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My Bookmarks

Menu:

› Epidemiology
› Virology
› Diagnostic testing and interpreting
› Prevention
› Clinical assessment
› Treatment and management
› The role of complementary medicine in hepatitis B
› Liver disease and HCC
› Pregnancy, children, co-infection and immunosuppression
› Occupational health: privacy and confidentiality

The role of complementary medicine in hepatitis B

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KEY POINTS

- Complementary medicines (CMs) are used by many patients with chronic liver disease and discussion of their use should be a part of routine clinical care.
- Some studies have linked vitamin D status to control of hepatitis B virus (HBV) infection and markers of response including alanine aminotransferase (ALT) levels. Vitamin D supplementation should be discussed in those with documented vitamin D deficiency as supplementation may assist with the efficacy of and response to antiviral treatment.
- In most clinical settings, apart from the specific situation of vitamin D deficiency, there are no convincing data that CMs or treatments alter the course of the illness significantly.
- Recent studies have shown certain activities for a range of herbal products, including anti-inflammatory, antifibrotic, anti-oxidant anticancer, immunomodulatory and antiviral activities. However, more work is needed in clinical situations before the use of these individual agents can be recommended.
- Much of the fear of toxicity relating to herbal products is based on studies that have been poorly carried out or reported. Use of the Roussel Uclaf Causality Assessment Method (RUCAM) to assess causality of drug-induced liver injury is recommended for clinicians to accurately assess hepatotoxicity.

Introduction

Complementary medicine (CM) is used by a large proportion of the Australian community, with more than half the population reporting use in 2004 (1) and 2005 (2). The estimated annual expenditure on CM products by Australians was \$1.86 billion, whereas the total national expenditure on CM (including visits to CM practitioners and the use of CM products) was about \$4.3 billion (2). This means that more than half of out-of-pocket health-care costs in Australia were spent on CM (2). Of interest, survey estimates of the 5.3 million Australians living with chronic illness found that approximately 1.3 million of those were using CM specifically to treat their chronic illness (3).

The increasing use of CM is occurring in the absence of convincing evidence of efficacy of various treatments, nevertheless, CM in liver disease is steeped in tradition, cultural belief systems and ancient prescribing patterns. Patients using CM may experience an improvement in symptoms and wellbeing while taking these products.

Complementary medicine manufacturers in Australia require certification by the Australian Therapeutic Goods Administration (TGA) to manufacture therapeutic goods under Good Manufacturing Practice standards. This certification ensures quality assurance and safety standards are met. It provides a guarantee to Australian consumers that they are purchasing a quality product which may not occur with self-importation for personal use.

Studies are underway of products in a range of clinical and laboratory settings, and the data from these trials may have the potential to influence clinical practice in the years ahead.

The role of complementary medicine in the treatment of chronic hepatitis B patients

Results of studies of CMs in a range of settings suggest that these products (or their isolated constituents) may be targeting different aspects of the hepatitis B virus (HBV) disease process, such as viral replication (4-7), by either inhibiting viral antigens or suppression of DNA replication (8), inflammatory mediators (9), fibrotic change and chemoprevention of malignant change (10-12). Some agents appear to improve overall wellbeing, at least initially (11).

The pharmacological approach to the use of complementary medicine

According to Wang (2012) (13), CM treatment in hepatitis B aims to

- relieve symptoms and improve the quality of life of patients
- ameliorate liver inflammation
- ameliorate hepatic fibrosis
- improve immune function
- regulate lipid metabolism.

Traditional Chinese medicine (TCM) and Western herbal medicine use a number of plant-based chemicals with synergistic and overlapping pharmacological actions to address these aims. Herbal medicines are chosen for their intrinsic characteristics to treat diseases, and to modulate viral and human physiological processes (14).

Studies demonstrating specific activities relevant to HBV management

A number of recent studies have attempted to randomise patients to active treatment with CM or control treatments, and have examined the effects of CM on both HBV kinetics and liver disease activity and severity. These studies have been analysed in a recent review (15), which makes it quite clear that – although many questions remain about the quality of some of the studies undertaken (an issue many reviewers have with studies from institutions in the western world) – the studies demonstrate some activity of the agents used against HBV.

The review shows that results can be achieved with TCM, although clinicians remain reluctant to take up the challenge of using them. The introduction of highly active and safe antiviral agents, such as entecavir and tenofovir, has radically changed the approach to the use of any other agents. The capacity of antiviral agents to control HBV DNA in over 90% of patients, with little drug resistance over 5 years of treatment, makes the use of interferon and lamivudine unnecessary in those countries where the new agents can be afforded and used widely. The role of TCM in this era needs further clarification.

Studies of the mechanism of action of complementary medicine products or their constituents

Other studies are seeking to define active components in CM medications, and the role of these components in treating various conditions. A recent paper examined the chemical nature of flavones isolated from one herbal product, and showed which components of the flavone molecules conferred anti-HBV activity. These data have been analysed in the review by Zhang et al (15). The mechanisms of action of CM products or constituents are summarised in Table 14.1.

Table 14.1 Mechanisms of action of complementary products or constituents

Agent or herb	Action	Reference	Comment
	SNPs in vitamin D cascade (CYP2R1 rs 12794714 TT genotype)	Therapeutic	Vitamin D and genetic variation of CYP2R1 in

Vitamin D	predicted sustained HBeAg seroconversion after completion of Peg-IFN treatment	11104941 (16)	Vitamin D cascade influence host immune response in HBV infection
Vitamin D	Higher Child-Pugh score was independently associated with vitamin D deficiency in CHB patients	Zhao et al. (2016) (17)	Decreasing vitamin D levels may be the result of liver dysfunction
Vitamin D	High baseline vitamin D levels were associated with low HBV DNA, normal ALT and HBSAg at week 48 independent of treatment group	Chan et al (2015) (18)	Higher vitamin D levels may correlate with a more stable ALT pattern over time
Vitamin E	Vitamin E may induce HBeAg seroconversion in children with HBeAg persistent CHB	Fiorino et al (2017) (19)	Promising systematic review and meta-analysis of RCTs. Further studies are required
Artemisinin/artesunate	Inhibitors of HBV production and potential use in HCC	Romero et al. (2005) (20) Blazquez et al. (2013) (21)	Strong inhibition of HBV DNA and HBSAg
A flavonoid, wogonin, from <i>Scutellaria baicalensis</i> (baical skullcap)	Suppressed HBSAg production in an HBV transfected liver cell line (MS-G2), and inhibited duck-HBV DNA polymerase in duck-HBV infected ducks	Guo et al. (2007) (7) Chen et al. (2013) (22)	Wogonin showed anti-HBV activity both in vitro and in vivo
A flavonoid apigenin/Ocimum basilicum (sweet basil)	Reduced production and release of HBs and e antigens in HepG2.2.15 cell lines	Chiang et al. (2005) (23)	
<i>Sophora flavescens</i> kurorinone	Kurorinone showed comparable complete response rates to IFN (ALT normalisation and HBeAg and/or HBV DNA loss) in RCT	Chen et al. (2000) (24) Zhang et al. (2016) (25)	Alkaloids exhibited anti-HBV activity
Radix <i>Sophorae flavescens</i> Oxymatrine	Down regulates the expression of heat stress cognate 70 (HSC70), which is required for HBV DNA replication	Wang et al. (2010) (26)	Host HSC70 could be a novel drug target against HBV
13 flavones in <i>Euphorbia humifusa</i> were tested for anti-HBV activity in vitro in HepG2.2.15 cells	Apigenin-7-O-β-D-glucopyranoside inhibited HBSAg by 77.2% and HBeAg by 55.5% (40 μg/ml ¹) and apigenin-7-O-(6'-O-galloyl)-β-D-glucopyranoside inhibited HBSAg by 88.2% and HBeAg by 65.6% (80 μg/ml ¹)	Tian et al. (2010) (5)	Galloyl group on the flavones (C-6 of glucoside) may be responsible for the anti-HBV activity
TCM formulation Compound 861 <i>Salvia miltiorrhiza</i> (scarlet root; Dan Shen), <i>Astragalus membranaceus</i> (milk-vetch root; Huang Qi) and <i>Spatholobus suberectus</i> (milletia root; Ji Xue Teng)	Inhibition of human hepatic stellate cell (LX-2) proliferation	Wang et al (2004) (27)	
Silibinin a flavonolignan in <i>Silybum marianum</i> (Saint Mary's thistle)	Significantly reduced viability of human hepatocellular carcinoma Hep3B cells after 12 hours of treatment (p ≤ 0.001); also induced apoptosis	Varghese et al. (2005) (28) Federico et al. (2017) (12)	Research shows that the anti-inflammatory, antioxidant and pro-apoptotic activity of silymarin may reduce onset and progression of hepatitis to cirrhosis and HCC
<i>Astragalus membranaceus</i> (Huang Qi)	Inhibition of HBV reverse transcriptase and DNA polymerase; inhibits secretion of HBSAg and HBeAg in HepG2.2.15 cell line; lowers ALT, HBeAg and HBV DNA in treated patients	Yang et al. (1997) (29)	May act in part by inducing endogenous IFN in vivo
<i>Astragalus membranaceus</i> (Huang Qi)	Astragaloside (100 μg) suppressed HBSAg by 23.6% and HBeAg by 22.9% after 9 days of treatment	Wang et al. (2009) (30)	Inhibitory effect of astragaloside is more potent than lamivudine
Astragali compound	Negative seroconversion of HBeAg by 27.7% (13/47) (p < 0.01) and 28% (14/50) of HBV DNA. (p < 0.05) compared to controls	Tang et al. (2009) (6)	May inhibit HBV replication to some degree (5)
<i>Polygonum cuspidatum</i> (Hu Zhang) (its most active and studied component, resveratrol)	Suppresses lipid peroxidation, may inhibit HBV replication in HepG2.2.15 cells	Huang et al. (1998) (31)	Resveratrol found in skin of red grapes
Radix et rhizome rhei (Da Huang); emodin an active component	Inhibits duck-HBV reverse transcriptase and DNA polymerase; inhibits secretion of HBSAg and HBeAg from HepG2.2.15 cell line	Li et al. (2007) (32)	
<i>Phyllanthus urinaris</i> (Ye Xian Zhu); ellagic acid, a flavonoid, an active component	May block HBV messenger RNA transcription in Huh-7 cell lines; may block HBeAg-induced immune tolerance	Ott et al. (1997) (33) Liu et al. (2001) (34) Xia et al. (2011) (35)	Expensive, not used as often as other cheaper herbal products Phyllanthus species plus antiviral drugs may be better than the same antiviral drug alone
Niranthin isolated from <i>Phyllanthus niruri</i>	In duck hepatitis B virus infected ducklings, niranthin significantly reduced serum DHBV DNA, HBSAg, HBeAg, ALT & AST	Liu et al. (2014) (36)	
Radix bupleuri Saikosaponin C	Inhibits viral DNA replication and HBeAg production	Chiang et al. (2003) (37)	Reduction in HBV DNA level was more potent than lamivudine
Chinese herbal formulae (CHF)	Reduction in HBV DNA >2 log ₁₀ IU/mL in 19% (38/200) in CHF group compared to 5% (5/100) in the control group at week 52 (p = 0.0011) Reduction in HBSAg by > 0.5 log ₁₀ in 27% (54/200) in CHF group compared to 7% (7/100) in the control group (p = 0.0000); no difference between HBeAg loss and seroconversion between the groups; increased IFN-γ and IL-2 and decreased IL-4 IL-6 and IL-10 in CHF group compared to control group (p = 0.0000)	He et al. (2013) (4)	Increases in the Th1 cytokines (IFN-γ and IL-2), which have been associated with viral clearance

ALT: alanine aminotransferase; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBSAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; IFN: interferon; IL: interleukin; Peg-IFN: pegylated interferon; RCT: randomised controlled trial; RDBPCT: randomised, double-blind, placebo-controlled clinical trial; SNP: single nucleotide polymorphisms; TCM: traditional Chinese medicine

Products

AC = *Radix Astragali* 45 g, *Bupleurum chinense* 12 g, *Curcumae* 12 g, *Paeoniae radix* 12 g, *Peony radix* 15 g, *Radix Salvia miltiorrhiza* 20 g in three divided doses in hot water infusion for 10 minutes. The control group = silibinin 77 mg, oleonolol acid 40 mg and Yi-Gan Ling 2 g.

CHF = *Achyranthes bidentata* 15 g, *Astragalus membranaceus* 15 g, *Attractylodes macrocephala* 15 g, *Cuscuta chinensis* 10 g, *Epimedium brevicornum* 30 g, *Eucommia ulmoides* 15 g, *Fructus aurantii* 15 g, *Lycium barbarum* 15 g, *Panax notoginseng* 5 g, *Phyllanthus urinaria* 15 g, *Polyphorus umbellatus* 10 g, *Poria cocos* 15 g, *Radix curcumae* 15 g, *Salvia miltiorrhiza* 20 g.

SPNS = *Radix Astragali*, *Placenta hominis*, *Zhiling hypha*, *Fructus Ligustri lucidi*, *Radix Panax notoginseng*. Each tablet containing 1.5 g crude drug, 4 tablets three times a day.

Previous claims that specific agents have had a beneficial role in the management of HBV have been questioned in more recent systematic reviews. These reviews have rigorously examined published work, and they conclude that the quality of the studies makes it impossible to recommend the use of agents reported in clinical treatment regimens. The call is for more and better research into the mechanisms of action and efficacy of herbal products, and their active components, in the treatment of HBV. Even for *Phyllanthus* species, which have been used in several countries for centuries, with clinical results that suggest an efficacy, it seems there is no documented evidence for the apparent efficacy (35).

Given the early stages of most of these clinical and laboratory studies, it is appropriate to suggest that none of these treatments should be given in place of the current highly effective antiviral agents available in Australia: entecavir and tenofovir (see: [Treatment of chronic hepatitis B virus infection](#)).

Safety of herbal medicines

The basic tenet of all medicine (evidence-based, mainstream, herbal medicine, traditional Chinese medicine) is first do no harm. Therefore, in all forms of practice patient safety is paramount.

Hepatotoxicity

Herbal medicines with well-documented evidence of hepatotoxicity are:

- *Teucrium chamaedrys* (wall germander) and *Teucrium polium*, both of which cause zonal necrosis, hepatitis and fibrosis (38-40)
- *Mentha pulgatum* (peppermint) which causes necrosis and microvesicular steatosis (39)
- *Atrocytis gumifera* (pine thistle) which leads to panlobular hepatic necrosis and renal failure (38-43)
- certain pyrrolizidine alkaloids that can cause veno-occlusive disease (38, 39, 41-43)
- *Larrea tridentata* (chapparal), the ingestion of which has led to zonal necrosis (38-43).

There are, however, conflicting reports of hepatotoxicity in the literature, and case reports alone (without laboratory testing and verification of the presence of each of the listed ingredients) mean that it is difficult to make firm conclusions about hepatotoxicity.

In Australia, a recent death was attributed to the ingestion of Kava 1800 Plus. On laboratory analysis, *Piper methysticum* (kava) and *Passiflora incarnata* (passion flower) were found to be present in the formulation. However, *Scutellaria lateriflora* (skullcap), which was also listed as an ingredient in this product, was not found. The identity of the third ingredient has yet to be established (44). *Teucrium* is similar in appearance to skullcap, and there have been other reports of substitution of *Teucrium* for *Scutellaria*. *Teucrium* can lead to hepatotoxicity and renal failure, and has been banned as a slimming agent in Europe.

When hepatotoxicity occurs, it is important to verify each listed ingredient in a formulation, to accurately identify the causative agent so that both general practitioners and CM practitioners are aware of herbal medicines with demonstrated hepatotoxicity. Regardless, kava should be avoided in patients with chronic liver injury.

The variability in potency among different crops, the use of incorrect plant species, lack of product standardisation and the possibility of contamination (by fungi, bacteria or pesticides) are specific challenges associated with the therapeutic use of botanical products (45, 46). These problems are compounded by the fact that the TGA considers CM as listed products (rather than registered products), which have to meet less stringent standards of safety and quality of manufacture (47).

The Australian and New Zealand expert group reviewing the safety of black cohosh (*Actea racemosa*, formerly named *Cimicifuga racemosa*) concluded that there appears to be an association between the use of black cohosh and liver damage, but that it is very rare. It is a TGA requirement that this advice appear on the label of products containing black cohosh (48).

From January to December 2004, all patients with chronic hepatitis B admitted to a Hong Kong hospital for liver biochemistry irregularities were prospectively screened for an intake of TCM within 6 months before admission. The inclusion criteria included a bilirubin of over two times the upper limit of normal (ULN), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) over five times the ULN; alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) over two times the ULN. Exclusion criteria were HBV exacerbation (associated with HBV DNA level > 180,000 IU/mL (4.3 log₁₀ IU/mL)); co-infection with hepatitis A, C, D or E virus; intake of western medicine with known hepatotoxicity; alcohol intake of over 20 g/day for women and over 30 g/day for men; and any other liver disease apart from chronic hepatitis B (CHB) (49).

Of the 45 hospital admissions due to liver dysfunction in CHB patients, 15.6% were attributed to TCM-induced hepatotoxicity. There were two deaths related to TCM intake, one of which appeared to be related to pre-existing cirrhosis. In another two patients, hepatotoxicity was based on a temporal relationship, although specific hepatotoxic elements were not found in the herbal formulae (49).

One study examined the risk of liver injury associated with Chinese herbal medicine products containing *Radix bupleuri* in 639,779 patients with HBV infection in Taiwan. It found that prescribing Xiao-Chai-Hu-Tang and Long-Dan-Xie-Gan-Tang, or Chinese herbal medicine products containing more than 19 g of *Radix bupleuri*, might increase the risk of liver injury (50). However, the authors did stress that this association may not be causal. Xiao-Chai-Hu-Tang contains 3-9 g of *Radix bupleuri* daily (50).

Roussel Uclaf Causality Assessment Method (RUCAM) is a prospective hepatotoxicity causality assessment tool which is recommended as the gold standard for drug-induced liver injury and herbal-induced liver injury (51). The authors of this chapter recommend its use. The RUCAM form can be accessed from the following weblink:
<https://www.ncbi.nlm.nih.gov/books/NBK548272/>

The authors also recommend reporting any suspected hepatotoxicity to the TGA through the following weblink:
<https://www.tga.gov.au/reporting-adverse-events>

Conclusion

The numerous studies investigating the role of vitamin D in HBV infection suggest that supplemental vitamin D3 could be recommended for use in some CHB patients, particularly to lower adverse clinical outcomes, lower the rate of HBV replication and influence the host response in HBV infection (16, 18, 52). This is specifically the case in those with vitamin D deficiency.

There are currently no herbal products that can be recommended for use by HBV patients, based on well-designed, large, randomised clinical trials. Some agents shown to have anti-inflammatory effects or antifibrotic effects will continue to be recommended by CM practitioners, and they may well have some beneficial effects in those with active inflammation. In an age where effective antiviral agents are available on the Pharmaceutical Benefits Scheme, it is imperative that, where appropriate, patients receive these drugs, which are safe, highly effective and funded by the government. Although the emphasis must be on effective antiviral therapy for the hepatitis B patient, many patients wish to use CM and may feel it has a role in improving their quality of life. Therefore understanding the implications (both beneficial and harmful) of these agents is important (15). Due to drug resistance and adverse side-effects of antiviral therapy, plant-based medicines may warrant further examination (53).

There is clearly a need for well-designed, multicentre studies of the role of CM agents in chronic hepatitis B. It is to be hoped that such studies are undertaken soon. The consensus is clear that more rigorous studies are required to provide more definite results to guide the management of our hepatitis B patients (54). However, the Cochrane Database of Systematic Reviews for TCM has concluded that true evidence-based TCM is becoming a reality (55).

Patients should consult an accredited practitioner of TCM or western herbal medicine if they are interested in pursuing CMs. Details of TCM practitioners can be obtained from the Australian Health Practitioner Regulation Agency (www.ahpra.gov.au or 1300 419 495), and details of western herbal medicine or naturopathic practitioners from the Naturopaths and Herbalists Association of Australia (56).

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