Xiao Chai Hu Tang for Liver Diseases: A Literature Review

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Abstract

The objective of this study is to summarize the pharmacological effects and the mechanisms of action of Xiao Chai Hu Tang (XCHT, Minor Bupleurum Decoction) on liver diseases, so as to give relevant researchers a valuable insight and benefit patients with hepatopathy. PubMed was used to search for and collect scientific publications related to XCHT and liver diseases from 1986 to 2016. The available scientific results or evidence were read, classified, and analyzed. XCHT showed clinical efficacy in patients with hepatic diseases including hepatitis, hepatic fibrosis, and hepatoma. The mechanisms involved the production of cytokines, the regulation of immune function, the suppression of lipid peroxidation, etc., XCHT might work on the metabolism of some medications such as tolbutamide by the regulation of gastric emptying and intragastric pH. XCHT exhibited a very low toxicity profile, such as interstitial pneumonia due to duration of medication, patients’ age, and drug combination. XCHT has been a eutherapeutic supplemental remedy for liver diseases. However, many mechanisms of action and effects of XCHT on new types of liver diseases still remain unclear, so more and more animal experiments and human clinical trials are needed to obtain enough proofs for the clinical use of XCHT in new types of hepatosis such as nonalcoholic fatty liver disease and autoimmune liver disease.

Keywords: Hepatic fibrosis, hepatitis, hepatoma, interstitial pneumonia, tolbutamide, Xiao Chai Hu Tang (minor bupleurum decoction)

Introduction

Xiao Chai Hu Tang (XCHT, Minor Bupleurum Decoction), also known as Sho-saiko-to in Japan, is a popular Chinese herbal formula applied in Asia, containing seven medicinal plants: bupleurum root, pinellia ternata, scutellaria root, jujubae fructus, panax ginseng, licorice, and ginger. Table 1 lists the principal constituents of each herb component. This formula is derived from the book Treatise on Cold Damage Diseases, written by Zhang Zhongjing (a famous physician of the late Eastern Han Dynasty, about 200 A.D.), and now, many experimental and clinical researches including prospective, randomized, and placebo-controlled trials have involved the clinic efficacy of XCHT. Although it has been widely used by patients with different kinds of hepatic diseases, such as hepatitis and liver fibrosis, its benefits claimed need an accurate assessment. This review sums up the available scientific findings about XCHT and hepatic diseases, pointing out the direction for further studies.

Mechanisms of Action

Hepatoprotective effects

XCHT helps to maintain the balance among the immunological cytokines, which may have immunological benefits to chronic viral hepatitis.[1] For example, scutellaria root and licorice in XCHT could induce the production of cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and granulocyte-colony stimulating factor (G-CSF) from monocytes/macrophages.[2] Kakumu et al.[3] found XCHT increased interferon-γ (IFN-γ) and antibody against HBV, strengthening cellular and humoral immune responses. To

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patients with chronic hepatitis C, Yamashiki et al.\[34\] pointed out that XCHT could mediate the levels of IL-4, IL-5, and IL-10 to prevent the disease progression. In imprinting control region (ICR) mice with liver injury induced by D-galactosamine, oral administration of XCHT for 14 days resulted in a significant decrease of IL-6 and TNF-α levels in the serum, a similar reduction of Fas mRNA, Fasl mRNA, and Bax protein expression, but an increase of the Bcl-2 mRNA expression in the liver tissues, and finally, XCHT relieved this kind of liver injury through the mechanism above.\[5\]

How XCHT and its components work on the count and proliferation of T-cell subsets in splenic cells and hepatocytes in vitro has also been examined. The data indicated that XCHT selectively inhibited the proliferation of CD8+ T-cell to regulate the CD4/CD8 ratio due to the constituent wogonin-7-O-glucoronide and its metabolite, which might take an essential role in the treatment of chronic hepatitis.\[6\] In other words, the therapeutic effect of XCHT might be improving body resistance, removing evil pathogen, and strengthening or regulating immune function.\[7\] The potent synergistic effect of XCHT on oposonic intracavitary of HBV carrier has also been confirmed in a mouse model, which inspires a widespread use of XCHT in immune therapies.\[8\]

Chang et al.\[9\] tested the anti-HBV activity of XCHT in HepG2 2.2.15 cell model and found XCHT could be supplementary to nucleotide analogs to minimize the recurrence of viremia after its discontinuation; however, this effect might not be mediated by saikosaponin A.

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of excessive fat in the liver of a patient who has no history of alcohol abuse. Db/db mice fed on a methionine- and choline-deficient diet, as animal models of nonalcoholic steatohepatitis (NASH), and were treated with XCHT for 4 weeks. After biochemical, pathological, and molecular analyses, it was revealed that the value of serum alanine aminotransferase (ALT) and the degree of liver necroinflammation and fibrosis, were dramatically improved by XCHT and meanwhile malondialdehyde levels in liver tissues were lower after treatment. All these suggested XCHT might inhibit hepatic necroinflammation and fibrosis in patients with NASH.\[10\] Studies of Nammi’s laboratory reported the underlying mechanisms of ginger as one component of XCHT formula in regulating hepatic cholesterol and lipid metabolism of high-fat diet (HFD)-fed rats,\[11,12\] whose hypercholesterolemia were mainly regulated by increased hepatic low-density lipoprotein receptor and reduced 3-hydroxy-3-methyl-glutaryl-CoA reductase. HFD-induced hepatic inflammation was proved to attenuate because of ginger extract through inhibition of nuclear factor-κB (NF-κB).\[13\] Gao et al. verified that ethanolic extract of ginger (50 mg/kg) significantly reduced dyslipidemia and hepatic lipid accumulation in fructose-induced NASH by modulation of the hepatic carbohydrate response element-binding protein-mediated pathway.\[14\]

**Table 1: Components and constituents of Xiao Chai Hu Tang**

<table>
<thead>
<tr>
<th>Components</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupleurum root</td>
<td>Saikosides, quercetin, α-chondrillasterol, polyaccharide, naphthas</td>
</tr>
<tr>
<td>Pinellia ternata</td>
<td>β-sitosterol, glucosides, amino acids, proteins, naphthas, saponin, alkaloids</td>
</tr>
<tr>
<td>Scutellaria root</td>
<td>Baicalins, chrysin, wogonoside, neobaiacalin, naphthas, amino acids</td>
</tr>
<tr>
<td>Jujubae fructus</td>
<td>Betulinic acid, oleanolic acid, crategolic acid, triterpenoids, alkaloids, flavonoids, saccharides, vitamins</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Ginsenosides, polyaccharide, α-panacene, panax acid, panasenoside</td>
</tr>
<tr>
<td>Licorice</td>
<td>Glycyrrhizin</td>
</tr>
<tr>
<td>Ginger</td>
<td>Naphthas (including gingerol and zingiberene), gingerol</td>
</tr>
</tbody>
</table>

**Antifibrogenic effects**

In rats whose bile ducts were ligated, XCHT was found to reduce cholestasis significantly, cut down the collagen content by 50%, and exert antifibrogenic effect by down-regulating hepatic mRNA expression of procollagen alpha-1 type I, type III, and tissue inhibitors of metalloproteinase (TIMP)-1.\[15\] The balance of matrix metalloproteinases (MMPs) and TIMPs was the further breakthrough point of research on XCHT. MMP had degradative activity against collagen, whereas TIMP controlled the active forms of MMP by blocking the active site of it. Sakaida et al.\[16\] claimed XCHT raised MMP-2, 13 activities and inhibited TIMP-1, 2 activities of hepatic stellate cells (HSCs) probably by P38 pathway. In an in vitro study,\[17\] XCHT significantly accumulated the stellate cells, transforming morphologically to myofibroblast-like cells in the G0/G1 phase, and decreased cell number subsequently in G2/M phase. From further insight into XCHT, baicalin and baicalein belonging to flavonoids had the ability to inhibit the activation of HSCs against fibrosis.\[18,19\]

XCHT also suppressed fibrogenesis by reduction of lipid peroxides, and this preventive effect was shown in inhibiting both lipid peroxidation in cultured rat hepatic cells which were in the state of oxidative stress, and generation of alpha-smooth muscle actin, type I collagen expression, cell multiplication, and oxidative burst in cultured rat HSCs considered as the main collagen-producing cells.\[19,20\] In addition, XCHT showed its dose-dependent suppression to Fe2+/adenosine 5’-diphosphate-induced lipid peroxidation in rat hepatic mitochondria and its ability of free radical elimination.\[19\]

Ono et al.\[21\] holded that administration of XCHT brought about an increase in retinoid level and a decrease in hydroxyproline level of liver, inhibiting activation of Ito cells, and then, causing inhibition of collagen production and prevention of liver fibrosis. However, when active constituents of XCHT were taken alone, liver retinoid levels remained low, implying that it was interaction among active constituents of XCHT that suppressed activation of Ito cell.\[22\]
Antihepatoma effects

XCHT-induced TNF-α and G-CSF in vitro in peripheral blood mononuclear cells of patients with hepatocellular carcinoma (HCC), which might be the source of benefits for patients taking administration of XCHT to deal with hepatoma.²²³

A subsequent study suggested that XCHT prevented hepatocarcinogenesis with inhibition of 8-hydroxy-2′-deoxyguanosine (8-OHdG) formation, which played an important role in oxidative stress.²²⁴ Meanwhile, the vicious circle between the oxidative stress and the alkaline phosphatase inactivation through lipopolysaccharides (LPS)-catecholamines interactions in the gut, liver, and brain could be attenuated by XCHT during CCl₄+ ethanol-induced mouse HCC.²²⁵

Besides, XCHT was proved to suppress the proliferation of the carcinoma cell lines in morphological, DNA, and cell cycle analyses, inducing apoptosis in the early period of exposure and arrest at the G0/G1 phase in the late period of exposure. The suppressive effect of XCHT was stronger than each of its major ingredients, and almost no inhibition was observed in normal human peripheral blood lymphocytes or normal rat hepatic cells.²²⁶ Other researches demonstrated that baicalein, baicalin, and saikosaponin A suppressed cultured human hepatoma cell proliferation in a dose-dependent manner but irrelevant to the cell cycle. Furthermore, it was reported that saikosaponin A possessed strong cell-killing ability, but saikosaponin C, ginsenoside Rb1, and ginsenoside Rg1 did not work on cell proliferation.²²⁷

Afterward, XCHT was shown to improve the immune function of tumor-bearing mice to inhibit the growth of solid liver cancer.²²⁸

However, Watanabe et al.²²⁹ found the number of Glutathione S-transferase placental form positive areas within the HCC lesions was smaller in both the control and the lycopene group than that in the XCHT group (P = 0.024 and P = 0.012, respectively), which meant long-term administration of XCHT did not reduce the risk of hepatocarcinogenesis in Long–Evans cinnamon rats.

HUMAN CLINICAL TRIALS

Hepatitis

In an in vivo study,²³⁰ XCHT seemed to help eliminate HBeAg in children. Among the 24 chronic hepatitis C patients who were not candidates for IFN-based therapy and received XCHT at the dose of 2.5 g three times daily for 12 months, aspartate aminotransferase of 67% of participants, ALT of 75% of participants, viral load response of 29% of participants and histology activity index scores of 38% of participants were improved according to the assay. The data supported the notion that XCHT could improve liver pathology in selected hepatitis C patients who were not candidates for IFN-based treatment.²³¹ Another trial, in which 26 healthy participants received XCHT at the dose of 2.5 g twice daily for 5 days and underwent the caffeine test on day 1 and day 5,²³² showed that the mean activity of cytochrome P450 enzymes 1A2 (CYP1A2) reduced by 16% on both 1st day and 5th day compared with the baseline; the mean activity of xanthine oxidase (XO) also dramatically reduced by 25% on 1st day and 20% on 5th day compared with the baseline; the activity of cytochrome P450 enzymes 3A tended to be lower on 5th day than the baseline. In brief, XCHT reduced CYP1A2 and XO activity in human.

Hepatic fibrosis

The herbal medicine XCHT has been administered to a huge number of patients with chronic liver diseases. In patients with HCV-positive liver cirrhosis, the life-extending effect of XCHT was attributed to two of its seven herb components, that was, scutellaria root and licorice. The mechanism might include the promotion of IL-12 production.²³³

Hepatoma

XCHT is known to dramatically inhibit development of hepatoma and plays a role in life prolongation. Oka et al.²³⁴ performed a prospective, randomized, nonblind controlled study that revealed XCHT could help to prevent the progression of HCC in patients with cirrhosis, especially in patients without HBs antigen.

POTENTIAL DRUG INTERACTION

Because of current popularity of XCHT in hepatic disease, cancer, and other diseases, it is essential to determine whether it has an effect on cytochrome P450, the hepatic enzyme system in charge of metabolism of many medications.

Nishimura et al.²³⁵ took the attitude that XCHT cut down the bioavailability of tolbutamide (a sulfonylurea hypoglycemic agent) in rats after oral administration, but it made no effect on the intravenous administration of tolbutamide. That was to say, the above change was not related to hepatic metabolism. Simultaneously, they claimed that XCHT had an inhibition on the gastric emptying and an increase on the intragastric pH, leading to the lower plasma concentration of tolbutamide after oral administration, but it affected neither the intragastric dissolution nor the gastric absorption of tolbutamide. This view contradicts the previous conclusion that XCHT slightly hastened the gastrointestinal absorption of tolbutamide, which might enhance the hypoglycemic effect of the sulfonylurea in the early period after oral administration.²³⁶,²³⁷

SIDE EFFECTS

Some case reports have shown the side effects of XCHT, most of which are interstitial pneumonia and acute respiratory failure in Japan.²³⁸ Patients often manifested with coughing, dyspnea, and acute episodes of fever. Chest radiographs revealed diffuse frosted glass shadows and infiltration. There were significant increases above normal in both serum C-reactive protein and lactate dehydrogenase level. Hypoxia was common. Analysis of bronchoalveolar lavage fluid showed abnormally high
proportions of lymphocytes and neutrophils and a low CD4/CD8 ratio. As report went, the youngest suffering from interstitial pneumonia attributed to XCHT in Japan was a 7-year-old boy with acute lymphoblastic leukemia complicated by type C hepatitis. At the same time, drug-induced pneumonia due to XCHT occurred in a 71-year-old woman with autoimmune hepatitis. In another autopsy case, it was inferred that the development of interstitial pneumonia was caused by HCV in combination with XCHT-induced lung injury. There was also someone getting hepatic injury and pneumonitis simultaneously after intake of XCHT. As these case reports show, the morbidity and risk of XCHT-induced interstitial pneumonia are increased by coadministration of IFN, duration of medication, and high in an elderly population. Murakami et al. made it clear that interstitial pneumonia was a side effect of treatment with IFN, and XCHT might potentiate this side effect. A possible mechanism was that XCHT could overstimulate the neutrophils which was caused by IFN to accumulate in the lung. Activated neutrophils released granulocytases elastase and oxygen radicals that might damage lung tissue. When the fibroblasts repaired the damaged tissue, pulmonary fibrosis might occur. Therefore, it is safer for XCHT to be used in patients with hepatic disease who contraindicate IFN. According to Sato, the mean treatment course of XCHT before the occurrence of pneumonitis was 50.2 ± 42.1 days and the mean age was 63.7-year-old.

Nevertheless, Ohtake et al. argued that glycyrrhizin, a metabolite of licorice as one of the primary components in XCHT, raised IL-6 in anti-CD3 monoclonal antibody (anti-CD3 mAb)-stimulated lung mononuclear cells in a cell-type specific and dose-dependent manner, so XCHT alleviated LPS-induced lung injury at the later phase when lung leak was obvious, but was ineffective on early neutrophil sequestration to the lung in BALB/c mice.

**CONCLUSIONS AND OTHER POTENTIAL USES**

XCHT, a traditional commonly applied Chinese herbal medicine formula, has long been used to patients with hepatic diseases in Asia. In fact, XCHT still has many other effects that have not been exerted. In liver diseases, more and more human clinical trials are needed to obtain enough proofs for the clinical use of XCHT in more aspects, such as NAFLD and autoimmune liver disease. XCHT exhibits a very low toxicity profile and appears to be safe for clinical use and consumption.

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**Conflicts of interest**

There are no conflicts of interest.

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