.8% patients had no change and 20.9% of the patients had an increase in fibrosis stage^[49]. In another study, FZHYC reversed the fibrosis at a rate of 57.9% early cirrhotic patients with CHB^[52].

To prevent esophageal variceal bleeding in cirrhotic patients, a multicenter randomized and placebo-controlled trial was carried out. The probability of survival in the FZHYC group was higher than that in the Propranolol group (90.22% vs 70.92%, $P=0.044$ 9). Compared to the Propranolol group the probability of esophageal variceal bleeding in the FZHYC group was significantly reduced (43.0% vs 23.9%, $P=0.013$ 1). When the two treatments were taken together there was an even lower probability of bleeding which was also significantly lower than the Propranolol alone (12.4% vs 43.0% $P=0.008$ 6). In patients with small esophageal varices, treatment with FZHYC reduced the size of the varices. Its effects may be related to the prevention of hepatic fibrosis, amelioration of liver function, and the decrease of ET-1 concentration in the blood plasma^[53].

A meta-analysis was conducted to evaluate the efficacy and safety of FZHYC combined with nucleoside antiviral

drugs in treating fibrotic patients with CHB. The analysis included seventeen RCTs, with a total of 1 320 patients with CHB, of which 636 were in control groups and 684 in trial groups. The meta-analysis showed that there was no significant improvement in serum HBeAg level and HBV-DNA copies. However, there was a statistically significant improvement in liver fibrosis and liver function after treatment for 24 or 48 weeks^[54].

4 Mechanisms of TCM in treatment of liver diseases are studied extensively

For the past six decades, many researchers have carried out extensive research to explore the mechanism of TCM in the treatment of liver diseases. It was found that TCM can improve hepatic microcirculation, scavenge oxygen free radicals, resist lipid peroxidation, promote bilirubin metabolism, accelerate synthesis of liver glycogen and protein, and increase the content of liver microsomal cytochrome P-450^[55]. These effects lead to a decrease in hepatocyte necrosis, inhibition of apoptosis and promotion of the hepatocyte regeneration^[56].

We searched the literature for studies exploring the mechanism of FZHYC's antifibrotic activity. It has been shown that FZHYC can protect hepatocytes, resist lipid peroxidation and inhibit some cytokines^[57,58]. FZHYC can also inhibit the activation and proliferation of hepatic stellate cells (HSCs), which play an important role in hepatic fibrogenesis and fibrosis^[58]. FZHYC can also promote apoptosis of activated HSCs, inhibit synthesis and secretion of collagen, inhibit angiogenesis and promote degradation of collagen^[59]. Studies showed that FZHYC achieved its antifibrotic activity through multiple signal pathways and targets^[57,58,60-63], such as transforming growth factor β -1 (TGF- β 1), SMADs, insulin-like growth factors-1 (IGF-1), phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38 MAPK), RhoA/Rho-associated coiled-coil forming protein kinase (ROCK) and renin-angiotensin system (RAS) signaling pathways^[64,65].

The elevation of portal vein pressure is a common symptom of liver cirrhosis. The portal vein pressure is positively correlated with endothelin-1 (ET-1) concentration in the liver tissue during the process of liver cirrhosis^[66]. FZHYC can dramatically decrease cirrhosis-induced elevation of portal vein pressure by reducing ET-1 levels in the liver tissue^[67].

Due to multiple ingredients in the Chinese formula, the compound could not be used to incubate cells directly *in vitro*. Only individual components or ingredients of herbal medicine are suitable for *in-vitro* research. To explore the underlying mechanisms of FZHYC's antifibrosis activity, we looked in the literature for research on salvianolic-acid B (SA-

B), a component of Danshen that is the main constituent herb of FZHYC. Studies show that the effects of SA-B are just like FZHYC in the treatment of hepatic fibrosis and cirrhosis^[64,65,68]. SA-B dramatically decreased the fibrosis level of rats with fibrotic liver, and also markedly decrease cirrhosis-induced elevated portal vein pressure and liver ET-1 levels^[16]. SA-B achieves its antihepatic fibrosis effect by inhibiting the ERK and the p38 MAPK pathways of TGF- β 1 in HSCs. It inhibits the ERK pathway by inhibiting phosphorylation of MEK. SA-B inhibits the p38 MAPK pathway by blocking phosphorylation of MKK3/6 and inhibiting expression of myocyte enhancer factor 2 (MEF2, a transcription factor), in HSCs with or without TGF- β 1 stimulation^[69]. Further, SA-B inhibits the cross-talk of the SAMD signaling pathway to the ERK signaling pathway^[63]. SA-B also significantly reduces ET-1-activated HSC contractility by inhibiting RhoA/ROCK II activation and the downstream MYPT1 phosphorylation at Thr696^[64].

5 Attention should be paid to hepatotoxicity of some Chinese herbal medicines

Although some positive effects of TCM in liver diseases are reported, we should also note the possibility of liver damage induced by some herbs during treatment. The perspective that herbs, as natural medicine, have no side effects is outdated and wrong. Some Chinese herbal medicines, which were used to treat liver diseases, have been reported to have hepatotoxicity in high doses or even in standard doses, such as Heshouwu (*Polygonum multiflorum* Thunb), Huangyaozi (*Dioscorea bulbifera*), Cangzhu (*Atractylodes lancea*), Bohe (*Mentha haplocalyx*), Wubeizi (*Rhus chinensis* Mill), Shiliupi (*Punica granatum* L.), Wangjiangnanzi (*Coix* seed or *Semen Coicis*), Tianhuafen (*Trichosanthes kirilowii* Maxim), Fanxieye (*Gassia angustifolia* Vahl), Dahuang (*Rheum palmatum* L.), Chaihu (*Bupleurum chinense* DC.) and Chuanlianzi (*Fructus Mediae toosendan*)^[70].

This potential toxicity should serve as a reminder that clinical practitioners should administer Chinese medicine with as much caution as Western pharmaceutical drugs. It is very important to take precautions against drug-induced liver injury when selecting herbs and their doses. Generally speaking, applying herbs in accordance with the pharmacopeia is quite safe. For example, an aqueous solution of Zhizi (*Gardenia jasminoides*) extract, which has been reported to have hepatotoxicity, has no significant side effects on mice liver at medium dose (equivalent to 18 g dose for adults) and low dose (equivalent to 9 g dose for adults). The medium and low doses of Zhizi extract did not obviously affect structure of the liver tissue or damage hepatocytes. We suggest that Zhizi is not suitable for chronic use at a high dose, but short-term use at a modest dose (9 g per

day) is still safe^[71]. Further, by appropriate preparation of herbal products, such as Heshouwu, the hepatotoxicity can be reduced^[72]. It is also important to note that in Chinese medicine, herbs with similar names cannot be used interchangeably. For instance, using Tusanqi (*Gynura segetum*), which has severe hepatotoxicity, as a substitute for Shensanqi (*Panax notoginseng*) is dangerous, and they come from very different plants.

6 New techniques and methodologies are needed for studying TCM

Although TCM therapy is effective in the treatment of liver diseases, more research is required to understand the underlying mechanisms of action.

At present, the pharmacological studies of Chinese medicinal formulae are carried out extensively *in vivo*, however, the induced animal models cannot be relied on to fully mimic clinical pathogenesis of human patients. Studies that examine the mechanisms behind TCM can only be conducted *in vitro*, are ill suited to the complex formulations of herbs used in Chinese medicinal remedies and are restricted by existing research techniques and methodology^[73]. Current research technology is not designed to evaluate responses from multi-dimensional variables, like the herbal formulations used in TCM. This may be one of the reasons that the curative effects of TCM have been slow to receive approval among Western medicinal practitioners. New research techniques and methodologies should be developed to evaluate the curative effects of TCM and to elucidate its mechanisms^[74,75].

We believe that as techniques and methodologies evolve to address the complex nature of TCM herbal formulations, a more mechanistic understanding of the use of TCM in treating liver diseases will emerge. These studies will thus lead to the improvement of clinical results and refinement of the contemporary practice of TCM. As a complementary and alternative therapy for the treatment of liver diseases, TCM is a powerful but underused tool in the present, and has great potential for future use.

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8 Conflicts of interests

The authors have no conflicts of interest to declare.

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