Short Communication

Herbal Supplements for Chronic Liver Disease: An Indian Perspective

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Abstract

Background: Around the world, 1.5 billion people are affected with chronic liver diseases, and the number is steadily rising. The treatment options available for various liver diseases such as non-alcoholic and alcoholic fatty liver diseases, cirrhosis, drug-induced liver injury, and hepatocellular carcinoma possess limited efficacy, carry colossal cost implications, and are linked with many adverse effects. The problem is pronounced in developing nations of the world. To fill this lacuna in the management of chronic liver diseases, the search for newer, efficacious, safer, and cost-effective therapies continues. Owing to their diverse effects and lower side effects, complementary and alternative therapies have received much interest in recent times for the treatment and management of liver diseases. Clinical trials and animal studies have established the hepatoprotective activity of several plants and polyherbal formulations. In this article, we review several widely used and identified medicinal herbs and phytochemicals in the treatment and management of chronic liver diseases including *Cichorium intybus, Phyllanthus niruri, Eclipta alba, Solanum nigrum, Terminalia arjuna, Picrorhiza kurroa, Andrographis paniculata, Tinospora cordifolia, Berberis aristata, Boerrhavia diffusa, Emblica officinalis, Terminalia chebula, Cassia occidentalis, Carum carvi, and Tamarix gallica.*

Key Words: Hepatoprotective herbs, herbal drugs, complementary and alternative medicine, chronic liver diseases, phytoconstituents

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INTRODUCTION

Chronic liver diseases (CLDs) cause significant morbidity and mortality across the globe[1]. WHO estimates suggest that 46% of global diseases and 59% of the mortality are attributed to chronic diseases with almost 35 million people in the world dying because of chronic diseases. Liver disease rates have been steadily increasing over the years[2]. Globally, 1.5 billion persons had chronic liver disease (CLD) in 2017, frequently resulting from nonalcoholic fatty liver disease (NAFLD; 60%), hepatitis B virus infection (29%), hepatitis C virus infection (9%), and alcoholic liver disease (2%). However, there is dearth of high quality, prospective data on the incidence of cirrhosis and CLD. The estimated incidence of cirrhosis in Europe is 26.0 per 100, 000, and the incidence in Asia ranges from 16.5 per 100, 000 in East Asia to 23.6 per 100, 000 in Southeast Asia[3]. Low- and middle-income countries are witnessing a demographic and epidemiologic transition in terms of disease burden, and India is one of the epicenters of this change[1]. An analysis conducted over three years (2010-2013) from 11 tertiary care centers across India demonstrated that at least one-third of patients with CLD have a remarkably advanced stage of decompensated cirrhosis. The study brought out the significance of alcoholism and diabetes in the development of CLDs in

India.1 In South Asia, NAFLD has also been shown to lead to significant CLDs at relatively low adiposity[1]. It has also been seen that 1%-2% of all hospital attendances in India were due to CLDs alone, and only one-fourth of all liver disease patients attending hospitals were newly diagnosed. Chronic liver disease mortality numbers in India have been progressively increasing since 1980[1]. Commonly occurring liver disorders include viral hepatitis, alcoholic liver disease, NAFLD, autoimmune liver disease, metabolic liver disease, drug-induced liver injury, and toxin-induced liver injury. Alcohol, viral infection, and drugs are the leading causes of liver toxicity. In the case of alcoholic liver diseases, pro-oxidant formation, inadequate intake of antioxidants, antioxidant depletion, and alcohol-mediated glutathione synthesis lead to oxidative stress[3]. Treatment options available for these liver disorders are often limited in efficacy, carry the risk of adverse effects and are often too costly, especially for the developing nations. The effectiveness of treatments such as interferon, colchicine, penicillamine and corticosteroids are inconsistent, and the incidence of side effects is profound[4]. These therapies, such as antiviral agents are often difficult for patients to tolerate[5]. Moreover, these treatment modalities do not yield satisfactory outcomes for patients[6]. Because of the scarce treatment options, limited efficacy, and significant adverse effects associated with conventional medicinal agents, there is an urgent need for novel prophylactic and therapeutic agents for the management of CLDs. Recent years have witnessed an increasing number of herbal products, including medicinal herbs and phytochemicals. These have been used for treating CLDs worldwide due to their high abundance, long-lasting curative effects, and fewer adverse effects[6].

Earlier studies have provided evidence that medicinal herbs and phytochemicals could protect the liver by several mechanisms such as eliminating virus, blocking fibrogenesis, inhibiting oxidative injury, and suppressing tumorigenesis[6]. Several phytomolecules obtained from plants sources have been reported to possess potent hepatoprotective, immunomodulatory, and antioxidant properties[7]. CLDs require long-term treatment; hence, reducing side effects of therapy is critical when developing novel hepatoprotective agents[6]. Till date, there have been very few universally effective options for the treatment of CLDs. Herbal treatment has been used to alleviate disorders related to liver and other internal organs for many centuries in the eastern world and have currently become a favorable therapy internationally for pathological liver conditions[8]. Usually, one natural agent has several therapeutic effects such as antioxidant, anti-inflammatory, antiviral, and antitoxic properties[9]. Treatment with herbal medicine focusses on re-establishing or reinforcing natural healing process and wellness. Phytomedicine has been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of liver disease. Clinical research and experimental studies on animal models have confirmed the efficacy of several plants in the treatment of liver disease, thereby causing patients to seek primary or adjunctive herbal treatments[10].

Phytoconstituents for liver diseases

The immunomodulatory, antioxidant, and hepatoprotective activities of herbal medicines have been used in the management of liver diseases of various etiologies. There are several plants and polyherbal formulations known to possess hepatoprotective activities. Almost 150 phytoconstituents from 101 plants have been identified to have liver-protecting activity. In India, more than 87 medicinal plants are used in different combinations in the preparation of 33 patented hepatoprotective herbal formulations[11]. In this paper, we review several widely used and recognized medicinal herbs and phytochemicals currently used for the treatment of CLDs, such as *Cichorium intybus, Phyllanthus niruri, Eclipta alba, Solanum nigrum, Terminalia arjuna, Picrorhiza kurroa, Andrographis paniculata, Tinospora cordifolia, Berberis aristata, Boerrhavia diffusa, Emblica officinalis, Terminalia chebula, Cassia occidentalis, Carum carvi, and Tamarix gallica.*

Cichorium intybus

Chicory or *Cichorium intybus* L. (*Kasani*) has several biological activities. Native to Europe and Asia, it has been widely used in traditional therapy for the management of gastrointestinal and inflammatory disorders. *In vivo* studies have shown hepatoprotective effects of *C. intybus* L. mediated by natural antioxidants in chicory roots, via significant attenuation of the oxidative threat and restoration of normal hepatic function[12]. Ethnobotanical studies have reported the use of leaves in treating jaundice, liver disorders, vomiting, loose motion, fever, and pleurisy. Various parts of the plant are noted to have a beneficial role in treating liver diseases and enlargement of spleen and liver, and as bitter tonic effective in jaundice[13]. Pharmacological studies of the root extracts from *C. intybus* have confirmed their anti-inflammatory and hepatoprotective activities[14]. *C. intybus* is one of the constituents of a traditional Indian tonic Liv-52 widely used as a hepatoprotective agent. In a randomized, double-blind clinical trial conducted on cirrhotic patients, a herbal formulation comprising *C. intybus* significantly lowered serum levels of hepatic enzymes alanine aminotransferase (ALT, $P<0.044$) and aspartate aminotransferase($P<0.029$), improved Child-

Pugh scores, and decreased the incidence of ascites[15]. Another herbal blend, Jigrine containing *C. intybus* as one of the constituents was evaluated for its hepatoprotective activity against galactosamine-induced hepatopathy in rats. The results showed a significant reduction in the levels of AST, ALT, and urea, and an increase in the levels of blood and tissue glutathione. Pre-treatment with the study formulation for 21 days decreased serum levels of AST), ALT, urea, and tissue thiobarbituric acid reactive substances significantly (P<0.01). Jigrine pre-treatment significantly prevented galactosamine toxicity as revealed by well-preserved cytoplasm of hepatic cells[16]. An aqueous-methanolic extract of seeds from *C. intybus* has also been investigated for its hepatoprotective activity against acetaminophen and carbon tetrachloride (CCl_4)-induced liver damage in mice. Results showed that it reduced mortality and serum levels of alkaline phosphatase (ALP), glutamyl oxaloacetate transaminase (GOT), and glutamyl pyruvate transaminase (GPT)[17]. CCl_4 and paracetamol-induced liver toxicities were also reported to be offset by intraperitoneal administration of crude extracts and fractions of *C. intybus.* The methanol and water-soluble fractions exhibited marked reductions in serum glutamyl pyruvate transaminase, serum glutamyl oxaloacetate transaminase, ALP, and total bilirubin levels[18]. A phenolic acid-rich seed extract of *C. intybus* was found to be effective in decreasing hepatic steatosis in vitro and in vivo. The seed extract also caused increased release of glycerol in steatotic cells. The hepatoprotective activity of *C. intybus* has been correlated to its ability to inhibit free radical-mediated damage. In a study evaluating the effect of chicory seed extract on hepatic steatosis in vivo in rats as a result of early or late-stage diabetes and in vitro in HepG2 cells via bovine serum albumin (BSA)-oleic acid complex, chicory extracts prevented significant histological damage (steatosis-inflammation-fibrosis) to cells and tissues and downregulation of sterol regulatory element-binding protein-1c (SREBP)-1c and peroxisome proliferator-activated receptor alpha (PPARα) genes that followed steatosis induction[19].

Phyllanthus niruri

Phyllanthus niruri sensu Hook. F. Non Linn *(Bhumyamalaki),* a herb found in South East Asia, has been traditionally used to treat many pathological conditions like dyspepsia, bronchitis, influenza, asthma, dysentery, tumors, diabetes, vaginitis, and tuberculosis[20]. It has also been used for its potent activity in the treatment of kidney stones, gallstones, and various liver disorders, especially hepatitis and jaundice[21]. Animal studies have shown that *P. niruri* possesses hepatoprotective properties against induced hepatitis in rats, and it has a therapeutic effect on type 2 diabetes mellitus, which is associated with hypercholesterolemia. Epicatechin pre-treatment increased all the antioxidant enzymes and decreased the levels of glutathione S transferase (GST), ALP, AST, and malondialdehyde (MDA) in rats with hepatitis. Moreover, histopathologic studies also established that (-)-epicatechin pre-treatment decreased hepatitis-induced tissue damage[22]. Flavonoids and phenolic compounds present in *P. niruri* are responsible for its potent antioxidant activity, which is in turn responsible for its role in hepatoprotection[23]. In another study, *P. niruri* reduced visceral adiposity, improved abnormalities in liver enzymes, and decreased hepatic lipid peroxidation and fat accumulation. It also reduced the risk of atherosclerosis related to NAFLD induced by a high-fat diet in Sprague-Dawley rats. This was the first study to establish the therapeutic use of *P. niruri* as a natural source for treating NAFLD. It has also been reported that *P. niruri* reduced hepatic fibrosis by reducing the levels of hepatic MDA, which is involved in hepatic stellate cell activation and thereby fibrosis. Moreover, *P. niruri* extract significantly reduced hepatomegaly (16%) and visceral fat weight (22%), decreased NAFLD score, prevented fibrosis, and reduced serum total cholesterol (TC; 48%), low-density lipoprotein cholesterol (LDL-C; 65%), free fatty acids (25%), ALT (45%), ALP (38%), insulin (67%), homeostatic model assessment of insulin resistance (73%), serum atherogenic ratios (TC/high-density lipoprotein cholesterol [HDL-C; 29%], LDL-C/HDL-C [66%], and non-HDL-C/HDL-C [64%]), hepatic cholesterol (43%), triglycerides (29%), and MDA (40%) in treated rats compared with non-treated rats[24]. Studies have also shown that the *P. niruri* extract possesses potent protective effects against viral hepatitis and against toxicity caused by different drugs or environmental toxicants. A preclinical study was performed to determine the protective role of *P. niruri* against liver cirrhosis induced by thioacetamide (TAA) in rats. Progression of liver cirrhosis induced by TAA in rats could be intervened using the *P. niruri* extract and these effects were comparable to those of silymarin. Treatment with *P. niruri* caused significant increases in serum ALP, ALT, bilirubin, and gamma-glutamyl transferase (GGT). It was also seen that levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX) increased in TAA-treated rats compared with control rats, and the total antioxidant capacity values were also substantially increased in the treatment groups[25]. In a study assessing the effect of a crude extract of *P. niruri* on alcohol and polyunsaturated fatty acid-induced oxidative stress, oxidative stress and associated damage were effectively reduced, and severity

of pathological change fibrosis was altered by the *P. niruri* extract. The hepatoprotective nature of *P. niruri* can be attributed to the presence of several bioactive compounds such as lignans, alkaloids, terpenoids, and tannins [26].

Eclipta alba

Eclipta alba (L.) Hassk. (*Bhringraj)* is reported to be the best drug for treating liver cirrhosis and infective hepatitis. The active principles responsible for its action are wedelolactone, demethylwedelolactone, and saponins[27]. Pharmacological activities of whole plant extract and individual phytoconstituents have shown anticancer, hepatoprotective, snake venom neutralizing, anti-inflammatory, and antimicrobial properties. Alcoholic extract of *E. alba* was found to have good anti-hepatotoxic activity as assessed in CCl_4-induced liver damage in albino rats[28]. *E. alba* extract also has inhibitory activity against hepatitis C virus (HCV). *In vitro* studies showed that its extract strongly inhibited RNA-dependent RNA polymerase activity of HCV replicase. In a cell-culture system, it effectively inhibited HCV replication, which resulted in reduced HCV titers and levels of viral proteins[29]. The whole plant extract has been tested for hepatoprotective effect against paracetamol-induced hepatotoxicity in mice. It was seen that serum ALT levels were significantly raised in animals receiving paracetamol and were reduced significantly (P<0.01) in animals receiving paracetamol and *Eclipta alba* extract. Histopathological studies also showed remarkable lowering of paracetamol-induced fatty degeneration and centrizonal necrosis in livers of extract-treated mice[30]. Similarly, fresh leaf powder and alcoholic extracts of leaves and roots caused significant hepatoprotective action against paracetamol-induced liver toxicity in rats and also normalized the levels of serum ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), and GGT [31-33]. Rats with paracetamol-induced hepatotoxicity showed an increase in serum enzymes ALP, acid phosphatase (ACP), and 5-nucleotidase, which are indicative of hepatic necrosis. A considerable decrease in serum urea and increase in serum cholesterol observed in rats with paracetamol-induced hepatotoxicity were found to be normalized by treatment with *E. alba.* The hepatoprotective activity of *E. alba* has also been proven effective in reducing side effects[34]. Ethanolic extract of *E. alba leaves* and leaf callus showed hepatoprotective effects by restoring the levels of serum parameters to near normal levels and by improving hepatic lesions caused by CCl_4. Oral administration of ethanolic extracts at 250 mg/kg and 300 mg/kg doses showed significant hepatoprotective effect from CCl_4-induced liver injuries. Callus extract (20 mg) had a higher cardiac inhibitory activity than leaf extracts (20 mg)[35].

Solanum nigrum

Solanum nigrum f. luridum Wessely *(Makoy, Kakamachi)* is a herbal plant that has been used as a hepatoprotective and anti-inflammatory agent. It has been extensively used in traditional medicine in India and other parts of the world to cure liver disorders, chronic skin ailments, inflammatory conditions, painful periods, fever, diarrhea, eye diseases, and hydrophobia, and as a folk medicine for the treatment of peptic ulcer. A study showed that *S. nigrum* offers potent hepatoprotection owing to its high flavonoid content[36]. In rats with CCl_4-induced chronic hepatotoxicity, an aqueous extract of *S. nigrum* was found to protect the liver against CCl_4-induced oxidative damage, and this hepatoprotection was attributed to modulation of detoxification enzymes, antioxidant properties, and free radical-scavenging effects[37]. Another study assessed the *in vivo* and *in vitro* effects of *S. nigrum* extracts on non-alcoholic fatty liver (NAFL)-induced hepatitis. *In vivo* data demonstrated that the *S. nigrum extract* reduced blood triglyceride, sugar, and cholesterol levels, as well as fat accumulation, oxidative stress, and lipid peroxidation in high-fat-diet treated mice. The extract could also alleviate NAFL-induced hepatitis and could potentially be used to develop health-food products for preventing NAFL. The results also showed that the *S. nigrum* extract also downregulated the expression of fatty acid synthase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and SREBP via the AMP-activated protein kinase pathway and upregulated the expression of carnitine palmitoyl transferase 1 and PPARα[38]. Another study had also shown protection of hepatocyte integrity via reduced release of liver GSTA1 in ethanol-induced injury, thereby causing liver detoxification`[39]. Earlier studies have proven the anti-fibrotic role of *S. nigrum* against TAA-induced toxicity[40]. The dried fruits of *S. nigrum* also possess anti-hepatotoxic potential when administered for 7 days on a pre-treatment basis against a single oral dose of CCl_4. A significant (P<0.001) reduction in AST, ALT, ALP, and total bilirubin levels was observed with restoration to near-control levels in rats treated with an ethanol extract of dried fruits of *S. nigrum* in comparison with CCl_4-treated rats[41]. In rats administered with a single intraperitoneal dose of CCl_4, pre-treatment with *S. nigrum* extract for 7 days caused reduction in the levels of liver marker enzymes, decrease in lipid peroxidation, and improvement in histopathological features. In the extract-treated group, the toxic effect of CCl_4 was controlled significantly (P<0.05) by the maintenance of structural integrity of hepatocyte cell membrane and normalization of the

functional status of the liver. Histology of liver sections from *Solanum nigrum* and *Cichorium intybus* possess significant hepatoprotective activity in comparison to standard drug silymarin[42].

Terminalia arjuna

Also known as an adaptogen, the bark of *Terminalia arjuna* Wight and Arn. (*Arjuna)* tree is used in Ayurvedic preparations for its hepatoprotective effect. In animals treated with an hydroalcoholic extract of *T. arjuna*, a dose-dependent and significant increase in the activity of enzymes ALP, GOT, and GPT. The extract also caused a significant increase in glutathione level[43]. Results of another study conducted to evaluate the protective effect of the aqueous extract of *T. arjuna* against CCl_4-induced hepatic and renal disorders in mice showed that the extract possesses protective action against both hepatic and renal dysfunctions. The extract caused an alteration in serum levels of GPT, ALP, GST, SOD, and catalase in liver and kidney tissue homogenates of CCl_4-treated mice. The extract was also found to have intense free radical-scavenging activity, which was comparable to that of vitamin C [44]. Another study showed that treatment with an extract of *T. arjuna* bark partially reversed the damage caused by alloxan, such as periportal fatty infiltration, and necrosis of hepatocytes. Results of another study revealed the regenerative effect of *T. arjuna* on exocrine cells of the pancreas, thereby indicating that this agent could have positive effects on insulin secretion. Evidence from animal studies has confirmed that *T. arjuna* extract can effectively improve liver, kidney, and pancreas function and reduce the lesions associated with the diabetic state in rats with alloxan-diabetes[45].

Picrorhiza kurroa

In India, *Picrorhiza kurroa* Royle ex Benth. (*Katuki)* has been commonly used and is a well-established treatment for jaundice. The plant has also been proven to be hepatoprotective in various animal models. In a double-blind trial in patients with viral hepatitis, *P. kurroa* rhizome powder was found to be hepatoprotective[46].

An Ayurvedic formulation containing 50% *P. kurroa* was found to be effective in viral hepatitis in a double-blind trial [47]. Extracts of roots and rhizomes of *P. kurroa* have shown hepatoprotective activity in diverse models of liver toxicity[48]. The iridoid glycosides present in *P. kurroa* are effective in treating hepatic, inflammatory, bacterial, viral, mutagenic, cancer, and other infections. Picrosides from *P. kurroa* due to their antioxidant potential are effective in treating hepatic and respiratory disorders[49]. A study has shown that intervention with standardized plant extracts of *P. kurroa* regressed several features of NAFLD, such as hepatic steatosis, fatty infiltration, and cholestasis. In male Wistar rats administered with 2 oral doses (200 and 400 mg/kg bid) of a hydroalcoholic extract of *P. kurroa* for 4 weeks, histopathological results showed reversal of fatty infiltration of the liver and reduction in the quantity of hepatic lipids as compared with control rats [50].

P. kurroa has also been found to be useful in clinical and biochemical recovery in acute hepatitis. Literature also shows that it is a powerful immunomodulator rather than an antiviral drug for liver diseases[51].

Andrographis paniculata

Traditionally used in Ayurvedic medicine, *Andrographis paniculata* (Burrn .f.) Nees (*Kalmegh)* has analgesic, antioxidant, antibiofilm, gastroprotective, wound healing, antifilarial, antimicrobial, anticancer, and antimalarial effects[52,53]. It has also been employed as a hepatostimulant and hepatoprotective agent[54,55]. The effect of andrographolide in *A. paniculata was* reported to be more potent than silymarin against acetaminophen-induced reduction of the volume and contents of bile[56]. It also showed a significant dose-dependent protective action against acetaminophen-induced toxicity in isolated rat hepatocytes. A hepatoprotective effect of andrographolide has also been observed against galactosamine-induced hepatotoxicity in rats.[4] It Supplementation with herbal formulations of andrographolide and arabinogalactan proteins at doses of 500 mg/kg and 125 mg/kg, respectively, was found to have efficacy comparable to 500 mg/kg of silymarin in mice with ethanol-induced hepatotoxicity in mice[56]. Another study has shown the hepatoprotective effects of a crude alcoholic extract of *A. paniculata* leaves against CCl_4 -induced liver damage. A dose of 300 mg/kg of the extract was found to be effective in preventing liver damage, as confirmed by morphological (significant changes in liver weight and volume), biochemical (significant reduction in ALT and ALP levels), and functional (significant [$P<0.05$] reduced sleeping time) parameters[57]. Similar effects have also been seen against paracetamol-induced toxicity in an *ex vivo* rat model of isolated hepatocytes[58]. An animal study showed that methanolic extract of *A. paniculata* could potentially inhibit the progression of hepatotoxicity in ethanol-fed rats. In this study, oral administration of 100 mg/kg and 200 mg/kg of the methanolic extract caused significant ($P = 0.05$) and dose-dependent protection against ethanol-induced hepatotoxicity[59]. This hepatoprotective activity of *A. paniculata* was also seen at a dose of 400 mg/kg[60].

Tinospora cordifolia

Tinospora species are used as herbal remedies for the treatment of various diseases and have very few toxic effects. Commonly known as 'Guduchi,' it is an important medicinal plant in Ayurveda, with its stems

and roots forming an integral constituent of several herbal formulations. It is a potent tonic and is effective for chronic debilitating ailments, dyspepsia, fever, and urinary diseases[61]. Existing evidence also suggests that it possesses potent immunomodulatory activity, which has been attributed to the presence of 7 active immunomodulatory compounds isolated from the herb[62,63]. *Tinospora cordifolia* (Thunb.) Miers (*Guduchi Ghan, Giloy satva*) is known to effectively prevent hepatotoxicity. However, *T. crispa*, another plant of the same genus, may induce hepatotoxicity; therefore, it is essential to differentiate between the 2 species[64]. Treatment with an aqueous extract of *T. cordifolia* was found to increase intestinal absorption and liver retention of vitamins in alcohol-induced multivitamin deficiency as confirmed by significant downregulation of GGT, ALT, AST, triglyceride, TC, HDL-C, and LDL-C levels (P<0.05), and restoration of 2-O-p-coumaroyltartronic acid and biotin levels in asymptomatic moderate alcoholic volunteers without CLD[65]. *T. cordifolia* extract also elicited inactivating property against hepatitis B and E surface antigens *in vitro*[66]. The hepatoprotective activity of different extracts of *T. cordifolia* has been attributed to the presence of biologically active phytoconstituents, such as flavonoids and alkaloids[67]. Suppressed Kupffer cell function, which is an indicator of liver damage, was found to be significantly (P<0.01) improved in a rat model of CLD following treatment with *T. cordifolia* compared with vehicle-treated animals[68]. A study conducted to assess the effect of *T. cordifolia* in 30 patients with malignant obstructive jaundice, phagocytic and killing capacities of neutrophils were optimized only in patients receiving *T. cordifolia* (28.2+/-5.5% and 29.47+/-6.5%, respectively) and not in those receiving conventional management. In the extract-treated group, post-drainage bactobilia was observed in 7 patients, while none of the patients in this group showed clinical evidence of septicemia[69].

Berberis aristata

Berberis aristata DC. (*Daruharidra*) is an important medicinal plant widely used for the treatment of a range of ailments like eye infection, skin diseases, jaundice, and rheumatism[70]. The plant bark contains alkaloids like berberine, aromoline, karachine, palmatine, oxyacanthine, and oxyberberine[71].Berberine has antioxidant activity. In Wistar albino rats with CCl_4-induced hepatotoxicity, extracts from roots of *B. aristata* reduced levels of serum and liver lipid peroxides. Doses of 200 mg/kg (aqueous extract) or 300 mg/kg (methanolic extract) offered significant (P<0.001) hepatoprotective action by reducing the serum marker enzymes like ALT, AST ALP, ACP, and serum bilirubin. These results were comparable with those of silymarin (100 mg/kg p.o)[72]. In another study in rats with CCl_4-induced hepatotoxicity, histological assessment of liver sections showed preservation of architecture of hepatic cords and reduction in necrosis and inflammatory cell infiltration following treatment with an ethanolic extract of *B. aristate*[73].

Boerrhavia diffusa

Boerhaavia diffusa L. nom. cons. (*Punarnava*) known as "Punarnava" has been widely used in the traditional system of medicine. In India, the roots of this plant have been used to treat liver diseases. A decoction of the whole plant is recommended to be taken with milk in the early morning to cure jaundice and weakness. The roots are widely used for the treatment of dyspepsia, jaundice, enlargement of spleen, abdominal pain, abdominal tumors, and cancers[74]. Both aqueous and ethanolic extracts of *B. diffusa* have shown anti-cirrhotic activity in rats with dimethylnitrosamine-induced liver cirrhosis, in addition to increase in life span, prevention of body weight loss, and correction of biochemical and hematological parameters[75]. Multiple studies have confirmed the hepatoprotective activity of *B.* against ethanol-induced[76]. CCl_4-induced [77], acetaminophen-induced[78], and paracetamol-induced hepatotoxicity[79].

Emblica officinalis

Emblica officinalis L. (*Amalaki*) contains several antioxidants with many pharmacological activities for the treatment of several diseases and is also an integral part of several hepatoprotective formulations[80]. Current evidence suggests that *E. officinalis* is effective in preventing/ameliorating the toxic effects of hepatotoxic agents like ethanol, paracetamol, CCl^4, heavy metals, ochratoxins, hexachlorocyclohexane, antitubercular drugs, and hepatotoxicity resulting from iron overload. It has shown protective effects against chemical-induced hepatocarcinogenesis in animal models[80]. Similarly, administration of *E. officinalis* fruit extract at a dose of 250 mg/kg/day to rats with alcohol-induced liver mitochondrial dysfunction offered protection by simultaneously reducing carbonyl content and lipid peroxidation, and elevating activities of antioxidative enzymes succinate dehydrogenase, nicotinamide adenine dinucleotide dehydrogenase, and cytochrome C oxidase, and concentrations of cytochromes in hepatic mitochondria[81]. Furthermore, The antioxidant and hepatoprotective effects of fruit extract of *E. officinalis* have been confirmed in multiple studies in rats with alcohol-induced, CCl_4-induced, or arsenic-induced hepatotoxicity[82-85]. The restricted generation of free radicals is correlated to DNA protection resulting in the prevention of tissue necrosis and possible carcinogenesis. In the human hepatoma cell line HepG2, incubation with *E. officinalis* for 24 h resulted in significant alleviation in

the levels of lipid hydroperoxide (18%-42%) and reactive oxygen species (11%-29%). Additionally, it also raised the levels of glutathione (GSH; 18%-32%), antioxidant capacity (19%-31%), and activities of antioxidative enzymes (SOD, 25%-41%; catalase, 39%-50%; GSH peroxidase, 20%-35%; GSH reductase, 26%-35%; and GSH S-transferase, 12%-30%[86].

Terminalia chebula

Armed with a broad spectrum of biological activities, *Terminalia chebula* Retz. (*Haritaki*) *is* an important medicinal herb in Ayurveda. It is one of the ingredients of a popular herbal blend used for chronic disorders like diabetes, nervine disorder, and epilepsy[87]. Studies have elucidated the hepatoprotective effect of *T. chebula* extract, which can be attributed to its prominent antioxidative and membrane stabilizing activities. The extract was found to prevent hepatotoxicity caused by the administration of rifampicin, isoniazid, and pyrazinamide in combination in a sub-chronic mode (12 weeks)[88]. Pretreatment of mice with *T. chebula* extracts significantly reduced levels of serum AST and ALT and prevented hepatocyte destruction and inflamed cell infiltrations in the hepatic tissue as compared with control mice[89]. In a study, *T. chebula* extract was found to be useful in preventing liver fibrosis. by inhibiting phenotypic changes in hepatic stellate cells by reducing α-smooth muscle actin gene expression and protein reduction[90]. *Terminalia* extract contains large amounts of tannins, flavonoids, sterols, resins, fructose, amino acids, and fixed oils. Thus, *T. chebula* fruit extracts were found to protect the liver against diazinon-induced hepatotoxicity in male rats, an effect attributed to its antioxidant and anti-inflammatory properties[91].

Cassia occidentalis

Cassia occidentalis L. var. arista sensu Hassk. (*Kasamarda, kasoundi*) commonly known as 'Coffee senna' has several pharmacological activities including antibacterial activity, antihistamine release, antiplatelet aggregation, memory protection, and neuroprotection. Roots, flowers, seeds, and leaves of *Cassia* have been used in herbal medicine[92]. The hepatoprotective and healing effects of *C. occidentalis* in paracetamol-induced hepatic tissue damage were attributed to stabilization of plasma membrane by protecting the structural integrity of cells and repair of tissue damage[92]. Aqueous and methanol leaf extracts of *C. occidentalis* have been shown to possess significant hepatoprotective activity against CCl_4-, paracetamol-, and ethanol-induced hepatotoxicity in rats[93, 94]. In another animal study where *C. occidentalis* extract was given to rats with CCl_4-induced liver damage, serum levels of liver enzyme ALP, AST, and ALT revealed substantial differences versus control rats. These effects were dose dependent and thought to be curative and protective[95].

Carum carvi

Carum carvi L. (*Krishna jeeraka, kala jeera*)or caraway is an essential, valuable aromatic herb and has been employed as household medicine for several diseases including hepatobiliary complications[96]. It is traditionally used for the treatment of indigestion, pneumonia, and as an appetizer, galactagogue, and carminative. Studies have shown that *C. carvi* oils significantly reverse depleted hepatic cellular glutathione as compared to indomethacin. Caraway essential oils have shown significant suppressive effects on AST and ALT [97]. The pharmacological activities of *C. carvi* are attributed to the presence of essential and volatile oils, flavonoids, proteins, carbohydrate, and many vitamins and trace elements[98]. Essential oils of *C. carvi* fruits were assayed for their hepatoprotective effect against CCl_4-induced damage. Essential oils of *Carum carvi* L. fruits were able to reduce stable 2,2-diphenyl-1-picrylhydrazyl in a dose-dependent manner and neutralize hydrogen peroxide, Thus suggesting a hepatoprotective effect and role in reducing oxidative damage[99].

Tamarix gallica

Tamarix gallica L. (*Bahugranthih*) is traditionally used as an expectorant, laxative, astringent, antidiarrheal, and antidysentry agent[100]. It is a hepatic stimulant and tonic and an essential constituent of Ayurvedic herbal formulations. Galls and manna (gummy exudation) are usually used for therapeutic purposes. Orally pretreating rats with *T. gallica* extract (25 and 50 mg/kg) prevented TAA-promoted oxidative stress and toxicity, , significantly reduced the susceptibility of hepatic microsomal membrane for iron ascorbate-induced lipid peroxidation, hydrogen peroxide content, glutathione S-transferase, and xanthine oxidase activities. Thus, *T. gallica* may be a potent chemoprotective agent with role in preventing hepatic oxidative stress, toxicity, and hyperproliferative response[101]. Another study where *T. gallica* leaf extracts were investigated in Sprague Dawley rats with rifampicin plus isoniazid-induced liver injury, the levels of serum bilirubin, ALT, AST, ALP, LDH, and cholesterol were decreased, while levels of total protein and albumin ($p<.05$-$p<.05$) were increased, thereby confirming the hepatoprotective potential of *T. gallica*[102].

Advantages of herbal blends

Polyherbal formulations contain extracts from 2 or more plants and are available as solid or liquid formulations in the market. Around 40 commercial hepatoprotective polyherbal formulations are currently available in the Indian market under various trade names[103]. Various herbs used in Ayurveda are liver protective and corrective and possess a regenerating effect on the dead

liver cells. Evidence has also shown that herbal drug formulations have established efficacy in treating patients with acute viral hepatitis and CLD, including alcoholic liver disease [104,105]. Combined extract of *E. alba* leaves and *P. longum* seeds exhibited better hepatoprotective action against CCl_4-induced hepatotoxicity in rats than either extract individually as confirmed by normalization of serum marker enzymes as well as the improvement in biochemical parameters like total protein, total bilirubin, TC, triglycerides, and urea[103]. Two other polyherbal formulations, one containing *E. alba* along with *Clitoria ternatea, Asparagus racemosus, Alpinia galangal,* and milk tuttam, i.e. copper-containing stone and another containing whole plant *E. alba,* leaves of *Melia azadirachta,* and seeds of *Piper longum*, also showed hepatoprotective activity in rats[106,107]. A standardized mixture of 4 Ayurvedic herbs including *Phyllanthus niruri, Tephrosia purpurea, Boerrhavia diffusa,* and *Andrographis paniculata* was assessed for its hepatoprotective activity, and the results showed that the herbal blend prevented alcohol-induced toxicity in both *in vitro* and *in vivo* models; thus, it was thought to be beneficial for the treatment of alcoholic liver diseases or other conditions that may cause liver toxicity[108]. Another polyherbal formulation containing *Terminalia chebula. Piper nigrum, Eclipta alba, Citrus limon,* and ferrous sulphate showed hepatoprotective effect against ethanol-induced liver damage in rats[109]. A herbal blend of *T. gallica, C. intybus, S. nigrum,* and *T. arjuna* showed significantly better Child-Pugh scores, decreased ascites, and decreased serum ALT and AST levels in cirrhotic patients after 6 months of treatment, indicating that the herbal blend possessed hepatoprotective effects, which could be attributed to the diuretic, anti-inflammatory, antioxidative, and immunomodulating properties of the component herbs[15]. Thus, multiple studies have established that herbal formulations for liver diseases have multiple therapeutic effects, based upon their antioxidant, anti-inflammatory, antiviral, and/or antitoxic properties. Natural medicine is also preferred by patients owing to the diverse therapeutic effects and relatively mild side effects.

CONCLUSION

While liver disease rates have been steadily rising worldwide, treatment options for chronic liver disorders such as cirrhosis, fatty liver, alcoholic liver diseases, NAFLD, autoimmune liver disease, metabolic liver disease, drug or toxin-induced liver injury, and chronic hepatitis have not yielded satisfactory outcomes in patients. This has triggered the need for more efficacious and safe therapeutic options. Herbal medicines these have multiple benefits in therapy owing to their antioxidant, immunomodulatory, hepatoprotective, antiviral, and antitoxic properties. Herbs such as *Cichorium intybus, Phyllanthus niruri, Eclipta alba, Solanum nigrum, Terminalia arjuna, Picrorhiza kurroa, Andrographis paniculata, Tinospora cordifolia, Berberis aristata, Boerrhavia diffusa, Emblica officinalis, Terminalia chebula, Cassia occidentalis, Carum carvi, and Tamarix gallica* have been beneficial in the management of chronic liver diseases. However, the lack of adequate clinical trials has limited their therapeutic value in the treatment of chronic liver diseases. Further evidence needs to be generated on the efficacy and safety of herbal formulations via large-scale clinical studies in patients with chronic liver diseases.

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