Herbs to Treat Liver Diseases: More Than Placebo?

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Chronic liver diseases are a major health burden worldwide, with liver cirrhosis being the ninth leading cause of death in Western countries.[1] Treatments of chronic viral hepatitis B and C have greatly improved lately, whereas therapies of metabolic, toxic, and genetic liver disease are still at best modestly effective. Largely unmet is the need to treat established cirrhosis and nonalcoholic fatty liver diseases (NAFLDs) and prevent hepatocellular carcinoma (HCC). With this in mind, the widespread and increasing use of herbal drugs in patients with liver disease is not surprising.[2,3] Herbals that interfere with progression of liver fibrosis have been studied extensively in experimental and clinical settings, and some are currently tested in clinical trials on chronic viral hepatitis, NAFLD, and HCC. Prominent examples of herbals used to treat liver diseases are listed in Table 1. (Silymarin is addressed in a separate article in this series.[4])

Glycyrrhizin

Glycyrrhizin is extracted from liquorice root (*Glycyrrhiza glabra*) and comprises glycyrrhetic acid, flavonoids, hydroxycoumarins, and beta-sitosterol as the major constituents. In experimental models, glycyrrhizin alleviates toxic liver injury, possibly through antioxidant properties.[5] Before the advent of potent virostatics, an intravenous preparation (Stronger Neo-Minophagen C) containing glycyrrhizin, cysteine, and glycine was an established treatment for chronic hepatitis in Japan. Numerous studies, mostly from Asia, tested glycyrrhizin formulations in various chronic liver diseases. Most trials were open label or pilot studies; only a few were placebo controlled.[5,6] Efficacy was limited to improvements of serum liver enzyme levels, whereas no effect on viral markers was recorded. Retrospective data show a significant reduction of the risk for development of HCC in patients with hepatitis C virus (HCV). Potential negative side effects are hypokalemia, sodium retention, worsening of ascites, and hypertension caused by aldosterone-like activities. Glycyrrhizin is currently not recommended because of the lack of compelling evidence and the availability of better alternatives.

Phyllanthus amarus

Phyllanthus contains phyllantins, hypophyllanthins, and several polyphenols for which data indicate an interference with the hepatitis B virus (HBV) life cycle. Clinical trials with *phyllanthus* species in patients with chronic HBV infection were recently reviewed in a Cochrane analysis.[7] In total, 16 trials with 1326 patients were included of which 15 trials tested *Phyllanthus* in combination with other antivirals, whereas 1 trial tested against placebo. The combined results showed that *Phyllanthus* species had a favorable effect on HBV DNA levels and hepatitis B e antigen seroconversion when given together with conventional antivirals. A second Cochrane metaanalysis examined five clinical trials comparing *Phyllanthus* species with antiviral drugs (lamivudine, interferon-alpha, and thymosin) in patients with HBV and found no superior effect from phyllanthus.[8] No trials with entecavir or tenofovir have been conducted yet. Altogether, *Phyllanthus* could be an interesting candidate for further testing in rigorously designed trials with clear endpoints.

Japanese Traditional Medicine (Kampo)

Numerous clinical reports exist for treating liver diseases with Kampo medicines originating from traditional Japanese and Chinese medicine. In particular, TJ-9 (Sho-saiko-to),

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease

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TABLE 1 Examples of herbs used to treat liver diseases

Herbal	Indication for Use	Clinical Efficacy	Mechanism
Silymarin (milk thistle)	*Amanitas phalloides* (death cup fungus) intoxication Chronic liver disease (fibrosis) Chronic hepatitis C (antiviral)	Antidote Conflicting data Reduction of HCV RNA levels	Multiple (see article by Ferenci[4] in this series)
Glycyrrhizin	Chronic viral hepatitis, HCC prevention	Acute and chronic hepatitis	Antioxidative, cytoprotection
Phyllanthus amarus	Chronic hepatitis B	Reduction of HBV DNA levels and hepatitis B e antigen seroconversion when given with conventional antivirals	Inhibition of polymerase activity? Inhibition of viral transcription/replication?
Plantago asiatica (ribwort)	Chronic hepatitis B	HBV DNA reduction	Unknown
TJ-9 (Sho-saiko-to)Kampo (Japanese traditional medicine)	No established indication but tested widely in experimental models	Few controlled studies, possible preventive activity on incidence of HCC in hepatitis B surface antigen--positive patients (one study)	Unknown Antifibrotic? Reduction of lipid peroxidation?
Compound 861 (*Salvia miltiorrhiza*, *Astragalus membranaceus*, *Spatholobus suberectus*, and others)	Chronic hepatitis B (fibrosis)	Reduction of liver enzymes, serum surrogate markers of fibrosis, and improvement of histological fibrosis	Unknown
CH-100 (19 herbs)	Chronic hepatitis C	Reduction of liver serum enzyme levels	Unknown
Liv.52 (*Capparis spinosa*, *Cichorium intibus*, *Terminalia arjuna*, *Solanum nigrum*, *Achillea millefolium*, and others)	Toxic liver damage (including alcoholic liver disease)	Conflicting (one trial showing increased mortality in decompensated cirrhosis)	Unknown

a mixture of seven herbals, has been studied extensively *in vitro* and *in vivo*. Clinical data on the efficacy of TJ-9 in liver disease are largely published as retrospective case series or small trials, and often in Chinese journals that are difficult to access. In a prospective, randomized, nonblinded, controlled study, hepatitis B surface antigen–positive patients received a TJ-9 extract together with standard interferon for 5 years and had a significantly lower HCC incidence than control subjects.[9] This HCC-preventive effect was confirmed in another prospective trial.[10] However, well-designed clinical trials testing the therapeutic effect of TJ-9 or its major active ingredients baicalin/baicalein in the treatment of viral or metabolic liver diseases are needed.

Traditional Chinese Medicine

Most traditional Chinese medicines are an amalgam of different herbs, with one or two as "King herbs" and others that act synergistically with the "King herb." Several herbal mixtures are approved in China and are used for the treatment of liver diseases. Randomized controlled trials have been published mostly in Chinese journals. A combination termed "compound 861" containing 10 herbs, including *Salvia miltiorrhiza* (sage), *Astragalus membranaceus*, and *Spatholobus suberectus* as "King herbs," was tested in a randomized controlled trial in 102 patients with HBV. Twenty-four weeks of treatment reduced liver enzyme levels and improved fibrosis on histology.[11] Another formulation of 19 different herbs termed CH-100 was tested in a double-blind, placebo-controlled study of patients with chronic HCV infection. This therapy was associated with a significant alanine aminotransferase (ALT) reduction; however, none of the patients became HCV RNA–negative.[12]

Miscellaneous

Liv.52 is an Ayurvedic herbal combination of *Capparis spinosa* (capers), *Cichorium intibus* (wild chicory), *Terminalia arjuna* (arjuna), *Solanum nigrum* (black nightshade), *Achillea millefolium* (yarrow), and others; it is available without prescription in many countries. Liv.52 was reported to have hepatoprotective effects toward toxic liver damage in experimental models. Three controlled clinical trials with Liv.52 were published with conflicting results,[6] of which the largest found no benefit of Liv.52, but patients with Child class C cirrhosis showed an increased mortality caused by liver-related complications, leading to the trial's termination.

Trans-resveratrol is a powerful antioxidant extracted from grapevine and has been extensively tested in cell culture and rodent models for hepatoprotective properties.[13] Although its precise mode of action is incompletely understood, positive effects on insulin resistance have been suggested. A recent randomized, double-blinded, placebo-controlled trial aimed to evaluate the effects of 12-week supplementation with resveratrol on cardiovascular risk factors in patients with NAFLD. No beneficial effects on anthropometric measurements, insulin resistance markers, lipid profile, and blood pressure were found, but resveratrol reduced ALT and hepatic steatosis significantly more than placebo.[14] Further rigorously designed trials with clear endpoints are needed to assess the efficacy of resveratrol in treating (fatty) liver disease.

Xanthohumol is the principal prenylated flavonoid of the hop plant. Several studies revealed its hepatoprotective effect and its inhibitory effects on inflammation, fibrosis, and carcinogenesis in response to experimental liver injury.[15] Xanthohumol also holds promise as a therapeutic agent for treating obesity and other components of the metabolic syndrome including steatosis. Efficacy in patients with liver disease has not been tested yet, but safety and pharmacology studies did not show any side effects in men.[16]

For the future, these and numerous other molecules extracted from plants and that proved to have hepatoprotective properties in experimental model systems could become candidate compounds for clinical testing in humans.[17] Moreover, such molecules may serve as lead compounds for pharmaceutical modeling of synthetic drugs with higher specificity and activity, and hopefully with good tolerability in the treatment of liver diseases.

Conclusion

So far, clinical studies analyzing the efficacy of herbals in the treatment of liver diseases provided only moderate evidence. Future efforts will have to implement extensive methodological improvements to separate the real therapeutic value from unfounded hopes. Rigorous scientific testing along the principles of evidence-based medicine is required for herbal medicine to become more than a fashionable trend.

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