

Evidence-based herbal treatments in liver diseases

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Abstract

The liver is the main organ for metabolic and detoxification reactions in the body. Therefore, its diseases can be associated with both metabolic disorders, such as insulin resistance, obesity, diabetes, or dyslipidemia, and exogenous insults such as drugs, xenobiotics, or alcohol. Indeed, lifestyle changes are the primary approaches for the prevention and treatment of liver diseases. Since ancient times, herbals have also been used for preventive and therapeutic purposes, because of their anti-apoptotic, anti-inflammatory, and antioxidant effects. Here, the literature was reviewed for potential therapeutic effects of plants and their compounds by including *in vitro* and *in vivo* studies, as well as clinical trials. Although the available data imply some beneficial roles of herbals on the liver, the indications and posology of specific plants need to be clarified through multicenter, randomized clinical trials.

Keywords: Alcoholic liver disease; fibrosis; herbal; liver disease; nonalcoholic liver disease; plant; silymarin.

Introduction

The liver is responsible for several physiological processes in the body, such as the production of proteins and bile acids, glycogen storage, lipid metabolism, and detoxification.^[1] These functions, particularly detoxification and metabolism, make the liver vulnerable to oxidative stress and inflammation. Besides oxidative stress and inflammation, lipid peroxidation and impaired immune response play important roles in the initiation and progression of hepatic damage.^[2] Excessive alcohol consumption, drugs, obesity, diabetes, and viral infections are all involved in the pathogenesis of liver diseases.^[3] Both alcoholic and nonalcoholic fatty liver diseases are common and lead to liver fibrosis, steatosis, hepatitis, cirrhosis, as well as hepatocellular carcinoma. Annually, approximately 2 million people worldwide die from liver diseases.^[4] Herbals have been used for the treatment of liver diseases since ancient times.^[5] Both *in vitro* and *in vivo* studies have shown

that herbals have beneficial effects on hepatic tissues through several mechanisms: (1) reducing peroxidation, (2) anti-inflammatory activity, (3) inhibiting collagen deposition and antifibrotic effect, (4) free radical scavenging and antioxidant activity.^[5,6] However, only a limited number of herbals have adequate clinical studies investigating their effects on liver diseases.

The benefits of plants traditionally utilized by indigenous healers to improve liver function and treat liver illnesses have been extensively investigated in recent years. Research has often supported traditional experience and wisdom by identifying the mechanisms and modes of action of various plants and reiterating the therapeutic efficacy of specific plants or plant extracts in clinical studies. In reality, the medicinal uses of plants are not etiology-specific. They treat several types of liver damage (acute damage, chronic inflammation, fibrosis, steatosis, etc.) regardless of the etiology by impacting various steps of the pathogenesis (antioxidant, anti-inflammatory, anti-fibrotic, lipid/glucose metabolism regulator, etc.).^[7]

This review included both *in vitro* and *in vivo* studies on the effects of herbals in liver diseases, but emphasizes clinical studies more. For instance, in dosage-dependent studies for *Camellia sinensis*, a dose containing 1080g of catechin reduced serum alanin aminotransferase (ALT) by 42.1±11.3%. The level of urine 8-isoprostane also decreased by 31.1±9%. Urine 8-isoprostane is a specific marker for oxidative stress. Compared to the placebo, there was no significant difference in the values for the 700 g dose.^[8] The molecular structures of these herbal compounds are shown in Figure 1, and images of the plants are in Figure 2. Indeed, the herbal compounds in Table 1, namely curcumin, berberine, silymarin, dihydromyricetin, and resveratrol, are components of some plants in Table 2.

Berberine

Berberine is an alkaloid featuring an isoquinoline ring in its chemical structure. It can be found in numerous plants of the *Berberis* sp.,^[9] such as *Coptis chinensis* Franch., *Berberis vulgare* L., *Berberis julianae* Schneid., and *Scutellaria baicalensis* Georg.^[10] Berberine has various clinical applications including antibacterial, anti-inflammatory, and gastroenteritis treatments. It has also been investigated for anti-cancer activity.^[11] The effectiveness of berberine against nonalcoholic steatohepatitis (NASH) was investigated in mice. The berberine group exhibited reduced values for ALT, aspartate aminotransferase (AST), total cholesterol, steatosis score, lobular inflammation score, and NAS (non-alcoholic fatty liver disease activity score). The progression of NASH is linked to the localization of inflammatory cells in the liver. Consequently, the study showed that the berberine-administered group demonstrated a decrease in IL-1, IL-8, and NF-κB expression.^[12]

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Table 1. Clinical studies of herbal compounds on liver diseases

	Liver disease	Study type	Study duration	Number of participants	Dosage	Results
Berberine						
Mei et al. ^[60] 2009	NAFLD	Clinical trial	8 w	47	3x0.5 g	ALT, colessterol, triglycerides, LDL, HbA1c reduced
Yan et al. ^[61] 2015	NAFLD	Randomized, parallel controlled, open label	16 w	184	Group 1: LSI Group 2: LSI and pioglitazone Group 3: LSI and 3x0.5g berberine	Body weight decrease and improving lipid profile effect: Berberine> pioglitazone Reduction hepatic fat content: LSI+ berberine 52.7%, vs LSI 36.4%, p=0.008
Harrison et al. ^[62] 2021	NAFLD	Randomized, Double-blind, Placebo-controlled (phase 2)	18 w	100	Group 1: 2x500 mg berberine ursodeoxycholate Group 2: 2x1000 mg berberine ursodeoxycholate Group 3: Placebo	ALT, GGT, LDL decreased in Group 2
Curcumin						
Panahi et al. ^[63] 2016	NAFLD	Randomized, Placebo-controlled	8 w	102	Control group: Placebo Curcumin group: 1000 mg/day	Triglycerides, non-HDL-C total cholesterol, LDL, uric acid decreased
Rahmani et al. ^[64] 2016	NAFLD	Randomized, Double-blind, Placebo-controlled	8 w	80	Control group: Placebo Curcumin group: 500 mg/day Dispersion curcumin formulation is equivalent to 70-mg curcumin	Liver fat improvement in the curcumin 78.9% vs placebo group 27.5% ALT, AST, BMI, HbA1c, total cholesterol decreased
Nouri-Vaskeh et al. ^[13] 2020	Liver cirrhosis	Randomized, Double-blind, Placebo-controlled	3 m	60	Control group: Placebo Curcumin group: 2x500 mg curcumin capsule	Disease activity scores, severity of cirrhosis decreased
Dihydromyricetin						
Chen et al. ^[65] 2015	NAFLD	Randomized, Double-blind, Placebo-controlled	12 w	60	Control group: 2 placebo capsules Dihydromyricetin group: 2x300 mg dihydromyricetin capsule	ALT, AST, GGT, LDL, Apo B, TNF- α , CK-18, FGF21 decreased APN increased
Resveratrol						
Faghihzadeh et al. ^[66] 2014	NAFLD	Randomized, Double-blind, Placebo-controlled	12 w	50	Control group: Placebo Resveratrol group: 500 mg resveratrol capsule	Improved steatosis grade ALT, nuclear factor κ B activity, inflammatory cytokines, cyokeratin-18 decreased ALT (resveratrol -32.38% \pm 25.63%, vs placebo -13.54% \pm 45.00%)
Chen et al. ^[67] 2015	NAFLD	Randomized, Double-blind, Placebo-controlled	3 mo	60	Control group: 2 placebo capsules, twice daily Resveratrol group: 2x150 mg resveratrol capsules twice daily (600 mg/day)	ALT, AST, serum glucose LDL, total cholesterol, HOMA-IR, TNF- α , CK-18 fragment, FGF21 decreased APN increased
Heebøll et al. ^[68] 2016	NAFLD	Randomized, Double-blind, Placebo-controlled	6 m	26	Control group: Placebo Resveratrol group: 1.5 g/day	Liver lipid decreased
Silymarin						
Salmi and Sama. ^[33] 1982	Alcoholic liver disease	Double-blind, Placebo-controlled	4 w	97 (78% with daily alcohol use)	Control group: Placebo Silymarin group: Silymarin 420 mg/day	ALT, AST decreased

Table 1 (cont). Clinical studies of herbal compounds on liver diseases

	Liver disease	Study type	Study duration	Number of participants	Dosage	Results
Ferenc et al. ^[39] 1989	Cirrhosis (Alcoholic and non-alcoholic)	Randomized, Double-blind, Placebo-controlled	41 m (median)	170	Control group: Placebo Silymarin group: 140 mg of silymarin	Improved in 4-year survival Lower mortality
Nanda et al. ^[35] 2014	Alcoholic liver disease	Retrospective	11 m	602 (alcohol induced: 230)	3x140 mg silymarin tablets	Improved hepatic biochemical profile (total bilirubin, AST, ALP).
Luanghosiri et al. ^[60] 2015	Liver injury (Antituberculosis drug-induced)	Randomized, Double-blind, Placebo-controlled	4 w	55	Control group: Antituberculosis drugs+Placebo tablet Silymarin group: Antituberculosis drugs+ 3x 140 mg silymarin tablet	28% reduction in the risk of antituberculosis-drug induced liver injury with silymarin
Hajiaghahammadi et al. ^[60] 2012	Non-alcoholic fatty liver disease	Randomized pilot study	8 w	66	Group I: 15 mg/d pioglitazone Group II: 500 mg/d metformin Group III: 140 mg/d silymarin	ALT, AST, FBS, lipid profile, insulin levels, HOMA-IR decreased most in silymarin group
Wah Kheong et al. ^[61] 2017	Nonalcoholic steatohepatitis	Randomized, Double-blind, Placebo-controlled	48 w	99	Control group: Placebo Silymarin group: 3x700 mg silymarin capsule	Improvement in fibrosis and AST to platelet ratio index, Fibrosis-4 score, NAFLD fibrosis score decreased

w: Weeks; m: Months; ALT: Alanin aminotransferase; APN: adiponectin; Apo: Apolipoprotein; AST: Aspartate aminotransferase; BMI: Body mass index; CK-18: cytokeratin 18; FGF21: Fibroblast growth factor 21; HOMA-IR: Homeostasis model assessment insulin resistance index; LDL: Low-density lipoprotein; LSI: Lifestyle style intervention; non-HDL: Non-high-density lipoprotein.

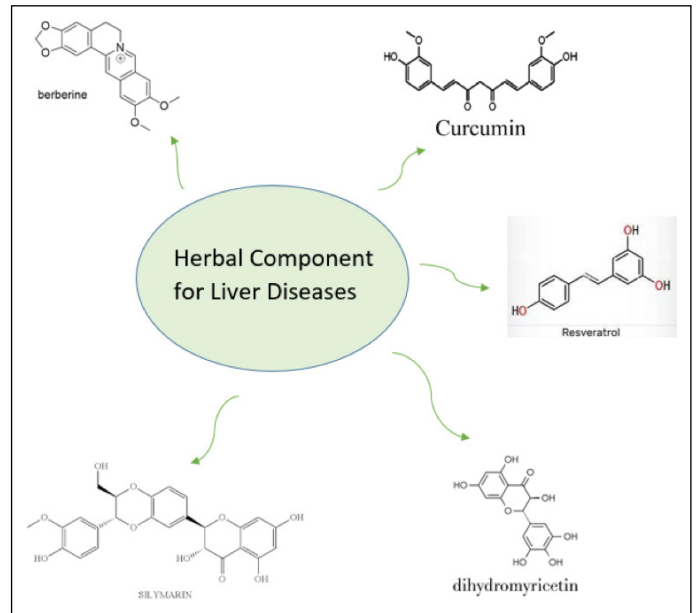


Figure 1. Herbal component for liver diseases.

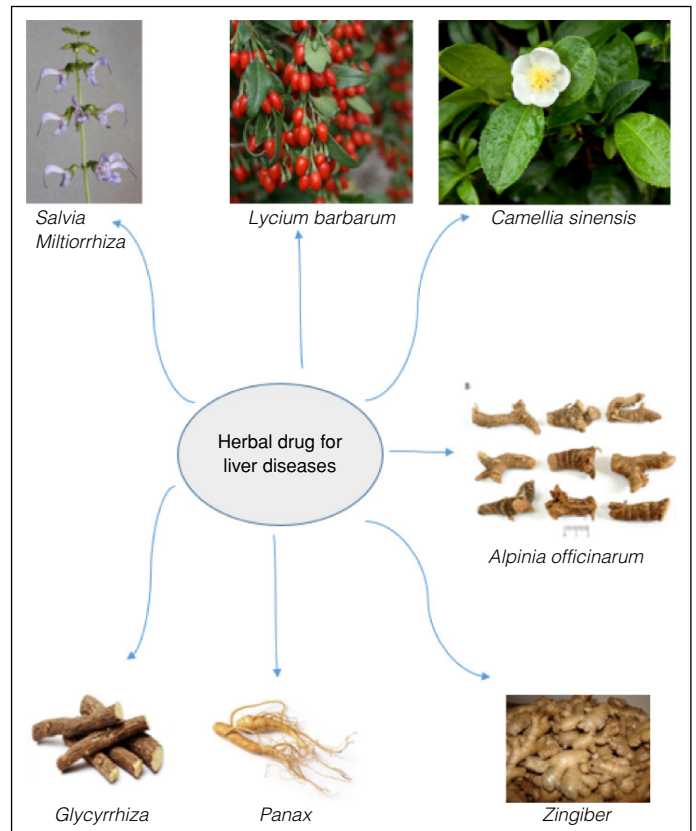


Figure 2. Herbal drug for liver diseases.

Curcumin

Curcumin is a natural compound found in the root of *Curcuma longa* L.^[13] Traditionally, it has been used as a topical analgesic for arthritis and chest pain and to treat atherosclerosis, diabetes, cancer, hepato-protective issues, and rheumatoid arthritis.^[14] Due to its ability to in-

Table 2. Clinical studies of plants on liver diseases

	Liver disease	Study type	Study duration	Number of participants	Dosage	Results
<i>Camellia sinensis</i> Sakata et al. ^[71] 2013	NAFLD	Randomized Double-blind, Placebo-controlled	12 w	17	Green tea group 1: 700 ml/day (1080 mg catechins) Green tea group 2: 700 ml/day (200 mg catechins) Placebo group 3: Green tea-flavored beverage (0 mg catechins)	>1 g catechin improved liver fat content and inflammation, ALT, body fat, urinary 8-isoprostane excretion decreased
Pezeshki et al. ^[72] 2016	NAFLD	Randomized, Double-blind, Placebo-controlled	90 d	80	Control group: Placebo tablet Green tea group: 500 mg green tea extract tablet	ALP, ALT, AST decreased
<i>Capparis spinosa</i> Khavasi et al. ^[73] 2017	NAFLD	Randomized, Double-blind, Placebo-controlled	12 w	44	Caper group: 40–50 gr caper fruit pickles/day	ALT, AST, disease severity decreased
<i>Cinnamomum</i> sp. Askari et al. ^[74] 2014	NAFLD	Randomized, Double-blind, Placebo-controlled	12 w	50	Control group: 2 placebo capsule Cinnamon group: 2x750 mg cinnamon capsule	ALT, AST, FBS, HOMA index, total cholesterol, triglycerides, hs-CRP decreased
<i>Curcuma longa</i> Kim et al. ^[75] 2013	Elevated ALT	Randomized Double-blind Placebo-controlled	12 w	8	Control group: Placebo Turmeric group: 3x1 g fermented turmeric powder capsule	ALT, AST decreased
<i>Glycyrrhiza</i> sp. Hajjaghahmohammadi et al. ^[76] 2012	NAFLD	Randomized Double-blind Placebo-controlled	2 m	66	Control group: 2 g starch Licorice group: 2 g aqueous licorice root extract	ALT, AST decreased
<i>Linum usitatissimum</i> Yari et al. ^[44] 2016	NAFLD	Randomized, Open labeled, Placebo-controlled pilot study	12 w	50	Control group: Lifestyle modification Flaxseed group: Lifestyle modification and 30 g flaxseed	ALT, AST, GGT, BMI Reduction hepatic fibrosis and steatosis
<i>Panax ginseng</i> (Korean Red Ginseng-KRG) Hong et al. ^[77] 2016	NAFLD	Randomized, Single-blind, Clinical trial	3 w	80	Control group: S. marianum (450 mg) and placebo KRG group: S. marianum (450 mg) and 3x1000 mg capsule	AST, ALT, GGT, TNF- α , adiponectine and fibrosis score decreased
<i>Phyllanthus urinaria</i> Wong et al. ^[78] 2013	NAFLD	Randomized, Double-blind, Placebo-controlled	24 w	59	Control group: Placebo P. urinaria group: 3x2400 mg	NAFLD activity score non-significantly (p=0.24)
<i>Rhus coriaria</i> Kazemi et al. ^[45] 2020	NAFLD	Randomized Double-blind Placebo-controlled	12 w	80	Control group: Placebo Sumac group: 4x500 mg powder	ALT, AST, HOMA-IR, FBS, HbA1c, hs-CRP, fibrosis score decreased

Table 2 (cont). Clinical studies of plants on liver diseases

	Liver disease	Study type	Study duration	Number of participants	Dosage	Results
Zingiber officinale						
Rahimiou et al. ^[46] 2016	NAFLD	Randomized, Double-blind, Placebo-controlled pilot study	12 w	44	Control group: Placebo Ginger group: 2x1 000 mg capsule	ALT, GGT, HOMA-IR, hs-CRP, TNF- α , Steatosis decreased
Rafie et al. ^[79] 2020	NAFLD	Randomized Double-blind Placebo-controlled	12 w	46	Control group: Placebo Ginger group: 3x500 mg capsule	ALT, LDL, total cholesterol, hs-CRP, fetuin-A decreased

w: Weeks; m: Months; d: Days; ALP: Alkaline phosphatase; ALT: Alanin aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; FBS: Fasting blood glucose; GGT: γ -glutamyltransferase; HOMA: Insulin resistance; hs-CRP: High-sensitivity C-reactive protein; NAFLD: Non-alcoholic fatty liver disease, TNF- α : Tumor necrosis factor- α .

hibit COX-2 and LOX, curcumin exhibits anti-inflammatory effects.^[15] Researchers have investigated how curcumin influences NAFLD. In a study on rats, a diet containing 0.2% curcumin led to decreased scores for hepatic steatosis and inflammation.^[16]

Resveratrol

Resveratrol is a phytoalexin with a polyphenolic structure, present in various plants. It is derived from *Theobroma cacao* L., *Vitis vinifera* L., and *Rubus idaeus* L. Resveratrol possesses anti-inflammatory and immune regulatory activities and is used in treating cardiovascular and ophthalmic diseases.^[17]

Silymarin

Silymarin is a polyphenolic mixture of flavonoids and flavonolignans. Its bioactive extract is obtained from the dried seeds and fruits of *Silybum marianum* L.^[18] It is a therapeutic agent for mushroom (*Amanita phalloides*) poisoning and liver protection.^[19]

Salvia Miltiorrhiza

Salvia miltiorrhiza, belonging to the family Lamiaceae, has roots that are medicinally used in the treatment of cardiovascular diseases and as antibacterial and anti-inflammatory agents.^[20]

Non-Alcoholic Fatty Liver Diseases

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases in which hepatic steatosis, the macrovesicular accumulation of triglyceride in hepatocytes, develops in the absence of secondary causes of hepatosteatosis (e.g., medications, excessive alcohol consumption, or certain heritable conditions).^[7] NAFLD is closely associated with obesity, insulin resistance, Type 2 diabetes mellitus, and hyperlipidemia.^[8] The three components of NAFLD — steatosis, inflammation, and fibrosis — can be slowed or improved with lifestyle changes, including weight loss and physical activity. However, in some patients, hepatosteatosis progresses into hepatitis, specifically NASH, which might lead to liver fibrosis, cirrhosis, and primary liver cancers.^[21]

Herbals have potential therapeutic effects on all components of NAFLD, namely reducing lipid accumulation, inhibiting inflammation, and preventing the development of liver fibrosis by suppressing hepatocyte apoptosis. In addition to plants, natural compounds such as flavonoids, alkaloids, polyphenols, terpenoids, and saponins obtained from plants have also been reported to have therapeutic effects on NAFLD.^[22] Citrus flavonoids, hesperidin, naringenin, nobiletin, and tangeretin increase fatty acid oxidation and inhibit hepatic fatty acid synthesis. Consequently, they prevent dyslipidemia and hepatic steatosis.^[23] Another flavonoid, baicalin, was shown to reduce NASH in mice by activating fatty acid β -oxidation, inhibiting lipogenesis, and reducing hepatocyte apoptosis.^[24] Berberine, curcumin, resveratrol, and silymarin are frequently investigated for the treatment of NAFLD.^[25] The efficacy of some herbs in the treatment of NAFLD was evaluated through meta-analysis of randomized controlled trials. However, the number of studies included in these meta-analyses is limited, and their durations are short, although NAFLD is a chronic disease.

The meta-analysis of *S. miltiorrhiza* Bunge (Danshen) included 800 patients from 8 randomized studies. *S. miltiorrhiza* was found to increase HDL levels and the liver/spleen ratio at computed tomography, while

decreasing levels of ALT, AST, triglyceride, LDL, and total cholesterol.^[26] The meta-analysis for curcumin included 9 randomized controlled trials with a duration of 2 to 3 months and doses ranging from 50 to 1500 mg/day. Curcumin was found to reduce waist circumference, serum levels of ALT, AST, LDL, and total cholesterol, as well as both fasting blood sugar and serum insulin levels, thus improving Homeostatic Model Assessment for Insulin Resistance. Curcumin did not cause significant reductions in triglyceride levels, although subgroup analyses showed significantly decreased triglyceride levels in patients aged 45 years or older.^[27]

Six randomized studies for berberine at doses of 1000 to 1500 mg/day were included in the meta-analysis. Berberine significantly reduced ALT, LDL, total cholesterol, 2-hour postprandial plasma glucose, and HbA1c levels in patients with NAFLD compared to controls. Subgroup analyses indicated that berberine, in combination with lifestyle modification or other medications, reduces triglyceride levels.^[28]

In a meta-analysis of 587 NAFLD patients from 8 randomized trials, silymarin had positive effects when administered for 8 to 24 weeks. Both ALT and AST levels decreased more in the silymarin groups than in the control group [(for ALT MD, -9.16 UI/L; 95% CI, -16.24 to -2.08 UI/L; $p=0.01$ and for AST MD, -6.57 UI/L; 95% CI, -10.03 to -3.12 UI/L; $p=0.0002$)]. Interestingly, the use of silymarin alone showed better therapeutic efficacy than when used in combination (with lifestyle modification or other drugs).^[29]

Alcoholic Liver Disease

Alcohol can cause a wide spectrum of liver diseases, including hepatosteatosis, steatohepatitis, acute liver failure, cirrhosis, and hepatocellular carcinoma (HCC). Since 90% of alcohol/ethanol metabolism occurs in the liver, produced reactive oxygen species and inflammatory cytokines lead to increased oxidative stress, inflammation, lipid peroxidation, mitochondrial damage, and hepatocyte apoptosis.^[30] Apart from alcohol itself, patient characteristics such as age, gender, obesity, nutritional factors, drugs, smoking, and concomitant viral infections also play a role in the pathogenesis and determine the type and severity of liver injury.^[31]

The most important approach for the treatment of alcoholic liver disease is cessation of alcohol consumption. However, herbals including silymarin, curcumin, resveratrol, green tea polyphenols, and ginseng have also shown positive effects on experimental models of alcoholic liver diseases.^[30-32] Clinical studies with silymarin date back to 1982 and 1989, and silymarin groups showed a significant reduction in liver enzymes compared to placebo controls.^[33,34] The reduction in liver enzyme levels with silymarin treatment was confirmed by a retrospective study conducted in 2014.^[35] Although similar doses of silymarin were administered, only one study showed reduced mortality in patients with alcoholic cirrhosis.^[36-39] Ferenci et al.^[39] administered silymarin at a dose of 140 mg three times a day orally, and the 4-year survival rates in the silymarin and placebo groups were 58% and 39%, respectively ($p=0.036$). Patients with NAFLD were also included in this trial, and those with alcoholic cirrhosis responded better to silymarin.

Liver Fibrosis

Hepatic fibrosis is a condition caused by excessive proliferation and deposition of extracellular matrix and collagen in the liver as a constant attempt to heal chronic tissue injury, impairing the normal physiological function of the liver. Fibrosis can lead to cirrhosis and HCC in later

stages.^[40,41] Increased secretion of certain cytokines and growth factors [i.e., TGF- β 1 (transforming growth factor beta-1)] and oxidative stress play a role in the initiation and progression of liver fibrosis.^[42]

Latief and Ahmad reviewed the antifibrotic effects of 50 plants.^[1] Plants belonging to the Asteraceae, Fabaceae, and Lamiaceae families were found to protect the liver from fibrosis by reducing oxidative stress and inflammation and inhibiting fibrogenesis. Silymarin, ginseng, epigallocatechin-3-gallate, curcumin, salvianolic acid, and ostiole are natural compounds with antifibrotic effects. El-Tantawy et al.^[42] investigated the antifibrotic effect of sources such as coffee, cucurbitacin E, apocynin, and gallic acid based on their antioxidant and anti-inflammatory capacities. Although the antifibrotic effects in these studies were demonstrated by *in vitro* and/or *in vivo* studies, few clinical studies on the use of plants in different liver diseases exist. Silybin phytosome complex with phosphatidylcholine and vitamin E has been shown to reduce liver fibrosis in patients with NAFLD.^[43] Similarly, *Linum usitatissimum*, *Rhus coriaria*, and *Zingiber officinale* have been found to decrease fibrosis in NAFLD patients.^[44-46]

Hepatocellular Carcinoma

HCC is the most frequent primary liver cancer and the fourth leading cause of cancer-related deaths.^[47] Risk factors for HCC include alcoholism, aflatoxin, diabetes, NAFLD, hepatitis B and hepatitis C virus (HCV), obesity, and iron overload.^[48] Studies have shown that herbs and natural compounds can abolish risk factors for cancer development through their antiviral effect, inhibition of fibrogenesis or oxidative damage, and suppression of tumor formation.^[49]

Lycium belongs to the Solanaceae family. Goji berries and *Cortex Lycii* have shown promising therapeutic results in several chronic conditions, including diabetes, hemoptysis, cough, frenetic fever, and night sweats. Additionally, recent medical studies have shown that these fruits' root bark possesses other pharmacological properties, including antiglaucoma, anticancer, antioxidant, antiaging, neuroprotective, and blood sugar level-lowering effects.^[50]

Camellia sinensis is in the Theaceae family. Teas are classified into three major types based on the manufacturing process:

1. "Non-fermented" product: green tea,
2. "Semi-fermented" product: oolong tea,
3. "Fermented" product: black tea.

Depending on how it is processed, *C. sinensis*'s chemical composition changes. Polyphenols are more prevalent before fermentation, while thearubigins are produced during fermentation. Consequently, green tea has a higher potential for antioxidants.^[51] Green tea polyphenols (GTP) are particularly effective against cancer, heart disease, and other illnesses. Additionally, several studies suggest the positive effects of green tea consumption on various factors, including kidney stones, dental caries, bone density, and cognitive performance.^[52] In HCC-derived cells, EGCG (epigallocatechin gallate) induces apoptosis and inhibits cell growth and proliferation. TNF, IL-6, and IL-18 expression in mice was found to be downregulated in a study. Due to a reduction in IGF-1R, ERK, and Akt phosphorylation, it prevented the growth of liver cell adenomas.^[53]

Alpinia officinarum is in the Zingiberaceae family. It utilizes the rhizome of *A. officinarum*. Generally, *Alpinia* species are frequently used to treat various illnesses, including hemorrhoids, general weakness, infantile weakness, and as blood purifiers, among others.^[54] Studies showed that the application of the extract from *A. officinarum* roots

led to a decrease in ALT and AST values. Additionally, a decrease was observed in the degenerated hepatocyte scores compared to the HCC group that did not receive treatment. Prophylactic as well as therapeutic uses of *A. officinarum* have been investigated. Degenerated hepatocyte scores, as well as ALT and AST values, were found to decline when used prophylactically.^[55]

The antiviral activity of silymarin and silibinin against HCV was demonstrated. *In vitro* antiviral mechanisms of action include inhibition of virus entry and fusion, protein synthesis, RNA synthesis, and RNA polymerase activity.

Lycium polysaccharides showed an anti-tumor effect by inhibiting proliferation and inducing apoptosis in human hepatoma cells.^[56]

The chemopreventive potential of green tea components in hepatocellular carcinoma has been demonstrated by cell culture and animal studies.^[53] Green tea's major active polyphenol, EGCG, suppressed NAFLD/NASH-associated liver tumorigenesis in rats. Chemoprevention was associated with decreased hepatic triglyceride content, oxidative stress, inflammation, hepatic fibrosis, and inhibition of hepatocyte proliferation.^[57] *A. officinarum* improved liver functions and oxidative stress markers when combined with cisplatin in HCC.^[55] Berberine exhibited anticancer activity in cell culture studies by inhibiting proliferation and inducing apoptosis in liver carcinoma.^[9,58] Its combination with vincristine enhanced its apoptotic effect.^[59] Resveratrol suppressed tumor growth by reducing hexokinase 2 and inducing apoptosis in HCC cells of mice.^[60] In another study, resveratrol inhibited tumorigenesis by reducing myosin light chain kinase expression.^[61]

Herbal Hepatotoxicity

In the latest published American Association for the Study of Liver Diseases practice guideline, it was reported that although herbal and dietary supplements (HDS) are mostly safe, they can cause various hepatotoxicities, such as acute liver failure.^[62] The toxicity of these products has been linked more to mislabeling, adulteration, and contamination of the product rather than the plant itself. Toxicity may occur due to unlisted plant parts, other plants, chemicals, pesticides, and heavy metals on the product label. Pharmaceuticals, such as sildenafil added to sexual performance products, may be incorporated into the herbal product and cause adverse effects. Genetic polymorphisms and the conditions under which a product is consumed may also affect an individual's likelihood of developing HDS hepatotoxicity.

Two herbs mentioned in this review for their hepatoprotective effects, green tea and turmeric (curcumin), have notable hepatotoxicity cases in the literature. These toxicities are not caused by the plants themselves but by the product properties, conditions of use, and dosage.

Cases associating green tea with hepatotoxic effects have been reviewed in the literature.^[63,64] Green tea is generally safe when consumed as a beverage, but hepatotoxic potential has been identified in products developed as weight loss aids. These products have generally been identified as multi-ingredient products containing high doses of green tea extract.^[64] It is recommended to avoid consumption of green tea on an empty stomach, for long periods, and in high doses.^[63] In a study investigating the hepatotoxic effect of green tea extract in mice, the effects of genetic predisposition, fasting, concomitant stimulants (caffeine), and impurities were minimized. The extract was administered by gavage at a dose range of 1X-10X (65.9–659 mg/kg) mouse equivalent for up to two weeks. No evidence of hepatotoxicity was observed as a result of the study.^[65]

Turmeric and its component curcumin have very low oral bioavailability. Therefore, it mostly does not show toxic effects in trials. Detected hepatotoxicity has generally been associated with turmeric formulations containing high bioavailability and high doses of curcuminoids. In a study of turmeric-associated cases of acute liver injury, highly bioavailable curcumin products were obtained by coadministration with Piper nigrum extract. However, these products produced toxicity. It was also found that most patients with toxicity in the 23 cases examined were concurrently taking at least one other drug.^[66]

Discussion

Many factors play a role in the complex pathogenesis of liver diseases, such as insulin resistance, oxidative stress, inflammation, apoptosis, fibrosis, and hyperlipidemia. Therefore, the herbal treatment of liver disease should target the use of plants that are active through more than one mechanism.

Data from clinical studies of herbs and herbal components are included in Tables 1 and 2, respectively. The levels of liver enzymes, important markers of liver function, were improved in most studies. The duration of treatment was usually 12 weeks, ranging from 8 weeks to 41 months, except for a silymarin study with a treatment period of 41 months.^[39] Considering the complex pathogenesis and chronic nature of liver diseases, we think that these periods are insufficient. Both herbs and herbal compounds were tested mostly on patients suffering from NAFLD. The increased interest in NAFLD may be due to its high prevalence and the huge projected burden of liver diseases associated with it. Although the initial stages of NAFLD can be reversible with lifestyle changes, the inconsistency in maintaining a balanced diet and regular exercise throughout life leads patients to seek alternatives, such as hepatoprotective and/or therapeutic herbals. Furthermore, patients try to fulfill the unmet need for treatment with herbals, due to a lack of NAFLD-specific drugs approved for clinical use.

Curcumin, berberine, and resveratrol, especially silymarin, have come to the fore in the treatment of liver disease since their efficacy has been supported by clinical studies and meta-analyses. While clinical data are promising, generally positive effects have occurred at high doses, due to the bioavailability of these compounds. Curcumin has poor bioavailability, which is why it has shown efficacy at high doses. To achieve adequate therapeutic efficacy, the dose must be increased without reaching the toxic dose, applied in combination with different compounds, or formulated using carrier systems.^[67] Similar bioavailability problems exist with berberine, resveratrol, and silymarin.^[68–70] This is an important point that should be evaluated both in terms of treatment compliance and cost.

Besides curcumin, berberine, and silymarin, many other herbs may have beneficial effects on liver diseases. *Camellia sinensis*, *Capparis spinosa*, *Cinnamomum* sp, *Glycyrrhiza* sp, *Linum usitatissimum*, *Panax ginseng*, *Phyllanthus urinaria*, *Rhus coriaria*, and *Zingiber officinale* also have clinical studies showed their effectiveness in liver diseases. However, the clinical study with these plants is too small number and include limited types of liver diseases at short treatment period.

Considering herbal products in terms of hepatotoxicity, the use of single-ingredient products is mostly safe. Toxicity cases have been mostly detected in multi-component herbal products. Bioavailability issues of plant phytochemicals have led herbal product manufacturers to develop preparation formulations to increase bioavailability or to use more than one plant together to increase efficacy. Attempts to increase bioavailabil-

ity obviously reach toxic doses. In products containing more than one plant, there may be pharmacodynamic interactions, untested or chemical substances added to the formulation, or the inability to adjust the dosage. In fact, all these toxicities stem from the lack of adequate evaluations and inspections of herbal products. The evaluation process of conventional drugs before they are put on the market is long and expensive, and these conditions are not required for herbal products. As a result, the product is produced without fully determining the content of the product, without toxicity studies, and reliability problems are experienced.

The Strengths and Weaknesses of this Review

To the best of our knowledge, this is the comprehensive review in the literature covering *in vitro*, *in vivo*, and clinical studies evaluating the role of herbals in the treatment of liver diseases. Since clinical studies are essential for the effective and safe use of herbals, this review is focused on them, and the most up-to-date data is presented at tables for clarity.

Conclusion

This review pointed out that herbals have important potential for the treatment of liver diseases. On the other hand, multicenter and large randomized studies for long-term efficacy and safety measurements are needed for herbals to be standard of care in routine hepatology clinical practice. By this way well-standardized herbal formulations of the right dose must be determined.

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