Therapeutic mechanism of Yīn-Chén-Hāo decoction in hepatic diseases

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Yīn-Chén-Hāo decoction (YCHD) is a traditional Chinese medicine formula composed of capillaris (Artemisia capillaris), gardenia (Gardenia jasminoides), and rhubarb (Rheum rhabarbarum) that is used for the treatment of damp-heat jaundice. In modern clinics, YCHD is mostly used for hepatic diseases. This review summarizes the biological activities of YCHD and its medical applications. The main active compounds of YCHD are chlorogenic acid, rhein, geniposide, emodin, and scoparone. The pharmacological actions of YCHD include inhibition of hepatic steatosis, apoptosis, necrosis, anti-inflammation, and immune regulation. YCHD could be developed as a new therapeutic strategy for the treatment of hepatic diseases.

Key words: Yīn-Chén-Hāo decoction; Hepatic disease; Clinical application; Effector mechanism; Review

Abstract

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Core tip: Yin-Chén-Hāo decoction (YCHD) was a classical prescription for more than 1800 years in China. This review summarizes the efficacy of YCHD in hepatic diseases.
liver disease from clinical trials and its mechanisms of action in vitro and in vivo. Studies indicate that YCHD can modulate various molecular pathways in liver disease. YCHD is widely used in clinical settings for the treatment of liver diseases, and could be a safe and novel therapeutic drug for liver injury worldwide.

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INTRODUCTION

Yīn-Chén-Hāo decoction (YCHD) was first described in the “Treatise on Febrile Diseases” by Zhong-Jing Zhang during the Eastern Han Dynasty (AD 25-220). It is a classic prescription in traditional Chinese medicine (TCM) that is mainly used for internal stasis heat and jaundice arising from Yang Ming disease and malnutrition, with doctors also widely using this prescription for heat jaundice. Modern usage of YCHD includes treatment for acute icteric infectious hepatitis along with other herbal medicines. YCHD is also used for hepatic diseases and has some uses in internal medicine, surgery, and pediatrics (Table 1). This paper discusses studies on YCHD and its mechanisms in the treatment of hepatic diseases.

Classical Chinese formulae include four elements: the monarch drug, the minister drug, the assistant drug, and the servant drug; the monarch drug plays the most important role in the formula, the assistant drug increases the effectiveness of the monarch drug, the minister drug helps the monarch and minister drugs reach their target positions, and the servant drug can reduce the adverse effects or increase the potency of the entire formula[1].

YCHD (Figure 1) is comprised of 12 g Capillaris (Artemisia capillaris), 9 g Gardenia (Gardenia jasminoides), and 9 g Rhubarb (Rheum rhabarbarum). Capillaris is the monarch drug, and can clear heat and dampness and remove jaundice. Gardenia is the minister drug, and can clear heat-fire and damp-heat in the triple burner, and remove pathogenic factors from the urine. Rhubarb is both the assistant and servant drug, and acts to purge heat from the bowels, cool the blood, detoxify, dispel stasis, and dredge the meridians. The three drugs together prevent stasis, promote bowel movement, and guide stagnant heat to be excreted alongside the stool. YCHD is usually used twice daily. In an animal study with rats, total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were improved and the blood level of scoparone was higher for longer when YCHD was administered once vs twice or three times daily. The exact mechanism of this effect has yet to be determined[2].

CHEMICAL COMPOSITION OF YCHD

YCHD has broad prospects for application in the field of liver disease, particularly in the treatment of hepatitis with jaundice; for example, it promotes bilirubin metabolism, can prevent liver damage, and inhibits hepatic apoptosis, hepatic stellate cell (HSC) activation, and collagen synthesis[3]. Studies on its chemical composition have determined some effective compounds found in YCHD. Capillaris mainly contains five classes of active compounds: anthraquinones (e.g., rhein, emodin, aloe emodin, chrysophanol, and physcion); and anthraquinones like anthraquinone glycoside and dihydrotheanine glucosides; tannins (e.g., gallic acid, D-catechin); stilbenes (e.g., rhapontin, piceatannol, resveratrol, 3',4',5-hydroxyl stilbene, rhapontin-2'-O-gallate, rhapontin-6'-O-gallate); volatile oils (e.g., palmitic acid, hexacosanoic acid, palmitic ethyl ester, dibutyl phthalate); and rhubarb polysaccharides. Gardenia mainly contains five classes of active compounds: flavonoids (e.g., geniposide, hydroxyl gardenoside, caryopyloside, gardsoside, scandoside methyl ester, geniposidic acid); pigments (e.g., crocin, crocetin); organic acids (e.g., chlorogenic acid, bitter saffron acid, alicyclic acid, 3-oxygen chlorogenic acid, bitter saffron acid, alicyclic acid, 3-oxygen chlorogenic acid, bitter saffron acid, alicyclic acid, 3-oxynex coffee α musturd acyl α 4-oxynex quinex acid); polyphenols (e.g., linoleic acid, palmitic acid); and gardenia polysaccharides.

One study identified 45 compounds from YCHD, with 21 found in rat blood after oral administration. After studying the influence of different herbs alone compared with the whole YCHD decoction, investigators found eight compounds that are selectively absorbed into the bloodstream only after administration of all herbs from the YCHD decoction. Each compound had a significant effect on protecting the liver and gallbladder[4].

The biological effects of many ingredients in YCHD reflect the therapy of the entire formula (Table 2). For example, rhein may relieve cellular insult through its anti-inflammatory activity and inhibit TGF-α activity and HSC activation[5]. Chlorogenic acid, another critical active ingredient of YCHD, can counteract liver injury at various levels by preventing apoptosis and oxidative stress damage. More specifically, both the glutathione and thioredoxin antioxidant systems and the mitogen-activated protein kinase (MAPK) signaling cascade appear to be engaged in the protective
mechanism of chlorogenic acid[8]. Geniposidic acid, the critical active ingredient of gardenia, alleviates liver injury by enhancing the antioxidative defense system and slowing the apoptotic signaling pathways[9].

One study used high-performance liquid chromatography-UV to test scoparone in rat plasma after intragastric administration of YCHD or water decoctions of capillaris, gardenia, and rhubarb separately. The study found that the scoparone level after YCHD administration was significantly higher than that of water decoctions alone. Moreover, the therapeutic effect of YCHD was found to be better than that of the herbs alone[10]. Another study used scoparone, geniposide, or rhein alone or in combination, and investigated their immunohistochemistry, biochemistry, metabolomics, and proteomics. The results showed that the scoparone, geniposide, and rhein combination exerts a more robust therapeutic effect than any one or two of the three individual compounds in a rat model of hepatic injury. Furthermore, scoparone, geniposide, and rhein synergistically cause intensified dynamic changes in metabolic biomarkers, regulate molecular networks through target proteins, have a synergistic effect, and activate both intrinsic and extrinsic pathways[11].

MECHANISMS OF YCHD EFFECTS

Liver injury repair
The liver is a major location for the metabolism and elimination of drugs, as well as being involved in their absorption. Therefore, the liver greatly influences the pharmacokinetics of compounds. Studies demonstrate that liver injury significantly influences the pharmacokinetics of scoparone, not only via changes in intestinal absorption, but also via changes in hepatic metabolism. In one study, the absorption and distribution of scoparone was accelerated in liver-injured rats at the cost of slowed metabolism and elimination. Changes in parameters like metabolism can explain some molecular mechanisms of YCHD in the treatment of liver injury[12].

Research into different drug-induced liver injury forms have been conducted with YCHD. One study explored liver injury induced by α-naphthyl isothiocyanate (ANIT) and carbon tetrachloride (CCl4). ANIT intoxication groups were given ANIT (in corn oil at a ratio of 10:1) at a single dose of 80 mg/kg orally, while CCl4 intoxication groups were given CCl4 (in corn oil at a ratio of 1:4) at a single dose of 1 mL/kg orally. In the ANIT group, the levels of ALT, alkaline phosphatase (AKP), and TBIL were significantly higher than those in the control group. In the CCl4 group, the malondialdehyde content was significantly higher and superoxide dismutase and glutathione peroxidase activities were significantly lower compared with those in the control group. YCHD significantly reduced AST, ALT, and AKP levels in the ANIT group and significantly reduced AST, ALT, AKP, and malondialdehyde levels in the CCl4 group. In addition, YCHD was also found to increase the ratio of liver weight to body weight[13].

Scoparone is an important compound found in capillaris that has been shown to be hepatoprotective, effective in the treatment of liver diseases, and contribute directly to the therapeutic effect of YCHD[14]. The metabonomic characteristics of CCl4-induced hepatotoxicity and intervention with scoparone illustrate that scoparone could have hepatoprotective effects via multiple pathways, including primary bile acid biosynthesis and pyrimidine metabolic pathways[15]. The hepatoprotective effects of scoparone in rat liver injury were associated with regulated expression of six proteins that appear to be involved in antioxidation and signal transduction, energy production, immunity, metabolism, and chaperoning[16].
Figure 2 Molecular structures of compounds found in Yin-Chén-Hāo decoction.
Table 1  Clinical trials using Yīn-Chén-Hāo decoction

| Herb or compound | Dose and course of treatment | Combined medication | Case/control | Disease type | Symptoms | Efficacy | Positive control drug | Side effects | Ref. |
|------------------|-----------------------------|---------------------|--------------|--------------|----------|----------|-----------------------|--------------|------|
| YCHD             | From 28th wk of pregnancy, decocted with water, daily, 4 wk | From 36th wk of pregnancy, both groups, + administration of 30 mg phenobarbital, twice a day, orally. 1000 mg transmetil injection, IVGTT | 81/76 | Maternal-fetal ABO blood group incompatibility | IgG anti-A/B antibody titer, growth in fetus, neonatal jaundice | Reduced antibody titer, reduced jaundice incidence rate, reduced TBIL | Vitamin C 0.5 g + 100 IU coenzyme A + 40 mg adenosine triphosphate, IVGTT | None | [61] |
| YCHD             | Modified YCHD, decocted with water daily; orally, twice a day | | 38/30 | Hyperbilirubinemia induced by viral hepatitis | Clinical symptoms, liver function, bilirubin | Symptoms, bilirubin levels significantly improved due to liver function | Vitamin C, vitamin B6, diaminonium | None | [62] |
| Modified YCHD    | Decocted with water, daily, 10 d | Routine Western medical treatment | 34/34 | Pathological neonatal jaundice | Time of jaundice disappearance, jaundice degree, TBIL | Time jaundice disappearance is shut down, liver TBIL significantly decreased | Routine Western medicine therapy, etiological treatment, light therapy, phenobarbital, albumin for patients with high bilirubin, gamma globulin for patients with hemolytic disease | None | [63] |
| Modified YCHD    | Decocted with water, daily, 14 d | Plasma exchange | 20/20 | Hepatitis B combined with hyperbilirubinemia | Liver function, prothrombin activity | TBIL significantly decreased effective rate of treatment group compared with significantly increased control group | Plasma exchange | None | [64] |
| Modified YCHD    | Decocted with water, daily, orally, 28 d | Mask with the function of removing heat and eliminating stasis | 31/29 | Gastrointestinal damp-heat acne | Acne coalescence condition | Increased total effective rate of acne coalescence, average efficacy index statistically significantly decreased | Danshentong capsules for oral use, vitamin E emulsifiable paste for external use | None | [65] |
| Modified YCHD    | Decocted with water, daily, orally, 7 d | None | 32/34 | Juvenile bronchial asthma | Asthma symptoms | Curative effect of treatment group significantly better than control group; fade time of cough, sputum, and wheezing in treatment group significantly shorter than control group ($P < 0.05$) | Normal saline, dexamethasone injection, ambroxol hydrochloride injection, aerosol inhalation, twice a day, 3-7 days, additional antibiotics for infected individual | None | [66] |
| Formula                        | Preparations                                                                 | Doses/Duration            | Disease                        | Clinical Indicators                                                                 | Observed Outcomes                                                                 | Anti-infection Measures                                                                 | Comments |
|-------------------------------|-------------------------------------------------------------------------------|---------------------------|--------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------|
| Modified YCHD                 | Decoction with water, daily, orally                                           | 24/24                     | Choledocholithiasis            | TBIL, DBIL, AKP, GGT, ALT, daily bile reflux                                         | Improved indicators improved significantly, daily bile reflux significantly higher than control group ($P < 0.05$) | None                                                                                   | [67]     |
| Yin-Zhi-Huang injection       | 10 mL + 20 mL glucose solution, IVGTT, daily, 15 wk                          | 18/14                     | Biliary atresia               | TBIL, DBIL, ALT, AST                                                                  | Observation target significantly improved ($P < 0.05$)                            | None                                                                                   | None     |
| Yin-Zhi-Huang granule         | 1.0 g, 3 times a day, orally, 7 d                                            | 150/133/141               | Neonatal jaundice             | Time of jaundice disappearance, transcutaneous bilirubin                             | Time of jaundice disappearance significantly reduced, transcutaneous bilirubin level significantly reduced ($P < 0.05$) | Blue light irradiation                                                                 | None     |
| Yin-Zhi-Huang granule         | 3.3 mL, 3 times a day, orally, 5 d                                           | None                      | Pathological neonatal jaundice | Bilirubin concentration, time of jaundice disappearance                               | Plasma bilirubin level significantly reduced, total effective rate significantly increased | Tuihuang mixture                                                                   | None     |
| Yin-Zhi-Huang injection       | 5 mL + 10% glucose solution 50 mL, IVGTT, daily, 10 d                       | 46/12                     | Infantile hepatitis syndrome  | Treatment results (cured, improved, invalid), serum TBIL, ALT value, size of liver and spleen | Cure rate, total effective rate significantly increased, plasma bilirubin level significantly reduced, obvious change to liver and spleen size | ATP, coenzyme A, inosine, vitamin C, glucuronolactone                               | None     |
| Modified compound             | Twice a day                                                                   | None                      | Maternal-fetal ABO blood group incompatibility-induced neonatal jaundice | Antibody titer, neonatal jaundice incidence, jaundice degree                        | Antibody titer and neonatal jaundice incidence much lower post-treatment, TCM treatment before delivery failed to reduce jaundice degree | None                                                                                   | None     |
| Yin-Chén recipe               |                                                                                |                           | Maternal-fetal ABO blood group incompatibility-induced neonatal jaundice | Antibody titer, neonatal jaundice incidence, jaundice degree                        | Antibody titer and neonatal jaundice incidence much lower post-treatment, TCM treatment before delivery failed to reduce jaundice degree | None                                                                                   | [72]     |
| ICKT                          | 7.5 g, daily, orally                                                         | None                      | Acute cholestatic hepatitis    | Clinical course of patient TBIL level began to decrease, liver biopsy showed chronic active hepatitis with mild fibrosis | Predonine                                                                      | None                                                                                   | [73]     |
| ICKT                          | 7.5 g, daily, orally                                                         | None                      | Persistent hyperbilirubinemia  | Choleretic effect ICKT group showed significant decrease compared with control group in indirect bilirubin levels | None                                                                                   | None                                                                                   | [74]     |
| Treatment | Modified Yīn-Chén recipe | Modified Yīn-Chén recipe decoction, orally | Routine Western medical treatment | 30/30 | Chronic severe hepatitis | Liver function indices, complication incidences, score of TCM syndromes, clinical effects | Treatment group better than control group ($P < 0.05$) | Basic Western medical treatment | None | [75] |
|-----------|--------------------------|------------------------------------------|---------------------------------|-------|--------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------|---------------|-------|
| Treatment | Modified Yīn-Chén recipe decoction | Retention enema, daily | Routine comprehensive treatment | 30/30 | Chronic severe hepatitis | Liver function indices, endotoxin, blood ammonia | Treatment group better than control group ($P < 0.05$) in improvement of clinical symptoms, endotoxin, blood ammonia, ALT, AST, and TBL | Lactulose medicated by retention enema | None | [76] |
| Treatment | Modified Artemisiae Scopariae decoction | Twice a day | Ursodeoxycholic acid | 30/30 | Primary biliary cirrhosis | Clinical effect, biochemistry indicators, immunoglobulin levels | Treatment group better than control group ($P < 0.05$) in clinical effect and biochemistry indicators, insignificantly decreased immunoglobulin levels ($P > 0.05$) | Ursodeoxycholic acid | None | [77] |
| Treatment | Modified Yīn-Chén recipe decoction | Twice a day | Conventional treatment, phenobarbital (blue light-struck) | 30/29 | Neonatal hyperbilirubinemia | Clinical effect | Treatment group better than control group ($P < 0.05$ in clinical effect | Conventional treatment (phenobarbital, blue light-struck) | None | [78] |
| Treatment | Lidan Xiaohuang decoction | 50-100 mL 2-3 times a day, orally | Routine Western medical treatment | 35/31 | Obstructive jaundice, post-operative persistent jaundice | Bilirubin | Treatment group better than control group ($P < 0.01$) | Acupuncture therapy | None | [79] |
| Treatment | Qing-Re-Li-Shi formula | Twice a day, 90 d | None | 60 | Chronic hepatitis B | Liver function, comparison, hepatitis B virus marker comparison | Contents of ALT, AST, AKP, G, TBL, DBIL improved ($P < 0.01$); negative conversion rates of 16.7% HbsAg, 21.2% HbeAg, and 35.0% HBV | None | None | [80] |
| Treatment | Modified compound Yīn-Chén recipe decoction | Twice a day | Triple anti-Hp therapy | 30/30 | Hp-positive rosacea | Clinical effective rate, Hp-positive rate, serum IL-8, TNF-α | Clinical effective rate in treatment group better than control group ($P < 0.05$); Hp-positive rate, serum IL-8, and TNF-α in treatment group significantly lower than control group ($P < 0.01$) | Triple anti-Hp therapy | None | [81] |
| Treatment | Modified compound Yīn-Chén recipe decoction | Twice a day | Routine Western medical treatment | 120/90 | Viral hepatitis jaundice | Jaundice disappearance, liver function improvement | Clinical effective rate and liver function in treatment group better than control group ($P < 0.05$) | Routine Western medical treatment | None | [82] |
Network reconstruction techniques were used to study the treatment of alcoholic hepatitis with scoparone. The metabolites after scoparone treatment in rats with alcoholic hepatitis were observed. The results showed that scoparone could regulate dysfunctions in the citrate cycle, sphingolipid metabolism, and taurine and hypotaurine pathways [17]. In addition, scoparone was distributed and eliminated rapidly in rats. Tissue distribution was highest in the liver, followed by the kidney and spleen. There were lower concentrations observed in the muscle, thyroid, and adrenal gland. Scoparone was not detected in the brain, which indicates that it does not cross the blood-brain barrier after oral administration [18].

YCHD combined with Da-Cheng-Qi decoction can reduce Bax and caspase-3 protein expression, increase Bcl-2 protein expression, regulate the balance of Bcl-2/Bax, and treat endotoxin-induced liver cell apoptosis [19].

Reverse steatosis
Recent studies have reported the efficacy of YCHD in reducing hepatic fat accumulation. Enhanced adiponectin and endothelial progenitor cells and upregulation of PPAR-γ might be responsible for the therapeutic effect of YCHD in the treatment of non-alcoholic fatty liver disease (NAFLD). In addition, the antioxidative effect of YCHD might be associated with the inhibition of hepatic-free fatty acid (FFA) concentrations and the elevation of glutathione levels in hepatic tissues. Furthermore, YCHD might promote senescence marker protein-30 metabolism, which increases resistance to hepatic oxidative stress [20].

In steatohepatitis experiments with rats, those treated with YCHD had lower serum ALT activity, tumor necrosis factor (TNF-α) levels, hepatic triglycerides, and FFA levels. Moreover, there was significantly less fat deposition in hepatocytes than in the steatohepatitis rats. Therefore, YCHD has good therapeutic effects on non-alcoholic steatohepatitis, can protect liver function, and can reduce fatty deposition in the liver. These effects are possibly related to reductions in FFA content and inhibition of TNF-α expression [21].

YCHD contains scoparone, geniposide, and rhein, with the three causing dynamic changes in metabolic biomarkers, regulating molecular networks through target proteins, having synergistic effects, and activating both intrinsic and extrinsic pathways to exert a robust therapeutic effect in a rat model of hepatic injury [11]. A meta-analysis was conducted on the role of YCHD in NAFLD. The results showed that YCHD can significantly regulate ALT, AST, gamma-glutamyl transpeptidase (GGT), triglycerides, total cholesterol, low-density lipoprotein cholesterol, and syndrome score. Total effective rate, syndrome effective rate, and B-type ultrasonography effective rate were significantly better in the test group than those in the control group. Therefore, YCHD has a satisfactory therapeutic effect on NAFLD.
Mechanisms of action

- Antineoplastic, anti-inflammatory, antimicrobial

Pharmacological activities

- Anti-inflammatory, analgesia, antioxidant
- Cholagogue, laxness, soft tissue injury repair, gastric acid secretion inhibition, amylopin secretion reduction
- Antineoplastic, anti-inflammatory, antimicrobial, immunosuppressive, diuresis and purgation, improve glycometabolic
- Antineoplastic, anti-inflammatory, antimicrobial, immunosuppressive, diuresis and purgation

Table 2  Mechanisms of action of compounds found in Yīn-Chén-Hāo decoction

| Compound          | Pharmacological activities                                      | Mechanisms of action                                                                                                                                                                                                                   | Ref. |
|-------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Chlorogenic acid  | Antibacterial, antiviral, antioxidation, free radical scavenging, mutation suppression, anti-tumor | Reversed liver reduced GSH levels and expression of TRX, triggering GSH and TRX antioxidant systems and MAPK signaling cascade                                                                                                           | [8]  |
| Scopolamine       | Anti-inflammatory, analgesia, antioxidation, immunosuppressive, cholagogue, blood pressure, hypolipidemic, anti-asthmatic | Inhibition of protein tyrosine kinase and release of arachidonic acid metabolites, reduced expression of tissue factor at mRNA level and thrombus generation; enhancement of prostacyclin release, protection against endothelium derived relaxing factor inactivation, and activating guanylate cyclase, relaxed bronchial smooth muscle | [86-89] |
| Geniposide        | Anti-inflammatory, analgesia, cholagogue, laxness, soft tissue injury repair, gastric acid secretion inhibition, amylopin secretion reduction | Enhancing antioxidative defense system and reducing apoptotic signaling pathways; regulating adipocytokine release and the expression of PPARα expression                                                                                                       | [9,90] |
| Rhein             | Antineoplastic, anti-inflammatory, antimicrobial, immunosuppressive, diuresis and purgation, improve glycometabolic | Inhibiting cytochrome P450 enzymes in liver microsomes                                                                                                                                                                                                                                             | [91]  |
| Emodin            | Antineoplastic, anti-inflammatory, antimicrobial, immunosuppressive, diuresis and purgation | Inhibiting HSC activation                                                                                                                                                                                                                                                                         | [92]  |

GSH: Glutathione; TRX: Thioredoxin; MAPK: Mitogen-activated protein kinase; PPARα: Peroxisome proliferator activated receptor-α; HSC: Hepatic stellate cell.

Anti-inflammatory and anti-viral effects

Hepatitis B is a major global health problem caused by the hepatitis B virus (HBV). Many clinical studies have reported that YCHD can reduce serum transaminase activity, elevate serum albumin, reduce the ratio of albumin and globulin (A/G), improve liver function, and provide satisfactory long-term effects\[^{25,24}\]. These effects could help in the treatment of hepatitis B.

The pathogenic process of HBV is immune-mediated inflammation. Cytotoxic T lymphocytes (CTL) recognize and destroy target cells by antigen presentation, and cause target-cell apoptosis when fas ligand protein on the membrane surface unites with target-cell Fas antigen. HBV infection activates the immune system to produce and release cytokines, which promote liver inflammation and cause liver damage.

One study found that, in the treatment of chronic hepatitis B, YCHD combined with Western medicine was significantly better than Western medicine treatment alone\[^{29}\]. In an experiment with concanavalin A-induced acute immune liver injury in mice infected with hepatitis B, YCHD was found to reduce AST, interferon-γ, and Fas gene levels, and increase the level of interleukin (IL)-4 in the liver. YCHD was also able to repair damage to liver cells, decrease the frequency of liver cell apoptosis, and reduce inflammatory response\[^{26}\].

Drug-induced hepatitis refers to liver damage caused by drugs or their metabolites. In recent years, increased usage of new drugs and drug combinations has increased the incidence of drug-induced hepatitis. YCHD plus glycyrrhizinate or transmetil was found to be more effective than Western medicine in the treatment of drug-induced hepatitis. A control group was treated with glycyrrhizinate capsules and transmetil, while a treatment group received the same drugs plus modified YCHD. The levels of ALT, TBIL, and globulin in the treatment group were lower than those in control group after treatment (P < 0.05). In addition, the level of albumin in the treatment group was higher than that in the control group\[^{27}\].

Chronic severe hepatitis is another common type of hepatitis. The treatment of chronic severe hepatitis is difficult, and usually results in such complications as ascites, hepatic encephalopathy, gastrointestinal bleeding, and hepatorenal syndrome. Clinical research indicates that YCHD can reduce liver cell inflammation, expand intrahepatic bile capillaries, promote bile secretion, increase bile flow, improve hepatic microcirculation, reduce the absorption of intestinal toxins, and increase the excretion of bilirubin. These effects can reduce symptoms and significantly improve liver function in patients with chronic severe hepatitis\[^{28}\]. Liver dialysis combined with YCHD is an especially effective therapeutic regimen for severe hepatitis\[^{29}\].

Anti-fibrotic effects

Fibrosis is a wound-healing response that engages a range of cell types and mediators to encapsulate an injury. During fibrogenesis, pathological factors including inflammation from Kupffer cells (KCs), angiogenesis, and HSC activation lead to collagen deposition\[^{30}\]. Cirrhosis, an advanced liver disease, is characterized by fibrosis, nodule formation, and inflammation\[^{31}\]. Despite the high incidence of hepatic fibrosis worldwide, no generally accepted antifibrogenic therapy is available. However, TCM has been widely used for treating chronic liver hepatitis and liver cirrhosis, with said treatments appearing to improve clinical symptoms, liver function, and patient quality of life\[^{32}\].

YCHD can significantly inhibit apoptosis in liver cells, inhibit HSC activation, and inhibit KC activation, thereby protecting liver function and preventing liver fibrosis.
Cirrhosis with ascites often occurs during chronic liver cirrhosis. The clinical manifestations of ascites are tympanites and edema. One clinical study found that YCHD combined with Jijiaolihuang bolus could clear heat and expel dampness, induce diuresis to remove edema, and reduce ascites.

**Effects in other liver diseases**

Since YCHD can clear heat, promote diuresis, and remove jaundice, it also plays an important role in the treatment of primary liver cancer.

Liver failure is caused by extensive liver cell necrosis, which results in severely impaired liver function, while chronic liver failure results from decompensation of the liver during cirrhosis and is accompanied by a poor prognosis and high mortality rate.

HBV is the most common cause of liver failure in China. Although nucleoside analogs can inhibit viral replication in the short-term, they usually result in drug resistance in the long-term. TCM enema can solve issues such as difficulties in oral administration, effectively removing harmful bacteria in the gut, improving intestinal endotoxemia, and promoting the recovery of liver function. In patients with HBV-induced liver failure, an enema of YCHD plus colon lavage was found to result in liver function and symptom improvement, jaundice improvement, TBIL reduction, and increased prothrombin time.

One study established a rat model with hepatic failure after 70% liver resection to research the therapeutic effect of capillaris. The results showed that the herb can improve IL-6 levels, increase serum IL-6 levels, and improve survival rate in rats with liver failure after surgery.

**OTHER PHARMACOLOGICAL ACTIVITIES**

YCHD-ameliorated alloxan (ALX) induced hyperglycemia in mice and significantly reduced fasting blood glucose (FBG) in normal mice and ALX-diabetes in mellitus model mice and rats. YCHD also improved impaired glucose tolerance in a dexamethasone-induced insulin resistance rat model and reduced 2-h post-prandial blood glucose after an oral glucose tolerance test. This suggests that YCHD has hypoglycemic effects like sulfonylurea or biguanide.

Clinical studies indicate that YCHD plus Bai-Tou-Weng decoction and hormones have a better treatment effect than Western medicine in the clinical treatment of Behçet’s disease. In one study, a control group was treated with prednisone, while a treatment group was treated with the same drug plus YCHD and Bai-Tou-Weng decoction. According to the diagnostic criteria of the International Society for Behçet’s Disease, the therapeutic effect in the treatment group was better than in the control group (P < 0.05).

YCHD has also been used clinically in neonatal hyperbiliurbinemia, neonatal jaundice, maternal-
YCHD: Yin-Chén-Hāo decoction; TCM: Traditional Chinese medicine.

fetal ABO blood type incompatibility[53-56], intrahepatic cholestasis of pregnancy[57], newborn pathological jaundice[58], and acne[59].

Compared with insulin and insulin analogs, combined therapy of NovoRapid and modified YCHD is an effective, safe, and economical approach to the treatment of chronic hepatitis B with diabetes[60].

DRUGS THAT INCLUDE THE HERBS FROM YCHD

Drugs that include the herbs found in YCHD have been on the market for many years and most have important therapeutic uses. Xiong-Dan-Yin-Chén Oral Solution® (XDYCKFY, Hei-Bao-Yao-Ye, Hei-Long-Jiang, China) is an effective and safe treatment for chronic liver diseases, and can slow down the progress of cholecytitis and cholelithiasis. Moreover, Ling-Zhi-Yin-Chén Capsule® (LZYC capsule, Zhong-Long-Yi-Yao, Hei-Long-Jiang, China) and Huang-Dan-Yin-Chén Granule® (HDYCKL, Fo-Ci-Zhi-Yao, Lan-Zhou, China) are used to improve the symptoms of idiopathic pain, abdominal distension, anorexia, malaise, fatigue, and greasy yellow coating. Yin-Chén-Tui-Huang Capsule® (YCHT capsule, De Shang Yao Ye, Jilin, China) is often used in the treatment of jaundice caused by acute and chronic liver disease.

CONCLUSION

This review summarized the efficacy of YCHD in liver disease from clinical trials and its mechanisms of action in vitro and in vivo. Studies indicate that YCHD can modulate various molecular pathways in liver disease. YCHD is widely used in clinical settings for the treatment of liver diseases, and could be a safe and novel therapeutic treatment for liver injury worldwide (Table 3). Future studies on YCHD could help define its various effective constituents, molecular mechanisms, and targets that help prevent inflammation and fibrosis. Although YCHD has been used clinically for thousands of years, most studies on it are basic, and so its material basis and mechanisms remain unclear. At present, there are few multicenter, large, randomized, double-blind, controlled clinical trials on YCHD. Extensive clinical research is warranted to evaluate the safety and efficacy of YCHD alone or in combination with other drugs.

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