Traditional Chinese medicine and related active compounds: A review of their role on hepatitis B virus infection

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ABSTRACT: Since the significant public health hazard of Hepatitis B virus (HBV) infection and obvious drug resistance and dose-dependent side effects for common antiviral agents (e.g., interferon-alpha, lamivudine, and adefovir), continuous development of agents to treat HBV infection is urgently needed. Traditional Chinese medicine (TCM) is an established segment of the health care system in China. Currently, it is widely used for chronic hepatitis B (CHB) in China and many parts of the world. Over a long period of time in clinical practice and in basic research progress, the effectiveness and beneficial contribution of TCM on CHB have been gradually known and confirmed. Based upon our review of related papers and because of our prior knowledge and experience, we have selected some Chinese medicines, including Chinese herbal formulas (e.g., Xiao-Chai-Hu-Tang, Xiao-Yao-San, and Long-Dan-Xie-Gan-Tang), single herbs (e.g., Phyllanthus niruri, Radix astragali, Polygonum cuspidatum, Rheum palmatum, and Salvia miltiorrhiza) and related active compounds (e.g., wogonin, artesunate, saikosaponin, astragaloside IV, and chrysophanol 8-O-beta-D-glucoside) and Chinese medicine preparations (e.g., silymarin, silibinin, kushenin, and cinobufacini), which seem effective and worthy of additional and in-depth study in treating CHB, and we have given them a brief review. We conclude that these Chinese herbal medicines exhibit significant anti-HBV activities with improved liver function, and enhanced HBeAg and HBsAg sero-conversion rates as well as HBV DNA clearance rates in HepG2 2.2.15 cells, DHBV models, or patients with CHB. We hope this review will contribute to an understanding of TCM and related active compounds as an effective treatment for CHB and provide useful information for the development of more effective antiviral drugs.

Keywords: Hepatitis B virus (HBV), chronic hepatitis B (CHB), traditional Chinese medicine (TCM), active compounds

1. Introduction

Hepatitis B virus (HBV) infection is a serious global public health problem, which can lead to liver failure, acute and chronic hepatitis, liver cirrhosis, and liver cancer. Approximately 2 billion people worldwide are reportedly infected with HBV, and more than 350 million of them are chronic carriers (1). It is estimated that worldwide more than 600,000 individuals die from HBV-related liver disease each year (2). Vaccination is considered to be the most effective way to control the spread of HBV and implementation of the HBV vaccine has led to a significant reduction in viral transmission; however, it remains highly endemic in many areas of the world, particularly in eastern Asia, India, and Pakistan (3). Currently, there are six agents approved for the treatment of chronic hepatitis B (CHB) by the US Food and Drug Administration (FDA), including interferon (interferon-alpha (IFN-α) and pegylated interferon-alpha (peg IFN-α)), nucleoside (lamivudine, entecavir, and telbivudine) and nucleotide analogues (adefovir) (4). However, their therapeutic effect is not satisfactory with obvious drug resistance and dose-dependent side effects.
Therefore, development of novel antiviral drugs and more effective therapies for the treatment of CHB are urgently needed.

Traditional Chinese medicine (TCM) has been widely used in Asia for more than two thousand years. At present, TCM serves as an established segment of the public health system in China and in recent years it has been gaining interest and acceptance as alternative or complementary medicine in Western countries. An estimated 1.5 billion people now use Chinese herbal medicine, an important category of TCM, for the treatment of various diseases including chronic HBV infection worldwide (6). In China, it is used as a treatment adjunct or alternative to anti-HBV drugs and accounts for 30% to 50% of total medicine consumption for CHB treatment (7). Because of its low cost and low toxicity, about 80% of the patients with CHB in China rely on Chinese herbal medicine (8). A number of clinical trials have been performed to assess the therapeutic efficacy and safety of Chinese herbal medicines in CHB treatment. According to the results from meta-analysis of clinical trials, they indicated that: (i) Chinese herbal medicines alone may have an equivalent or better effect when compared with interferon or lamivudine in CHB treatment as evidenced by HBeAg and HBsAg seroconversion as well as HBV DNA clearance; (ii) Chinese herbal medicines combined with interferon or lamivudine significantly enhanced the anti-viral activities of these agents; (iii) Chinese herbal medicines have a beneficial effect on improving liver function (7,8).

Although Chinese herbal medicines are widely used in the clinic in China, their active ingredients are complex and their mechanisms in CHB treatment are not clear, so that at present it is difficult for them to be popular in the world. In recent decades, as the HBV-transfected cell lines and duck HBV (DHBV) model are widely used for the study of anti-HBV drugs in vitro and in vivo, the anti-viral effects of many Chinese herbal medicines and their active ingredients have been gradually known and confirmed, which will provide evidence for developing novel antiviral drugs. Therefore, in this article, the authors review some Chinese herbal medicines, including Chinese herbal formulas, single herbs and their active ingredients, and Chinese medicine preparations, which are widely reported to have antiviral effects in basic or clinical studies. We hope this review will contribute to an understanding of Chinese herbal medicines as an effective treatment for CHB and provide useful information for the development of more effective antiviral drugs.

2. Traditional Chinese herbal formulas commonly used with anti-HBV activities

Traditional Chinese herbal formulas (or Kampo in Japanese) are a combination of compatible herbs in fixed dosages, most of which come from classical or well-known Chinese textbooks of medicine (e.g., "Shang Han Lun" and "Jin Gui Yao Lue", two classics of traditional medicine edited by Zhang Zhongjing, a well-known Chinese physician during the Han Dynasty) (9). Currently, several traditional Chinese herbal formulas, such as Xiao-Chai-Hu-Tang (also called Sho-saiko-tó in Japan), have been found to have a potentially beneficial effect for treating CHB (10). A brief outline of the antiviral pharmacology of the most commonly used traditional Chinese herbal formulas is presented below (Table 1).

2.1. Xiao-Chai-Hu-Tang

Xiao-Chai-Hu-Tang, a famous traditional Chinese herbal formula originally recorded in "Shang Han Lun", has been used to treat liver diseases especially chronic hepatitis for thousands of years in China and Japan. It consists of seven medicinal herbs (Bupleurum falcatum, Scutellaria baicalensis, Panax ginseng, Ziziphus jujube, Pinellia ternate, Zingiber officinale, and Glycyrrhiza glabra) (11). Much pharmacological research has shown that Xiao-Chai-Hu-Tang has potent anti-inflammation, anti-oxidation, immunomodulation, hepatoprotective, anti-hepatic fibrosis, and antitumor properties (12-16). Recently, a lot of basic or clinical studies have been conducted to assess the beneficial effects and safety of Xiao-Chai-Hu-Tang for CHB treatment. Chang et al. found that Xiao-Chai-Hu-Tang could inhibit the replication of HBV DNA and decrease the expression of HBsAg in HepG2 2.2.15 cells (17). Tajiri et al. found that Xiao-Chai-Hu-Tang could promote the clearance of HBeAg in children with chronic HBV infection (18). Qin et al. gave a systematic review of randomized trials on treatment of CHB using Xiao-Chai-Hu-Tang (19). Sixteen randomized trials (involving 1,601 CHB patients) were included in this review. The pooled results showed that Xiao-Chai-Hu-Tang combined with antiviral drugs (e.g., lamivudine and IFN-α) was more effective in serum loss of hepatitis B viral markers and in improving liver function compared to antiviral drugs alone. Moreover, there were no adverse effects reported in the trials regarding Xiao-Chai-Hu-Tang.

2.2. Xiao-Yao-San

Xiao-Yao-San is a famous Chinese herbal formula originally recorded in "Tai Ping Hui Min He Ji Ju Fang" (a classical Chinese medicine book of the Song Dynasty). It is a mixture of eight crude herbs (Bupleurum falcatum, Angelica sinensis, Paonia lactiflora, Atractylodes lancea, Wolfiporia cocos, Zingiber officinale, Mentha arvensis, and Glycyrrhiza uralensis) (20). This herbal prescription is reported to possess hepatoprotective, anti-inflammation, anti-oxidation, anti-cancer, and immunomodulation activities, and is commonly used in the clinic to treat functional dyspepsia, postmenopausal women with
Table 1. Traditional Chinese herbal formulas commonly used with anti-HBV activities

<table>
<thead>
<tr>
<th>Common name</th>
<th>Source</th>
<th>Composition</th>
<th>Biological activity</th>
<th>Evidence of anti-HBV activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiao-Chai-Hu-Tang</td>
<td>&quot;Shang Han Lun&quot; (the Eastern Han Dynasty (25-220 AD))</td>
<td>Includes 7 herbs: Bupleurum falcatum, Scutellaria baicalensis, Panax ginseng, Ziziphus jujube, Pinellia ternata, Zingiber officinalis, Glycyrrhiza glabra</td>
<td>Hepatoprotective, anti-hepatitis, anti-inflammation, anti-oxidation, immunomodulation, antitumor</td>
<td>In HepG2 2.2.15 cells: inhibits HBV DNA replication and HBeAg secretion; (ii) combined with antiviral drugs (e.g. lamivudine and IFN-α) exhibits more effectiveness in serum loss of HBV markers and in improving liver function</td>
<td>11-19</td>
</tr>
<tr>
<td>Xiao-Yao-San</td>
<td>&quot;Tai Ping Hui Min He Ji Ju Fang&quot; (the Song Dynasty (960-1279 AD))</td>
<td>Includes 8 herbs: Bupleurum falcatum, Angelica sinensis, Paonia lactiflora, Atractylodes lancea, Wolfiporia cocos, Zingiber officinalis, Mentha arvensis, Glycyrrhiza uralensis</td>
<td>Hepatoprotective, anti-inflammation, immunomodulation, anticancer</td>
<td>In patients: improves the negative conversion rates of HBV markers (HBeAg and HBV-DNA) and liver function</td>
<td>20-23</td>
</tr>
<tr>
<td>Long-Dan-Xie-Gan-Tang</td>
<td>&quot;Tai Ping Hui Min He Ji Ju Fang&quot; (the Song Dynasty (960-1279 AD))</td>
<td>Includes 10 herbs: Gentiana scabra, Scutellaria baicalensis, Gardenia jasminoides, Alisma plantago, Plantago asiatica, Akebia trifoliate, Rheum annua, Gynostemma pentaphyllum, Angelica sinensis, Bupleurum chinense, Glycyrrhiza uralensis</td>
<td>Anti-inflammation, anti-oxidation, hepatoprotective, immunomodulation, anti-herpetic virus, anti-HBV</td>
<td>In CCl₄-induced hepatic injury rats: improves liver function; in patients: combined with IFN-α improves the negative conversion rates of HBeAg</td>
<td>24-27</td>
</tr>
</tbody>
</table>

Recent studies have shown that Xiao-Yao-San has a potent effect on treating CHB. Xiao-Yao-San could improve the clinical symptoms (e.g., weak, inappetence, and hepatalgia) of patients with CHB. Furthermore, the patients’ liver function (ALT and AST) and liver fibrosis indexes, including hyaluronic acid (HA), laminin (LN), procollagen III peptide (P-III-P), and collagen type IV (IV-C), were improved significantly after treatment with Xiao-Yao-San (22). Furthermore, Xiao-Yao-San combined with adefovir dipivoxil could significantly improve the negative conversion rates of HBeAg and HBV-DNA in the treatment of CHB (23). Although Xiao-Yao-San has its unique advantages in treating CHB, a far larger body of literature only exists in Chinese language journals. It is reasonable to publish some well-designed, efficacy-based basic or clinical trials to evaluate the efficacy of Xiao-Yao-San in treating CHB in the future in English language journals.

2.3. Long-Dan-Xie-Gan-Tang

Long-Dan-Xie-Gan-Tang is a famous Chinese herbal formula which also originally came from "Tai Ping Hui Min He Ji Ju Fang". It was recorded to have inhibitive effects on inflammatory diseases of the liver or gall bladder. There are ten medicinal herbs in Long-Dan-Xie-Gan-Tang including Gentiana scabra, Scutellaria baicalensis, Gardenia jasminoides, Alisma plantago, Plantago asiatica, Akebia trifoliate, Rheum annua, Gynostemma pentaphyllum, Angelica sinensis, Bupleurum chinense and Glycyrrhiza uralensis. Recently, much pharmacological research has shown that Long-Dan-Xie-Gan-Tang has potent anti-inflammation, anti-oxidation, immune modulation, anti-herpetic virus, and anti-HBV properties (24,25). It is reported that Long-Dan-Xie-Gan-Tang is the most commonly prescribed Chinese herbal formula for subjects with CHB in Taiwan (25). It has a hepatoprotective effect on CCl₄-induced hepatic injury in rats with the level of serum ALT and AST decreased significantly after treatment with Long-Dan-Xie-Gan-Tang (26). In addition, Long-Dan-Xie-Gan-Tang combined with IFN-α could significantly improve the negative conversion rates of HBeAg in the treatment of CHB (27).

3. Single Chinese herbs commonly used with anti-HBV activities

In 1982, Thiyagarajan et al. confirmed Phyllanthus niruri with anti-HBV activity for the first time. Since then, the anti-HBV activity of single Chinese medicines has gradually got the attention of researchers. Many single Chinese medicines have been found to have potentially beneficial effects treating CHB. However, because the majority of herbs were administered in combination with other herbs in Chinese herbal formulas, it is not possible to determine exactly which...
individual herbs in the formulas have the greatest therapeutic potential in the treatment of CHB. Thus, based upon our review of the related papers and upon our prior knowledge and experience, we have selected some herbs (Table 2) that seem effective and worthy of additional and in-depth study, and we will give them a brief commentary below. Especially these 5 herbs (Phyllanthus niruri, Radix astragali, Polygonum cuspidatum, Rheum palmatum, and Salvia miltiorrhiza) will be introduced in detail concerning their anti-HBV activities.

3.1. Phyllanthus niruri

Phyllanthus niruri (Ye Xia Zhu or Zhen Zhu Cao) is widely distributed in most tropical and subtropical countries of the globe (e.g., China, South Asia, and America) and have long been used as traditional medicines to treat chronic liver disease, as well as a wide number of traditional ailments such as kidney disease, urinary bladder and intestinal infections, jaundice, gonorrhea, frequent menstruation, diabetes, skin ulcers, sores, swelling, and itchiness (28-30). It is reported to have many pharmacological effects including antiviral, antibacterial, antihepatotoxic, antihypertensive, and anticancer properties (31,32). Many active compounds, such as gallic acid, geraniin, quercetin glucoside, and quercetin rhamnoside, have been identified from Phyllanthus niruri (32). Since Phyllanthus niruri has been used to treat chronic liver disease for thousands of years, a lot of basic or clinical studies have been conducted recently to assess the beneficial effects and safety of Phyllanthus niruri for CHB treatment. Lam et al. showed that the ethanolic extract of Phyllanthus niruri exhibited potent antiviral activity against HBV (33). It produced a suppressive effect on HBsAg secretion, HBsAg mRNA expression, and HBV replication in vitro. Liu et al. conducted a systematic review of randomized trials on the treatment of CHB using Phyllanthus niruri (34). Twenty-two randomized trials \( (n = 1,947) \) were included in this review. The combined results showed that: (i) Phyllanthus niruri had a positive effect on clearance of serum HBsAg compared with placebo or no intervention; (ii) There was no significant difference on clearance of serum HBsAg, HBeAg and HBV DNA between Phyllanthus niruri and IFN; (iii) There was a better effect of Phyllanthus niruri plus IFN combination

<table>
<thead>
<tr>
<th>Common name</th>
<th>Name in Chinese</th>
<th>Major active compounds</th>
<th>Biological activity</th>
<th>Evidence of anti-HBV activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phyllanthus niruri</td>
<td>Ye Xia Zhu, Zhen Zhu Cao</td>
<td>Gallic acid, ellagic acid, geraniin, quercetin glucoside,</td>
<td>Antiviral, antibacterial, antihypertensive, anticancer</td>
<td>In HepG2 2.2.15 cells: inhibits HBsAg secretion; HBsAg mRNA</td>
<td>33,34</td>
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<tr>
<td></td>
<td></td>
<td>quercetin rhamnoside</td>
<td></td>
<td>expression, and HBV replication; In patients: combined with IFN</td>
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<td>exhibits more effectiveness on the clearance of serum HBsAg, HBeAg</td>
<td></td>
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<tr>
<td>Radix astragali</td>
<td>Huang Qi</td>
<td>Astragaloside, calycosin-7-O-beta-D-glucoside, calycosin,</td>
<td>Immunomodulation, antiviral, anti-fatigue, antiviral</td>
<td>In patients: improves the negative conversion rates of HBeAg and</td>
<td>35-37</td>
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<tr>
<td></td>
<td></td>
<td>formononetin</td>
<td></td>
<td>HBV DNA</td>
<td></td>
</tr>
<tr>
<td>Polygonum cuspidatum</td>
<td>Hu Zhang</td>
<td>Resveratrol, polydatin</td>
<td>Antiviral, antimicrobial, hepatoprotective, neuroprotective, cardioprotective</td>
<td>In HepG2 2.2.15 cells: inhibits HBeAg secretion and HBV DNA</td>
<td>8,38-40</td>
</tr>
<tr>
<td>Rheum palmatum</td>
<td>Du Huang</td>
<td>Emodin, rhein, sennoside A, chrysophanol</td>
<td>Antiviral, antibacterial</td>
<td>In HepG2 2.2.15 cells: inhibits HBV DNA production and HBsAg</td>
<td>38,41-44</td>
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<tr>
<td></td>
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<td></td>
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<td>secretion; In DHBV models: inhibits HBV DNA production</td>
<td></td>
</tr>
<tr>
<td>Salvia miltiorrhiza</td>
<td>Dan Shen</td>
<td>Tanshinone, salvianic acid, protocatechuic aldehyde,</td>
<td>Antiviral, antibacterial, cardioprotective, anti-thrombosis</td>
<td>In patients: improves the negative conversion rates of HBeAg and</td>
<td>46-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cryptotanshinone</td>
<td></td>
<td>liver function</td>
<td></td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>Jiang Huang</td>
<td>Curcumin, demethoxycurcumin, bisdemethoxycurcumin</td>
<td>Antiviral, anti-inflammation, anti-oxidation, anticancer</td>
<td>In HepG2 2.15 cells: suppresses the secretion of HBsAg, the production of HBV particles and the level of intracellular HBV RNAs</td>
<td>35,49</td>
</tr>
<tr>
<td>Glossogyne tenuifolia</td>
<td>Lu Jiao Cao</td>
<td>Luteolin-7-O-beta-D-glucopyranoside, luteolin</td>
<td>Anti-inflammation, antiviral, antipyretic, hepatoprotective</td>
<td>In PLC/PRF/5 cells: inhibits HBsAg secretion</td>
<td>50</td>
</tr>
<tr>
<td>Arenaria kansuensis</td>
<td>Xue Ling Zhi</td>
<td>Arenarine, tricin, beta-sitosterol-3beta-D-glucopyranoside,</td>
<td>Antiviral, immunomodulation, hepatoprotective</td>
<td>In HepG2 2.15 cells: inhibits HBsAg and HBeAg secretion</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 2. Single Chinese herbs commonly used with anti-HBV activities

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on clearance of serum HBeAg and HBV DNA than IFN alone; (iii) No serious adverse event was reported.

3.2. Radix astragali

Radix astragali (Huang Qi) has been used in China for thousands of years and is one of the most widely prescribed Chinese herbs in many formulas. The major active constituents of Radix astragali are saponins and flavonoids, such as astragaloside, calycosin-7-O-beta-D-glucoside, calycosin, and formononetin. It is traditionally considered to be a tonic that can improve the functioning of the lungs, adrenal glands, and the gastrointestinal tract, increase metabolism, promote healing, and reduce fatigue (35,36). Moreover, it can balance serum hormone levels and improve liver function in patients with chronic viral hepatitis (37). A clinical evaluation of Radix astragali was performed in 208 patients with CHB (37). The treatment group (n = 116) was treated with the Radix astragali compound (containing Radix astragali and adjuvant components), and the control group (n = 92) was treated with regular drugs used for viral hepatitis. The results indicated that negative conversion rates of HBeAg and HBV DNA were significantly higher in the treatment group than in the control group.

3.3. Polygonum cuspidatum

Polygonum cuspidatum (Hu Zhang), as an herbaceous perennial plant, is widely distributed in the world and has been used as folk medicine in countries such as China, Japan and Korea for thousands of years. It is frequently prescribed by TCM practitioners for the treatment of hepatitis, cough, jaundice, amenorrhea, leukorrhea, arthralgia, hyperlipidemia, scalding and bruises, snake bites, and carbuncles, etc. (38). The major active compounds isolated from this herb include resveratrol, polydatin, and anthraquinones (e.g., emodin and its glycoside) (39). Recent pharmacological and clinical studies have indicated that Polygonum cuspidatum has antiviral (e.g., HBV and HIV), antimicrobial, hepatoprotective, neuroprotective, and cardioprotective functions (39,40). It is also reported that Polygonum cuspidatum is widely used for treating CHB. Zhang et al. published a review to summarize and critically meta-analyze the results of randomized, controlled, clinical trials of TCM formulations reported from China in 1998-2008 for treatment of CHB. They found that Polygonum cuspidatum is ranked in the top five of individual herbs used most frequently in TCM formulations for CHB (8). Chang et al. found that the water extract of Polygonum cuspidatum at higher concentrations (30 μg/mL) could inhibit the expression of HBeAg. Furthermore, the ethanol extract of Polygonum cuspidatum could inhibit the production of HBV DNA dose-dependently with an effective minimal dosage (10 μg/mL) (40).

3.4. Rheum palmatum

Rheum palmatum (Da Huang) is an important Chinese medicinal herb with a long history of over 2,000 years and has been commonly used as an antibacterial or laxative agent in treating gastroenteritis and viral diseases (38). About 200 chemical compounds have been isolated or identified in Rheum palmatum, among which anthraquinone and its derivatives (e.g., emodin, rhein, sennoside A, and chrysophanol) are considered as the main active ingredients (41). Recent pharmacological and clinical studies have indicated that Rheum palmatum and its active ingredients have showed activities against some viruses including vesicular stomatitis virus, herpes simplex virus types 1 and 2, parainfluenza, vaccinia virus, human cytomegalovirus and poliovirus (42). It is also reported that Rheum palmatum could inhibit HBV. Both the aqueous extract and ethanol extract of Rheum palmatum demonstrated inhibitory effects on HBV DNA production and HBsAg expression in HepG2.2.15 cells (42,43). Furthermore, in DHBV models, the aqueous extract of Rheum palmatum showed suppression of plasma HBV DNA levels and HBV DNA polymerase activity (44).

3.5. Salvia miltiorrhiza

Salvia miltiorrhiza (Dan Shen) was originally recorded in "Shen Nong Ben Cao Jing" (a classical Chinese herbal medicine book of the Dong-Han Dynasty). As a promoting blood circulation and removing blood stasis herb of the nontoxic superior class, it has been widely used for more than 2000 years to prevent and treat various human diseases, such as hepatitis, coronary artery disease, apoplexy, tumor growth and immunological disorders (45). Currently, there are numerous pharmaceutical dosage forms (e.g., tablets, capsules, granules, injections, and oral liquids) of Chinese medicine preparations containing Salvia miltiorrhiza, such as Fufang Dan Shen tablet, Dan Shen injection, and Fufang Dan Shen dripping pills, which are commercially widely available for use in clinics in China (38). According to the pharmacological investigations, the major active constituents of Salvia miltiorrhiza can be divided into two groups: the water soluble phenolic acids such as, salvianic acid, protocatechuic aldehyde, rosemarinic acid and salvianolic acid B, and the lipophilic tanshinones such as, tanshinone I, dihydrotanshinone I, cryptotanshinone, tanshinone IIA, tanshinone IIB and hydroxtanshinone (46). According to pharmacological and clinical studies,
Salvia miltiorrhiza and its active constituents are not only used in coronary artery disease but also widely used for treating CHB. In a clinical evaluation, 30 patients with CHB were treated with Salvia miltiorrhiza (47). After 3 months of treatment, the negative conversion rate of HBeAg was 16.7%. A follow up of 3 and 9 months after the end of treatment showed the negative conversion rates of HBeAg were 22.7% and 25.0%, respectively. Ye et al. found that different dosages of Salvia miltiorrhiza injection (Dan Shen injection, 8 mL, 16 mL, and 24 mL) could improve the clinical symptoms and significantly reduce the level of ALT, total bilirubin (TBIL), and liver fibrosis indexes (pro-collagen type III (PC III), collagen type IV (IV-C) and hyaluronic acid (HA)) in hepatitis B cirrhosis patients. Furthermore, the large dosage (24 mL) of Salvia miltiorrhiza injection had the best effect treating the HBV-induced cirrhosis patients, particularly in patients with compensated cirrhosis (48).

3.6. Others

Except for the above 5 herbs, we will give a brief commentary on some other Chinese herbs commonly used for treating CHB. Curcuma longa (Jiang Huang), a rhizomatous herbaceous perennial plant of the ginger family, has been used for treating various liver diseases caused by HBV in Asia for many years with antiviral, anti-inflammation, and anti-oxidation activities (35,49). Kim et al. found that the aqueous extract of Curcuma longa could suppress the secretion of HBsAg, the production of HBV particles and the level of intracellular HBV RNAs in HepG2.2.15 cells (49). They also found that the anti-HBV activity of Curcuma longa was mediated through enhancing the cellular accumulation of p53 protein by trans-activating the transcription of the p53 gene as well as increasing the stability of p53 protein. Glossogyne tenuifolia (Lu Jiao Cao) is a special medicinal plant of the compositae family in the Pescadores Islands. It has been shown to exhibit good anti-inflammatory and antiviral activity, as a traditional antipyretic and hepatoprotective herb used in Chinese medicine. Wu et al. found that Glossogyne tenuifolia had potent anti-HBV effects on the human hepatocellular carcinoma cell line PLC/PRF/5 (30). Glossogyne tenuifolia exhibited a dose-dependent inhibition of the release of HBsAg by repressing the expression of HBsAg with an IC_{50} of 0.093 mg/mL. Arenaria kansuensis (Xue Ling Zhi) is from the highest elevation for flowering green plants in the world. It belongs to the family Caryophyllaceae and is mainly located in the Qinghai-Tibet Plateau near the permanent snowline around 4,700 to 5,500 meters above sea level. Arenaria kansuensis has been shown to exhibit good antiviral and immunomodulation activity. Tang et al. found that both the ethanol extract and aqueous extract of Arenaria kansuensis could inhibit the release of HBsAg and HBeAg in HepG2.2.15 cells (51). Moreover, the aqueous extract of Arenaria kansuensis exhibited more obvious anti-HBV activity with lower toxicity than that of the ethanol extract. The maximum inhibition rates of the aqueous extract of Arenaria kansuensis on the levels of HBsAg and HBeAg at 96 h were 52.5% and 72.8%, respectively.

4. The active compounds of Chinese medicines commonly used with anti-HBV activities

Although Chinese medicines play an important role in drug discovery and human health, the actual value of them has not been fully recognized worldwide due to their complex components and uncontrollable quality. In recent years, with the developing modernization of TCM and continuing emergence of new theories, methods and techniques, very rapid and significant development has been achieved in the pharmacology of TCM. Many active compounds of Chinese medicines have been found and their activities have been studied. Some active compounds isolated from Chinese herbal medicines have been reported to possess anti-HBV activities. Zuo et al. gave a summary of the active compounds of Chinese herbal medicines with anti-HBV activities (52). They reported that these anti-HBV active compounds mainly included alkaloids, flavonoids, terpenoids, glycosides, lignans, plant polyphenols, saccharides, and so on. Based upon our review of the related papers, we have selected some active compounds of Chinese herbal medicines with anti-HBV activities (Table 3) that seem effective and worthy of additional and in-depth study in treating CHB, and we will give them a brief commentary below.

4.1. Alkaloids

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms, which can be isolated from many Chinese herbal medicines. Matrine, oxymatrine, sophoridine and sophocarpine are the major bioactive alkaloids extracted from Chinese herbal medicine Sophora flavescens (Ku Shen) (28). Ye et al. found that the aqueous extract of Sophora flavescens possessed anti-DHBV activity (53). Furthermore, they found the above four alkaloids (matrine, oxymatrine, sophoridine and sophocarpine) were identified in the duck serum, of which oxymatrine, sophoranol and matrine were the effective substances for anti-HBV activity in aqueous extracts of Sophora flavescens. Ma et al. investigated the anti-HBV activity of the combination of 3TC and either oxymatrine or matrine on HepG2 2.2.15 cells (54). They found that the combination of 3TC (30 μg/mL) with oxymatrine (100 μg/mL) or matrine (100 μg/mL) showed significant inhibitory effects on the secretion of HBsAg, HBeAg, and HBV-DNA into culture media, that were higher

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Table 3. Typical active compounds of Chinese medicines commonly used with anti-HBV activities

<table>
<thead>
<tr>
<th>Category</th>
<th>Typical compounds</th>
<th>Source</th>
<th>Biological activity</th>
<th>Evidence of anti-HBV activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Oxytetracycline</td>
<td><em>Sophora flavescens</em> (Ku Shen)</td>
<td>Antiviral, anti-inflammatory</td>
<td>In HepG2.2.15 cells: inhibits the secretion of HBsAg, HBeAg, and HBV-DNA; In patients: combined with lamivudine exhibits higher HBeAg/anti-HBe seroconversion rate</td>
<td>28,53-58</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Wogonin</td>
<td><em>Scutellaria baicalensis</em> (Huang Qin)</td>
<td>Antiviral, hepatoprotective</td>
<td>In MS-G2 cells: suppresses HBsAg secretion and HBV DNA production; In HepG2.2.15 cells: inhibits the secretion of HBsAg, HBeAg, and HBV-DNA; In DHBV models: inhibits DHBV DNA polymerase; In human HBV-transgenic mice: inhibits plasma HBsAg levels</td>
<td>28,60,61</td>
</tr>
<tr>
<td>Glycoside</td>
<td>Saikosaponin c</td>
<td><em>Bupleuri radix</em> (Chai Hu)</td>
<td>Anti-hepatitis, anti-nephritis, anti-hepatoma, anti-inflammatory, immunomodulation, antibacterial</td>
<td>In HepG2 2.2.15 cells: inhibits HBsAg secretion and HBV DNA production</td>
<td>68</td>
</tr>
<tr>
<td>Glycoside</td>
<td>Astragaloside IV</td>
<td><em>Radix astragali</em> (Huang Qi)</td>
<td>Antiviral, anti-oxidation, anti-inflammatory, anti-cancer, immunomodulation, regulation of the calcium balance</td>
<td>In HepG2 2.2.15 cells: suppresses the secretion of HBsAg and HBeAg; In DHBV models: reduces serum DHBV DNA levels</td>
<td>36,41, 69</td>
</tr>
</tbody>
</table>

than or equivalent to the use of 3TC alone at 100 μg/mL. Chen et al. conducted a study to investigate the effect of lamivudine, IFN-α and the combination of lamivudine and oxytetracycline on surviving hepatic failure patients with HBV infection (55). They found that the HBeAg/anti-HBe seroconversion rate in patients treated with the combination of lamivudine and oxytetracycline was lower than that in patients treated with IFN-α, but was higher than that in patients treated with lamivudine alone. Moreover, lamivudine or lamivudine in combination with oxytetracycline significantly inhibited the intrahepatic inflammatory activities of subacute or acute-on-chronic hepatic failure survivors. Li et al. prepared liposome-encapsulated matrine and studied its anti-HBV effect on HepG2 2.2.15 cells and DHBV models (56). They found that liposome-encapsulated matrine could evidently inhibit the replication of hepatitis B virus in vitro and in vivo, and its anti-HBV effect was better than that of matrine. Nie et al. conducted a series of studies to investigate the anti-HBV activities of sophoridine and sophocarpine in HepG2 2.2.15 cells (57,58). The results showed that sophoridine could significantly inhibit the secretion of HBsAg, HBeAg, and pre-antigen S1. When the HepG2 2.2.15 cells were treated with 0.001 mmol/L sophoridine for 9 days, the inhibition rate of the secretion of pre-antigen S1 was 62.20%. Furthermore, they made a comparison between sophocarpine and lamivudine on inhibiting the secretion of HBeAg. The results showed that the inhibition rate of the secretion of HBeAg in the sophocarpine group was higher than that in the lamivudine group. In summary, these alkaloids are much cheaper than INF-α for the treatment of CHB, which makes them attractive therapeutic options and warrants further clinical and basic trials. Moreover, if some other alkaloids possess anti-HBV activity they need further study.

4.2. Flavonoids

Flavonoids are a group of plant secondary metabolites with variable phenolic structures and can be found in many Chinese herbal medicines. They are usually divided into seven classes including flavonols, flavones, flavanones, flavononol, flavanols, isoflavones, and anthocyanidins. Some of these flavonoids have been reported to have activities in treatment of various diseases such as heart disease, cancer, and virus infection (e.g., HBV and HCV) as well as potential protective activity against artificially induced-liver damage (59).

Wogonin is a flavone derived from the Chinese herbal medicine *Scutellaria baicalensis* (Huang Qin), which has been widely used for treatment of inflammatory and liver diseases for thousands of years in Asia (28). In recent years, wogonin has been found to have anti-HBV activity. Huang et al. found that
wogonin could suppress HBsAg secretion and HBV DNA production in a HBV transfected liver cell line (MS-G2) without cytotoxicity (60). Guo et al. found that wogonin effectively suppressed the secretion of HBsAg and HBeAg with an IC$_{50}$ (drug concentration inducing 50% inhibition in HBsAg or HBeAg or HBV DNA release) of 4 μg/mL and reduced HBV DNA levels in a dose-dependent manner in HepG2.2.15 cells (61). They also found that DHBV-infected ducks wogonin dramatically inhibited DHBV DNA polymerase with an IC50 of 0.57 μg/mL, and significantly improved duck liver function in histopathological evaluations. In addition, wogonin significantly reduced plasma HBsAg levels in human HBV-transgenic mice.

Ellagic acid, a flavonoid isolated from Phyllanthus niruri, exhibited a unique anti-HBV function in a HBV infected cell line and in HBeAg transgenic mice. It has been found to effectively block HBeAg secretion in HepG2 2.2.15 cells with an IC50 of 0.07 μg/mL, but been found to effectively block HBeAg secretion in infected cell line and in HBeAg transgenic mice. It has found that, compared with saikosaponins a and d, saikosaponin c showed a significant effect on inhibiting HBsAg secretion with an IC50 of 0.2 μmol/L and reduced the HBV DNA level with an IC50 of 0.5 μmol/L. In addition, although the anti-HBV effect of artemesate was not as good as lamivudine which inhibited HBsAg secretion with an IC50 of 0.2 μmol/L and reduced the HBV DNA level with an IC50 of 0.3 μmol/L, and by combining both agents, a synergetic anti-HBV effect could be observed (67). This warrants further evaluation of artemisinin and artemesate as antiviral agents against HBV infection.

4.4. Glycoside

Glycosides are the major active ingredients isolated from Chinese herbal medicines. They are rich with candidate compounds for drug discovery and possess many pharmaceutical functions including antibacterial, anti-neoplastic, antiviral, and so on. Recently, some of the glycosides have been reported to have anti-HBV activities.

*Artemisia annua* (Qing Hao) has been used as a Chinese herbal medicine to treat fever and malaria in China for thousands of years. Artemisinin is a family of sesquiterpene trioxane lactones derived from *Artemisia annua* and it has been identified as the best medicine with the highest efficiency, the most effective and the lowest toxicity in treating ague, which represents one of the great events in medicine in the latter third of the 20th Century (66). In recent years, artemisinin and its derivative artemesate has been reported to have an antiviral effect against HBV. Both artemisinin and artemesate inhibit HBsAg secretion and HBV DNA production in HepG2 2.2.15 cells at concentrations at which host cell viability was not affected, and artemesate had better anti-HBV effects than artemisinin. Artesenate inhibited HBsAg secretion with an IC$_{50}$ of 2.3 μmol/L and reduced the HBV DNA level with an IC$_{50}$ of 0.5 μmol/L. In addition, although the anti-HBV effect of artemesate was not as good as lamivudine which inhibited HBsAg secretion with an IC$_{50}$ of 0.2 μmol/L and reduced the HBV DNA level with an IC$_{50}$ of 0.3 μmol/L, and by combining both agents, a synergic anti-HBV effect could be observed (67). This warrants further evaluation of artemisinin and artemesate as antiviral agents against HBV infection.

4.3. Terpenoids

Terpenoids are the largest and most widespread class of secondary metabolites. They can be found in all classes of living things especially in Chinese herbal medicines. Terpenoids are a rich reservoir of candidate compounds for drug discovery and they are under investigation for antibacterial, anti-neoplastic, antiviral and other pharmaceutical functions. Recently, some of these terpenoids have been reported to have anti-HBV activities.

*Artemisia annua* (Qing Hao) has been used as a Chinese herbal medicine to treat fever and malaria in China for thousands of years. Artemisinin is a family of sesquiterpene trioxane lactones derived from *Artemisia annua* and has been identified as the best medicine with the highest efficiency, the most effective and the lowest toxicity in treating ague, which represents one of the great events in medicine in the latter third of the 20th Century (66). In recent years, artemisinin and its derivative artemesate has been reported to have an antiviral effect against HBV. Both artemisinin and artemesate inhibit HBsAg secretion and HBV DNA production in HepG2 2.2.15 cells at concentrations at which host cell viability was not affected, and artemesate had better anti-HBV effects than artemisinin. Artesenate inhibited HBsAg secretion with an IC$_{50}$ of 2.3 μmol/L and reduced the HBV DNA level with an IC$_{50}$ of 0.5 μmol/L. In addition, although the anti-HBV effect of artemesate was not as good as lamivudine which inhibited HBsAg secretion with an IC$_{50}$ of 0.2 μmol/L and reduced the HBV DNA level with an IC$_{50}$ of 0.3 μmol/L, and by combining both agents, a synergic anti-HBV effect could be observed (67). This warrants further evaluation of artemisinin and artemesate as antiviral agents against HBV infection.

4.4. Glycoside

Glycosides are the major active ingredients isolated from Chinese herbal medicines. They are rich with candidate compounds for drug discovery and possess many pharmaceutical functions including antibacterial, anti-neoplastic, antiviral, and so on. Recently, some of the glycosides have been reported to have anti-HBV activities.

*Bupleuri Radix* (Chai Hu) is one of the most important traditional Chinese crude drugs for treating hepatitis, malaria and intermittent fever. Saikosaponins, the main active constituents of *Bupleuri Radix*, have been shown to possess various biological activities, specifically anti-hepatitis, anti-nephritis, antinephritis, anti-inflammation, immunomodulation, and antibacterial effects. Chiang et al. conducted a study to evaluate the cytotoxicity and anti-HBV activities of saikosaponins a, c and d. The results showed that, compared with saikosaponins a and d, saikosaponin c showed a significant effect on inhibiting HBsAg secretion and HBV DNA production without cytotoxicity in HepG2 2.2.15 cells (68).

Astragaloside IV, a cycloartane-type triterpene glycoside, is one of the major active constituents of *Radix astragali*. It is used as a marker compound for quality control of *Radix astragali* in the Chinese Pharmacopoeia (2005 version), and has various
pharmacological activities including antiviral, anti-oxidation, anti-inflammation, anti-cancer, immunomodulation, regulation of the calcium balance, and so on (69). Wang et al. conducted a study to investigate the anti-HBV activities of astragaloside IV in HepG2 2.2.15 cells and DHBV-infected ducklings (36). The results showed that astragaloside IV effectively suppressed the secretion of HBV antigens with inhibition rates of 23.6% for HBsAg and 22.9% for HBeAg at 100 μg/mL after 9 days of treatment in HepG2 2.2.15 cells. The inhibitory activity of astragaloside IV on the secretion of HBV antigens is more potent than that of 3TC without significant cytotoxicity. Furthermore, in DHBV-infected ducklings, astragaloside IV caused 64.0% inhibition at 120 mg/kg on serum DHBVs after 10 days of treatment and also reduced serum DHBV DNA levels. In summary, these results demonstrated that astragaloside IV possessed potent anti-HBV activity.

In addition, the compound chrysophanol 8-O-beta-D-glucoside isolated from *Rheum palmatum* was found to display strong anti-HBV activity. Li et al. isolated six anthraquinones from the ethanol extract of *Rheum palmatum* by using reverse phase-high performance liquid chromatography (RP-HPLC) and evaluated their anti-HBV activities (41). The results showed that five free anthraquinones showed weak or slightly inhibitory activities against HBV, and the only combined anthraquinone chrysophanol 8-O-beta-D-glucoside exhibited significant activity against HBV DNA production with an IC$_{50}$ of 36.98 μg/mL and antigens expression with an IC$_{50}$ value of 237.4 μg/mL for HBsAg and 183.41 μg/mL for HBeAg. Furthermore, they observed that chrysophanol 8-O-beta-D-glucoside is a potential inhibitor of HBV-DNA polymerase. Therefore, they concluded that the combined anthraquinone chrysophanol 8-O-beta-D-glucoside was the major active compound in the ethanol extract of *Rheum palmatum* and could be a promising candidate for the development of new anti-HBV drugs in the treatment of HBV infection.

5. The Chinese medicine preparations commonly used with anti-HBV activities

Chinese medicine preparations are a form of Chinese medicines that are isolated from single herbs or traditional herbal formulas and that are prepared using modern advanced pharmaceutical technology. There are various dosage forms including injections, tablets, pills, capsules, and liquids. Compared to traditional decoctions, Chinese medicine preparations are safer, more effective, and easier to use. Thus, Chinese medicine preparations are becoming increasingly popular in China and are attracting worldwide attention. Based upon our review of the related papers, we have selected some Chinese medicine preparations with anti-HBV activities (Table 4) which have been approved by the State Food and Drug Administration (FDA) of China and seem effective and worthy of additional and in-depth study, and we will give them a brief commentary below.

### 5.1. Silymarin and Silibinin

*Silybum marianum* or milk thistle (Shui Fei Ji), a member of the Asteraceae family, is one of the most ancient and extensively used medicinal plants for its beneficial effects on liver and other organs (38). Silymarin is a standardized extract from the fruits and seeds of *Silybum marianum* and it is composed of a mixture of several flavonolignans, with the most important being silybinin, isosilybinin, dehydroisosilybinin, silidianin and silichristin. Some studies demonstrate that silymarin possesses powerful antioxidant and hepatoprotective activities. It has beneficial effects on various hepatic disorders, including cirrhosis, fatty liver hepatitis, viral hepatitis, and so on (70). Recently, some Chinese medicine preparations containing silymarin (e.g., Silymarin tablet and Silibinin capsule) have been approved for the treatment of hepatic diseases such as CHB in China. Xie et al. conducted a study to evaluate

<table>
<thead>
<tr>
<th>Common name</th>
<th>Source</th>
<th>Dosage form</th>
<th>Biological activity</th>
<th>Evidence of anti-HBV activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silymarin</td>
<td><em>Silybum marianum</em> (Shui Fei Ji)</td>
<td>Tablet, capsule</td>
<td>Antioxidant, hepatoprotective, antiviral</td>
<td>In patients: improves liver function</td>
<td>70,71</td>
</tr>
<tr>
<td>Silibinin</td>
<td><em>Silybum marianum</em> or milk thistle (Shui Fei Ji)</td>
<td>Tablet, capsule</td>
<td>Antioxidant, hepatoprotective, antiviral</td>
<td>In patients: prevents liver necrosis and repairs liver cells</td>
<td>70,72</td>
</tr>
<tr>
<td>Kushenin</td>
<td><em>Sophora flavescens</em> (Ku Shen)</td>
<td>Injection, tablet, capsule</td>
<td>Antiviral, anti-fibrosis, anti-arthrythmia, antibacterial, immunomodulation, enhancing leukocytes</td>
<td>In patients: improves the level of ALT, the negative rate of HBV DNA and HBeAg, and the positive rate of HBeAb</td>
<td>73,74</td>
</tr>
<tr>
<td>Cinobufacini</td>
<td><em>Bufo bufo gargarizans</em> Cantor</td>
<td>Injection, tablet, oral solution, capsule</td>
<td>Antiviral, antancer</td>
<td>In HepG2 2.2.15 cells: inhibits the secretion of HBsAg, HBeAg, and HBcrAg; In patients: improves the level of ALT and the negative conversion rates of HBV DNA and HBeAg combined with IFN-α 2b</td>
<td>75,78,79</td>
</tr>
</tbody>
</table>
the efficacy of Silymarin tablets on patients with CHB (71). After treatment for 12-weeks, ALT and AST levels decreased significantly in the Silymarin tablet group compared to the control group, which indicated that Silymarin tablets might be an effective agent for CHB treatment. Guo et al. conducted a study to observe the effect of Silibinin capsules on patients with CHB (72). The results showed that the total effective rate and symptom normalization of the Silibinin capsule group improved significantly compared to the control group with ALT, AST and TBIL levels decreased significantly after treatment for three months. These indicated that Silibinin capsules could effectively prevent necrosis of liver cells and repair liver cells in CHB treatment.

5.2. Kushenin

Kushenin is a mixed alkaloid of oxymatrine with a little oxysophocarpine, extracted from the root of Chinese herbal medicine *Sophora flavescens*. It has various pharmacological activities including antiviral, anti-fibrosis, anti-arrhythmia anti-inflammation, antibacterial, immunomodulation, enhanced leukocytes, and so on (73). Nowadays, many dosage forms containing kushenin, such as injection, tablets, and capsules, have been prepared and approved for treatment of CHB. Yu et al. conducted a study to investigate the effect of kushenin on patients with CHB (74). In this study, 196 patients were randomly divided into four groups (kushenin group, kushenin + arabinofuranosyl adenine monophosphate (Ara-AMP) group, IFN-α 1b group, and glucose group), and the levels of ALT, AST and viral markers were observed. After treatment for 30 days, the improvement on the level of ALT, the negative rate of HBV DNA and HBeAg, and the positive rate of HBeAb were similar in the kushenin group, kushenin + Ara-AMP group, and IFN-α 1b group, which were better than that of glucose group (P < 0.05). After 12 months follow up, the total effective rates were 40.8%, 60.8% and 43.1% in the kushenin group, kushenin + Ara-AMP group, and IFN-α 1b group, respectively. These indicated kushenin might have better long term efficacy for treating CHB.

5.3. Cinobufacini

Cinobufacini (Huachansu), an aqueous extract from the skin and parotid venom glands of the toad (*Bufo bufo gargarizans* Cantor) that contains Chansu which has been widely used in China as an anodyne, cardiotonic, antimicrobial, local anesthetic, and antineoplastic agent for thousands of years (35,75). Pharmacological studies demonstrate that the major active constituents of cinobufacini are bufodienolides (which primarily include bufalin, cinobufagin, resibufogenin, bufotalin, and Lumichrome), biogenic amines, alkaloids, peptides, and proteins (73). Recently, many dosage forms containing cinobufacini, such as injection, tablets, oral solution, and capsules, have been prepared and approved by the Chinese State Food and Drug Administration (SFDA) (ISO9002) and widely used in clinical cancer and CHB therapy in China (76). Our research team has committed to the anti-cancer and anti-HBV activities of cinobufacini for several years. We found that cinobufacini and its active compounds (bufalin and cinobufagin) could induce human hepatocellular carcinoma (HCC) cells apoptosis via Fas- and mitochondria-mediated pathways (75,77). We also found that after treatment for 6 days in HepG2 2.2.15 cells, cinobufacini at 1 μg/mL effectively inhibited the secretion of HBsAg, HBeAg, and HBcAg by 29.58, 32.87, and 42.52%, respectively, which was more potent than lamivudine (100 g/mL) (78). Furthermore, some clinical studies have indicated that cinobufacini used alone or in combination with other anti-HBV agents (e.g., IFN-α and lamivudine) possesses a significant effect on patients with CHB. Yu et al. conducted a study to observe the efficacy of the combination of cinobufacini and IFN-α 2b on patients with CHB (79). In this study, 142 patients were randomly divided into two groups (cinobufacini + IFN-α 2b group and IFN-α 2b group). After treatment for 48 weeks, the level of ALT and the negative conversion rates of HBV DNA and HBeAg were improved significantly in the cinobufacini + IFN-α 2b group compared to the IFN-α 2b group (P < 0.05). These findings indicated that IFN-α combined with cinobufacini could effectively improve liver function and inhibit HBV DNA replication.

6. Conclusion

Given the significant public health hazard of CHB and the high rates of non-response to interferon and nucleoside antiviral agents, continuous development of agents to treat HBV infections is urgently needed. Over a long period in clinical practice and with progress in basic research, especially advanced and interdisciplinary technology and methodology, the effectiveness and beneficial contribution of Chinese herbal medicines on CHB have been gradually discovered and confirmed, which will provide evidence for development of novel antiviral drugs. Based upon our review of the related papers and upon our prior knowledge and experience, we have selected some Chinese herbal medicines (including Chinese herbal formulas, single herbs and related active compounds, and Chinese medicine preparations) that seem effective and worthy of additional and in-depth study in treating CHB, and we have given them a brief review. According to basic and clinical studies, we conclude that these Chinese herbal medicines exhibit significant anti-HBV activities which improve liver function, and enhance HBeAg and HBsAg sero-conversion rates as well as HBV
DNA clearance rates in HepG2 2.2.15 cells, DHBV models, and patients with CHB. We hope this review will contribute to an understanding of Chinese herbal medicines as an effective treatment for CHB and provide useful information for the development of more effective antiviral drugs. However, more information is needed regarding anti-HBV Chinese herbal medicines, including preparation, standardization, identification of active ingredients, and toxicological evaluation. Moreover, further investigation in well-designed trials with a better understanding of mechanisms, therapeutic effects, and the safety profile, will be helpful for developing effective anti-HBV Chinese medicines.

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