Xiao Chai Hu Tang for Liver Diseases: A Literature Review

Yi Wang¹, Li Li², Yan-Mei Cheng³, Sheng-Liang Zhu*

¹Department of Gastroenterology, Yueyang Hospital of Integrated Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China
²Yueyang Hospital and Clinical Research Institute of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China
³Correspondence: Sheng-Liang Zhu, Prof, Department of Gastroenterology, Yueyang Hospital of Integrated Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China. E-mail: zhushengliang999@126.com

ABSTRACT

Objective: 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 hepatitis.

Methods: 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 evidences were read, classified and analyzed for.

Results: XCHT showed clinical efficacy in patients with hepatic disease 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 like 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.

Conclusion: 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 like nonalcoholic fatty liver disease (NAFLD) and autoimmune liver disease.

Keywords: Xiao Chai Hu Tang (XCHT, Minor Bupleurum Decoction); Hepatitis; Hepatic fibrosis; Hepatoma; Tolbutamide; Interstitial pneumonia

Received 1 September 2016; Accept 3 May 2017

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: Bupleuri radix, Pinelliae tuber, Scutellariae radix, Zizyphi fructus, Ginseng radix, Glycyrrhizae radix, and Zingiberis recens rhizoma. Table 1 lists the principal constituents of each component herbs. 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, Scutellariae radix and Glycyrrhizae radix in XCHT can make high inductions of cytokines as interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and granulocyte-colony stimulating factor (G-CSF) on 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 patients with chronic hepatitis C, Yamashiki et al.[4] 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].

The effects of XCHT and its various constituents on the count and proliferation of T-cell subsets in cultured splenocytes and hepatic mononuclear cells have also been examined. The data indicated that XCHT could regulate the CD4/CD8 ratio via the selective inhibition of CD8+ T-cell proliferation by the constituent wogonin-7-O-glucuronoside or its metabolite wogonin, 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[23]. The potent synergistic effect of XCHT on vaccine therapy in a mouse model of hepatitis B virus carrier has also been confirmed, which inspires a widespread use of XCHT in immune therapies[6].

Chang et al.[9] tested the anti-HBV activity of XCHT in HepG(2) 2.2.15 cell model and found XCHT could be supplementary to nucleotide analogues to minimize the recurrence of viremia after its discontinuation; however, this effect might not be mediated by saikosapogenol.

Nonalcoholic fatty liver disease (NAFLD) is a condition in which excessive fat accumulates in the liver of a patient who does not have a history of alcohol abuse. Db/db mice fed on a methionine- and choline-deficient (MCD) 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 serum alanine aminotransferase (ALT) levels and liver histology, including necroinflammation and fibrosis, were dramatically alleviated by XCHT and meanwhile malondialdehyde levels in liver tissues were lower after treatment. All these suggest XCHT inhibits the necroinflammation and fibrosis in the liver of a mouse model of NASH[18]. 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 expression protein of hepatic low-density lipoprotein (LDL) receptor and reduced 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase. HFD-induced hepatic inflammation was proved to be attenuated because of ginger extract via inhibition of nuclear factor-kB (NF-kB)[13]. Gao et al. verified that ethanol 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 (ChREBP)-mediated pathway[14].

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 the mRNA expression of procollagen alpha1 types (I) and (III), and tissue inhibitors of metalloproteinase-1 (TIMP-1) in liver tissue[50]. To gain further insights into the effect of XCHT, the matrix metalloproteinases (MMPs)/tissue inhibitors of metalloproteinases (TIMPs) balance were tested. MMP had degradative activity against collagen, while TIMP controlled the active forms of MMP by blocking the active site of it. Sakaïda et al.[16] claimed XCHT increased MMP-2, 13 activities and decreased TIMP-1, 2 activities on hepatic stellate cells (HSCs) possibly via 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. It should be noted that baicalin and baicalein were flavonoids with chemical structures very similar to silybinin, which showed anti-fibrogenic activities by inhibition of the activation of HSCs[18, 19].

XCHT also suppressed fibrogenesis by reduction of lipid peroxides and this preventive effect is considered to inhibit not only lipid peroxidation in cultured rat hepatocytes that are undergoing oxidative stress, but also the production of type I collagen, alpha-smooth muscle actin (alpha-SMA) expression, cell proliferation, and oxidative burst in cultured rat HSCs which are considered to be the main collagen-producing cells[16, 20]. In addition, XCHT inhibited Fe2+/adenosine 5'-diphosphate-induced lipid peroxidation in rat liver mitochondria in a dose-dependent manner and showed radical scavenging activity[19].

Ono et al.[21] holid 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].

Anti-hepatoma 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[23].

Subsequent study suggested that XCHT prevented hepatocarcinogenesis with inhibition of 8-hydroxy-2’-deoxyguanosine (8-OHG) formation, which played an important role in oxidative stress[24]. Meanwhile, the vicious circle between the oxidative stress and the alkaline phosphatase (ALP) inactivation through lipopolysaccharides (LPS)-catecholamines (CA) interactions in gut, liver and brain could be attenuated by XCHT during CCl4+ethanol-induced mouse HCC[25].

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 suppressive effect was detected in normal human peripheral blood lymphocytes or normal rat hepatocytes. Other researches demonstrated that baicalein, baicalin and saikosaponins suppressed cultured human hepatoma cell proliferation dose-dependently but irrelevant to the cell cycle. Furthermore, it was reported that saikosaponin A possessed strong cell-killing ability, on the other hand, saikosaponin C, ginsenoside Rb1 and ginsenoside Rg1 had no effect on cell proliferation. Afterwards, XCHT was shown to improve the immune function of tumor-bearing mice to inhibit the growth of solid liver cancer.

However, Watanabe et al. found the number of Glutathione S-transferase placental form (GST-P)-positive areas within the HCC lesions was greater in the XCHT group than that in the control or lycopene 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 (LEC) rats.

### Human Clinical Trials

**Hepatitis**

In an in vivo study, XCHT seemed to help eliminate HBeAg in children with both chronic HBV infection and sustained liver disease. Among the 24 chronic hepatitis C patients who were not candidates for interferon-based therapy and received XCHT at the dose of 2.5 g three times daily for 12 months, aspartate aminotransferase (AST) of 67% participants, ALT of 75% participants, viral load response of 29% participants and histology activity index (HAI) scores of 38% 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 interferon based treatment.

Another trial, in which 26 healthy subjects 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, showed that the mean activity of cytochrome P450 enzymes 1A2 (CYP1A2) decreased by 16% on both day 1 and day 5 compared with the baseline; the mean activity of xanthine oxidase (XO) also significantly decreased by 25% on day 1 and 20% on day 5 compared with the baseline value; the activity of cytochrome P450 enzymes 3A (CYP3A) tended to be lower on day 5 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 due to two of its seven herb components, that is, scutellaria root and glycyrrhiza root. One possible mechanism may be the promotion in IL-12 production.

**Hepatoma**

XCHT is known to dramatically inhibit cancer development in the liver and has life-extending effects. Oka et al. performed a prospective, randomized, non-blind 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’s 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. took the attitude that XCHT cut down the bioavailability of tolbutamide (a sulphonylurea hypoglycaemic agent) in rats after oral administration, but it made no effect on the intravenous administration of tolbutamide. That is to say, the above change is 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 hypoglycaemic effect of the sulphonylurea in the early period after oral administration.

### Side effects

Some case reports have shown the side effects of XCHT, most of which are interstitial pneumonia and acute respiratory failure in Japan. Patients often manifested with coughing, dyspnea, and fever of acute onset. Chest X-ray films showed diffuse ground-glass shadows and infiltration. Abnormally high levels of C-reactive protein and lactate dehydrogenase were common, as was hypoxia. Analysis of bronchoalveolar lavage fluid revealed abnormally high percentages 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 showed, the morbidity and risk of XCHT-induced interstitial pneumonia are increased by co-administration of interferon, 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 interferon, and XCHT might potentiate this side effect. A possible mechanism was that XCHT could overstimulate the neutrophils which was caused by interferon to accumulate in the lung. Granulocytes elastase and oxygen radicals released
from activated neutrophils might damage lung tissue. The fibroblasts that repaired the damaged tissue might increase the risk of pulmonary fibrosis. Therefore, it is safer for XCHT to be used in patients with hepatic disease who contraindicate interferon. According to Sato[47], the mean duration of XCHT therapy before the occurrence of pneumonitis was 50.2 +/- 42.1 days and the mean age was 63.7-year-old.

Nevertheless, Ohtake et al.[49] argued that glycyrrhizin, a metabolite of glycyrrhiza radix as one of the primary components in XCHT, raised in vitro 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 disease in Asia[40]. In fact, XCHT still has many other effects that haven’t 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, like NAFLD and autoimmune liver disease. XCHT exhibits a very low toxicity profile, and appears to be safe for clinical use and consumption.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>XCHT</td>
<td>Xiao Chai Hu Tang</td>
</tr>
<tr>
<td>NAFLD</td>
<td>nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte-colony stimulating factor</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>ICR</td>
<td>imprinting control region</td>
</tr>
<tr>
<td>NAFLD</td>
<td>nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>MCD</td>
<td>methionine- and choline-deficient</td>
</tr>
<tr>
<td>NASH</td>
<td>nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>HFD</td>
<td>high fat diet</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>HMG</td>
<td>3-hydroxy-3-methyl-glutaryl</td>
</tr>
<tr>
<td>NF</td>
<td>nuclear factor</td>
</tr>
<tr>
<td>ChREBP</td>
<td>carbohydrate response element-binding protein</td>
</tr>
<tr>
<td>TIMP</td>
<td>tissue inhibitors of metalloproteinase</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>HSC</td>
<td>hepatic stellate cells</td>
</tr>
<tr>
<td>SMA</td>
<td>smooth muscle actin</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>B-OHdG</td>
<td>8-hydroxy-2’-deoxyguanosine</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharides</td>
</tr>
<tr>
<td>CA</td>
<td>catecholamine</td>
</tr>
<tr>
<td>GST-P</td>
<td>Glutathione S-transferase placent form</td>
</tr>
<tr>
<td>LEC</td>
<td>Long-Evans Cinnamon</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>HAI</td>
<td>histology activity index</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>cytochrome P450 enzymes 1A2</td>
</tr>
<tr>
<td>XO</td>
<td>xanthine oxidase</td>
</tr>
<tr>
<td>mAb</td>
<td>monoclonal antibody</td>
</tr>
</tbody>
</table>

Acknowledgments

This work was supported by grants from the Science and Technology Commission Foundation of Shanghai Municipality; China (grants 13401902801).

Conflicts of interest

The authors declare that there are no conflicts of interest.

References


