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REVIEW ARTICLE

Recent advances in herbal medicine for treatment of liver diseases

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Abstract

Context: Liver disease is a serious ailment and the scenario is worsened by the lack of precise therapeutic regimens. Currently available therapies for liver ailments are not apposite and systemic toxicity inhibits their long term use. Medicinal plants have been traditionally used for treating liver diseases since centuries as the toxicity factor appears to be on the lower side.

Objective: Several phytochemicals have been identified which have significant hepatoprotective activity with minimal systemic adverse effects which could limit their long term use. The scenario calls for extensive investigations which can lead to development of lead molecules for hepatoprotective molecules of future. This review deals with the biological activity, mode of action and toxicity and forthcoming application of some of these leads.

Methods: These generally have strong antioxidative potential and cause induction of antioxidant enzymes like superoxide dismutase, reduced glutathione and catalase. Additional mechanisms of hepatoprotection include stimulation of heme oxygenase-1 activity, inhibition of nitric oxide production, hepatocyte apoptosis and nuclear factor- κ B activation.

Results and conclusion: Out of the several leads obtained from plant sources as potential hepatoprotective agents, silymarin, andrographolide, neoandrographolide, curcumin, picroside, kutkoside, phyllanthin, hypophyllanthin, and glycyrrhizin have been established as potent hepatoprotective agents. The hepatoprotective potential of several herbal medicines has been clinically evaluated. Significant efficacy has been seen with silymarin, glycyrrhizin and Liv-52 in treatment of hepatitis, alcoholic liver disease and liver cirrhosis.

Keywords: Andrographolide, antioxidant, curcumin, glycyrrhizin, hepatoprotective, kutkoside, phyllanthin, picroside, silymarin

Introduction

Chronic liver diseases represent a major health burden worldwide, with liver cirrhosis being the ninth leading cause of death in Western countries (Kim et al., 2002). Chronic viral hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, and hepatocellular carcinoma are the major entities and many problems remain unresolved. Treatment options for common liver diseases such as cirrhosis, fatty liver, and chronic hepatitis are often limited in efficacy, carry the risk of adverse effects and are often too costly, especially for the developing world. The effectiveness of treatments such as interferon, colchicine, penicillamine and corticosteroids

are inconsistent and the incidence of side-effects profound. Physicians and patients are in need of effective therapeutic agents with a low incidence of side-effects. Herbal medicines potentially constitute such a group. In recent years many researchers have examined the effects of plants used traditionally by indigenous healers to support liver function and treat diseases of the liver (Schuppan et al., 1999). In most cases, research has confirmed traditional experience and wisdom by discovering the mechanisms and modes of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies (Strader et al., 2002).

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Therefore, treating liver diseases with plant-derived compounds which are accessible and do not require arduous synthetic steps seems highly attractive (Fogden & Neuberger, 2003). In spite of the advances in conventional medicine in the last decades, research professionals are paying increasing attention to phytomedicine. Several recent surveys from Europe and the United States have demonstrated a sharp rise in the use of phytomedicine within a few years, and up to 65% of patients with liver disease take herbal preparations (De Smet, 2002). Many factors contribute to herbal medicine's appeal, including the claim that herbal medicine may both treat and prevent diseases. This adds to a deep belief that these treatments are safe because they are "natural" and, therefore, harmless alternative to conventional medicine. In addition, herbal products are often exempt from rigorous regulations, such as in the US, and prescriptions are usually not required for these inexpensive products. The following review describes the current scientific evidence regarding herbal drugs and the liver, especially in regard to their presumed beneficial effect.

Hepatotoxicity

Liver is one of the largest organs in the human body that performs numerous interrelated vital functions. Some of the commonly known disorders include viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, metabolic liver disease, drug induced liver injury, toxin-induced liver injury, etc. As a consequence of chronic liver disease, patient may develop portal hypertension and liver cirrhosis. Liver toxicity mainly occurs due to alcohol, viral and induced by drugs.

Alcoholic liver disease, including acute alcoholic hepatitis and alcoholic cirrhosis, is a major cause of morbidity and mortality in the Western world. In alcoholic liver disease, oxidative stress is caused by pro-oxidant formation, inadequate intake of antioxidants, antioxidant depletion, and alcohol-mediated inhibition of glutathione synthesis. Acetaldehyde is the most important metabolite of ethanol leading to liver damage. Alcohol-induced liver diseases are mediated by cytokines, which are secreted by liver and other parts of the body. In the liver, persistent cytokine secretion results in chronic inflammation leading to the conditions such as hepatitis, fibrosis, and cirrhosis. Cytokines, tumor necrosis factor- α (TNF- α) and transforming growth factor- β (TGF- β) regulate apoptosis, which is in part responsible for alcohol-induced destruction of liver tissue. Fibrogenesis within the liver takes place due to the activation of collagen-producing stellate cells which is mediated through expression of interleukins (ILs), such as IL-1, IL-6, IL-8 ultimately causing precipitation of collagen deposition (Tome & Lucey, 2004). Viral hepatitis is responsible for both acute and chronic liver diseases. Hepatitis A is caused by hepatitis A virus, a picornavirus transmitted by the fecal-oral route often associated with ingestion of contaminated food. Hepatitis

B is caused by hepatitis B virus, a hepadnavirus that can cause both acute and chronic hepatitis. Identified methods of transmission include blood, tattoos, sexual, or via mother to child by breast feeding. Hepatitis C may lead to chronic form of hepatitis culminating to cirrhosis. Hepatitis A is rarely life threatening, while B and C are quite serious and may be fatal. Several cytokines, including interferon- γ (IFN- γ) and TNF- α , are implicated in the pathogenesis of hepatitis. Chronic hepatitis B and C, mostly in the cirrhotic stage, are responsible for the great majority of cases of hepatocellular carcinoma worldwide (Michielsen et al., 2005).

Phytoconstituents with hepatoprotective potentials

Compounds with different structure but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of various diseases. Several phytomolecules including flavonoids, alkaloids, glycosides and saponins obtained from various plant sources have been reported as potent hepatoprotective agents (Flora et al., 1996). Plant tissues contain a wide variety of compounds with antioxidant activity. Phenolic compounds (flavonoids and phenolic acids), nitrogen compounds (alkaloids, chlorophyll derivatives, amino acids and amines), carotenoids, lignans and terpenes were reported to possess antioxidative activity in suppressing the initiation or propagation of the chain reactions (Hall & Cuppett, 1997). Flavonoids and phenolic compounds are the main antioxidative compounds of herbal drugs. The phenolic compounds exhibit considerable free radical scavenging activities, through their reactivity as hydrogen or electron-donating agents, and metal ion chelating properties (Rice-Evans et al., 1996). Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described. They may have beneficial health effects because of their antioxidant properties and their inhibitory role in various stages of tumor development (Levy et al., 2004). Some potent herbs with established hepatoprotective activity are described in the following section and in Table 1, where as some investigational lead molecules with significant hepatoprotective effects are mentioned in Table 2.

Silymarin

Silymarin obtained from *Silybum marianum* (L.) Gaertn. (Asteraceae/Compositae) commonly known as "milk thistle," is one of the oldest and thoroughly researched plants in the treatment of liver diseases (Luper, 1998; Mayer et al., 2005). It is the gold standard of hepatoprotective agents and has been widely used as comparative standard for test drugs in preclinical studies. It is a polyphenolic flavonoid that has anti-inflammatory, cytoprotective and anticarcinogenic effects. The pharmacological profile of silymarin has been well defined and hepatoprotective properties of silymarin have been investigated both *in vitro* and *in vivo*

Table 1. Herbs which are being investigated for use as hepatoprotective agents.

Plant	Plant	Major active components	Hepatoprotective activity	Type of study	Mechanism	References
<i>Byrsocarpus coccineus</i>	Connaraceae	Flavonols, glycosides	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Akidele et al., 2010
<i>Trichosanthes cucumerina</i>	Cucurbitaceae	CucurbitacinB, cucurbitacinE	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Sathesh et al., 2009
<i>Eruca sativa</i>	Brassicaceae	Fatty acids, glucoerucin, isothiocyanates	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Alqasoumi, 2010
<i>Alocasia indica</i>	Araceae	Cynogenetic glycosides, Alocasin, β-lectins	CCl ₄ and paracetamol induced	<i>In vivo</i>	Antioxidant effects	Mulla et al., 2009
<i>Forsythiae fructus</i>	Oleaceae	Pinoresinol, saponins, flavonoids	CCl ₄ -induced	<i>In vivo</i>	Antioxidative activity, inhibition of NF-κB	Kim, 2010
<i>Polygala arvensis</i>	Polygalaceae	Flavonoids, saponins	D-galactosamine induced	<i>In vivo</i>	Antioxidant effects	Dhanabal et al., 2006
<i>Cassia fistula</i>	Fabaceae	Antraquinone, polyphenols	Paracetamol induced	<i>In vivo</i>	Antioxidant effects	Bhakta et al., 2001
<i>Clerodendrum inerme</i>	Verbenaceae	Iridoid glycosides, verbascoside	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Gopal and Sengottuvelu, 2008
<i>Adhatoda vasica</i>	Acanthaceae	Quinazoline alkaloids, vasicine	D-galactosamine induced	<i>In vivo</i>	Antioxidant effects	Bhattacharyya et al., 2005
<i>Momordica dioica</i>	Cucurbitaceae	Flavonoids, saponins, momordicin	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Jain et al., 2008
<i>Amaranthus spinosus</i>	Amaranthaceae	Flavonoids, phenolic glycosides	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Zeashan et al., 2008
<i>Tinospora cordifolia</i>	Menispermaceae	Tinosporone, tinosporic acid, cordifolisides A to E	CCl ₄ -induced; Isoniazid + Rifampicin + Pyrazinamide induced	<i>In vivo</i>	Antioxidant effects	Bishayi et al., 2002; Parabia et al., 2007
<i>Nymphaea stellata</i>	Nymphaeaceae	Flavonoids, astragalin	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Bhandarkar and Khan, 2004
<i>Phellinus rimosus</i>	Hymenochaetaceae	Polyphenols	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Ajith and Janardhanan, 2002
<i>Cytisus scoparius</i>	Fabaceae	Flavonoids, sparteine, scoparin	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Raja et al., 2007
<i>Helminthostachys zeylanica</i>	Botrychiaceae	Flavonoids, quercetin, ugonin	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Suja et al., 2004
<i>Camellia oleifera</i>	Theaceae	Tannins, ellagitannins, sesamin	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Lee et al., 2007
<i>Strychnos potatorum</i>	Loganiaceae	Triterpenes, sterols, diabolone	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Sanmugapriya and Venkataraman, 2006
<i>Premna tomentosa</i>	Verbanaceae	Limonene, premnones A-C	Acetaminophen induced	<i>In vivo</i>	Antioxidant effects	Devi et al., 2004
<i>Lycium chinense</i>	Solanaceae	Cerebroside, glycolipids	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects and regulation of CYP2E1	Ha et al., 2005
<i>Azadirachta indica</i>	Meliaceae	Nimbin, nimbinin, nimbidin, azadirachtin	Paracetamol induced	<i>In vivo</i>	Antioxidant effects	Chattopadhyay et al., 1992; Yanpallewar et al., 2003
<i>Vitis vinifera</i>	Vitaceae	Resins	CCl ₄ -induced	<i>In vivo</i>	Antioxidant effects	Orhan et al., 2007
<i>Boerhaavia diffusa</i>	Nyctaginaceae	Punarnavine, punarnavoside, liiodendrin	Thioacetamide induced	<i>In vivo</i>	Antioxidant effects	Rawat et al., 1997

Table 2. List of lead molecules with hepatoprotective activity.

Isolated lead	Family	Hepatoprotective activity	References
Asiaticoside	<i>Centella asiatica</i>	Lipopolysaccharide (LPS)/D-galactosamine induced	Zhang et al., 2010
Cleomiscosins	<i>Cleome viscosa</i>	CCl ₄ -induced; thioacetamide induced	Gupta and Dixit, 2009a,b
Puerarin	<i>Pueraria lobata</i>	CCl ₄ -induced	Hwang et al., 2007
Celosin A (1) and celosin B (2)	<i>Semen celosiae</i>	CCl ₄ -induced	Sun et al., 2010; Xue et al., 2010
α - and β -amyrin	<i>Protium heptaphyllum</i>	Paracetamol induced	Oliveira et al., 2005
Rubiadin	<i>Rubia cordifolia</i>	CCl ₄ -induced	Rao et al., 2006
Dehydrocavidine	<i>Corydalis saxicola</i>	CCl ₄ -induced	Wang et al., 2008
Wedelolactone	<i>Eclipta alba</i>	CCl ₄ -induced	Singh et al., 2001
cichotyboside	<i>Cichorium intybus</i>	CCl ₄ -induced	Ahmed et al., 2008

(Pradhan & Girish, 2006). Experimental studies have demonstrated antioxidant and free radical scavenging properties. Silymarin also has significant antifibrotic activity. The active constituents of the plant are obtained from the dried seeds, where it is present in higher concentrations and consist of four flavonolignans which are collectively known as silymarin. Silymarin is a complex mixture of four flavonolignan isomers (Flora et al., 1998), namely silybin, isosilybin, silydianin and silychristin with an empirical formula C₂₅H₂₂O₁₀. The structural similarity of silymarin to steroid hormones is believed to be responsible for its protein synthesis facilitatory actions (Saller et al., 2001). Among the isomers silybin is the major and most active component and represents about 60–70%, followed by silychristin (20%), silydianin (10%), and isosilybin (5%). Most of its hepatoprotective properties are attributed to silybin (Figure 1).

Hepatoprotective activity against ethanol, acetaminophen, *Amanita phalloides* (Vaill. ex Fr.) Link and carbon tetrachloride (CCl₄) induced liver injury has been demonstrated (Muriel et al., 1992). It also produced hepatoprotective effects in acute viral hepatitis and alcohol related liver cirrhosis. The cytoprotective effects of silymarin are mainly attributable to its antioxidant and free radical scavenging properties (Miller, 1996). Silymarin also interacts directly with cell membrane components to prevent any aberration in the content of lipid fraction responsible for maintaining normal fluidity (Muriel & Mourelle, 1990; Wiseman, 1996). Anti-inflammatory actions of silymarin are due to inhibition of 5-lipoxygenase pathway which results in impaired leukotriene synthesis (Dehmlow et al., 1996). Liver fibrosis can result in remodeling of liver architecture leading to hepatic insufficiency, portal hypertension and hepatic encephalopathy. The conversion of hepatic stellate cells (HSCs) into myofibroblasts is considered as the central event in fibrogenesis. Silymarin inhibits nuclear factor- κ B (NF- κ B) and retards HSC activation. Silymarin blocked TNF-induced activation of NF- κ B in a dose- and time-dependent manner, mediated through inhibition of phosphorylation and degradation of I κ B α , an inhibitor of NF- κ B. Silymarin blocked the translocation of p65 to the nucleus without affecting its ability to bind to the DNA. NF- κ B dependent gene transcription was also suppressed by silymarin.

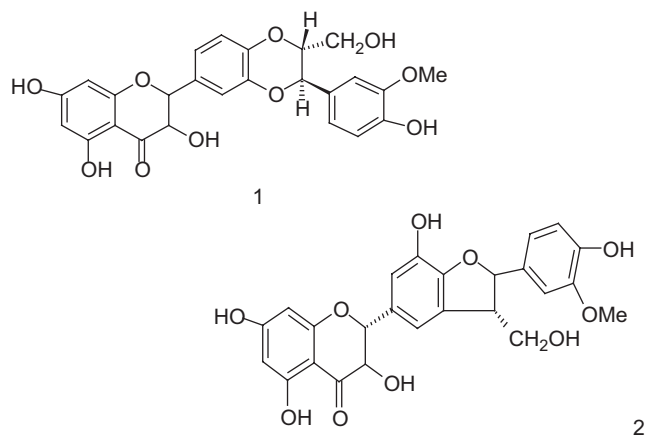


Figure 1. Structures of components of silymarin: (1) silybin; (2) silychristin.

Silymarin also inhibited the TNF-induced activation of mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase and abrogated TNF-induced cytotoxicity and caspase activation. Silymarin suppressed the TNF-induced production of reactive oxygen intermediates and lipid peroxidation (LPO) (Manna et al., 1999). It also inhibits protein kinases and other kinases involved in signal transduction and may interact with intracellular signaling pathways (Saliou et al., 1998; Johnson et al., 2002). Stimulation of protein synthesis by silymarin has important therapeutic implications in the repair of damaged hepatocytes and restoration of normal functions of liver (Sonnenbichler & Zetl, 1986). Silymarin has inhibitory effect on nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) gene expression in macrophages. Silymarin dose-dependently suppressed the lipopolysaccharide (LPS) induced production of NO in isolated mouse peritoneal macrophages and RAW 264.7 (murine macrophage-like cell line). Silymarin inhibits NO production and iNOS gene expression by inhibiting NF- κ B activation (Kang et al., 2002).

Glycyrrhizin

Glycyrrhizin is the major active constituent liquorice root [*Glycyrrhiza glabra* L., (Leguminaceae)] and has been used in traditional medicine to alleviate bronchitis, gastritis and jaundice. It is a mixture of calcium and potassium

salts of glycyrrhizic acid. The major constituents are glycyrrhetic acid (GA), flavonoids, hydroxycoumarins, and β -sitosterol, the latter with probable glucocorticoid and mineralocorticoid properties. Standardization of liquorice is done based on glycyrrhizin content. Enzymatic hydrolysis of glycyrrhizin using glucuronidase yields GA as an aglycone. Chemically, glycyrrhizin is a triterpenoid saponin named as (3- β , 20- β) -20- carboxy-11-oxo-30-norolean-12-en-3-yl 2- O- β - D-glucopyranuronosyl- α -D-glucopyranosiduronic acid (Figure 2).

Glycyrrhizin possesses anti-inflammatory and antioxidant activities. Glycyrrhizin inhibits CD4⁺T cell and TNF-mediated cytotoxicity (Yoshikawa et al., 1997). Glycyrrhizin has a membrane stabilizing effect (Shiki et al., 1992) and also stimulates endogenous production of interferons (Abe et al., 1994). In cell culture experiments, glycyrrhizin modifies glycosylation and blocks sialylation of hepatitis B surface antigen (HBsAg), leading to its retention in the Golgi apparatus (Takahara et al., 1994). Glycyrrhizin counteracts several forms of experimental hepatic injury and inhibits the activity of 11- β -hydroxysteroid dehydrogenase, PGE₂ production by macrophages, and has antioxidant properties through induction of glutathione S-transferase (GST) and catalase. Antifibrotic activity of glycyrrhizin could be attributed to its inhibitory activity on NF- κ B (Wang et al., 1998).

The beneficial effect of glycyrrhizin in CCl₄-induced liver injury has been evaluated. The serum activities of alanine transaminase (ALT) and aspartate aminotransferase (AST) and the hepatic level of malondialdehyde (MDA) were significantly higher after the CCl₄ treatment, while the concentration of reduced glutathione (GSH) was lower. These changes were attenuated by glycyrrhizin. CCl₄ increased the level of circulating TNF- α markedly, which was reduced by glycyrrhizin. The levels of hepatic iNOS, cyclooxygenase-2 (COX), and heme oxygenase-1 (HO-1) protein expression were markedly higher after the CCl₄ treatment. The mRNA expression of HO-1 was augmented by the glycyrrhizin treatment, while glycyrrhizin attenuated the increase in TNF- α ,

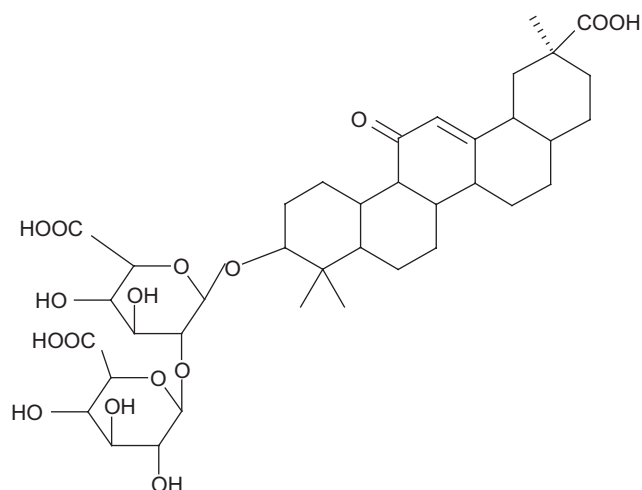


Figure 2. Structure of glycyrrhizin.

iNOS, and COX-2 mRNA expressions. These results suggest that glycyrrhizin alleviates CCl₄-induced liver injury, and this protection is likely due to the induction of HO-1 and the downregulation of proinflammatory mediators (Lee et al., 2007).

The protective effects of 18 β -GA, the aglycone of glycyrrhizin derived from liquorice, on CCl₄-induced hepatotoxicity and the possible mechanisms involved in this protection were investigated in mice. Pretreatment with GA prior to the administration of CCl₄ significantly prevented an increase in ALT, AST activity and hepatic LPO in a dose-dependent manner. In addition, pretreatment with GA also significantly prevented the depletion of GSH content in the livers of CCl₄ intoxicated mice. Protective effects of GA against the CCl₄-induced hepatotoxicity may be due to its ability to block the bioactivation of CCl₄, primarily by inhibiting the expression and activity of P450 2E1 (Jeong et al., 2002). In Japan, a standardised extract containing glycyrrhizin, cysteine and glycine is an established treatment for chronic hepatitis as Stronger Neominophagen C (SNMC) (Hidaka et al., 2007). SNMC can effectively protect liver against fulminant hepatic failure induced by galactosamine (D-GalN) and LPS. The levels of plasma TNF- α , NO, IL-6, and the degree of hepatic tissue injury were decreased in the SNMC-treated groups. SNMC prevented hepatocyte apoptosis evident from decreased expression of Cyt-C and caspase-3. SNMC stabilizes mitochondria membrane to suppress the release of Cyt-C and sequent activation of caspase-3 (Yang et al., 2007).

Andrographolide

Andrographis paniculata Nees. (Ap) (Acanthaceae) is a herbaceous plant native to India and Sri Lanka. *Andrographis* is called "king of bitters" due to its extremely bitter taste. Mostly the leaves and roots are used for medicinal purposes. The principal constituents are 14-deoxy-11-dehydroandrographolide, 14-deoxy-11-oxoandrographolide, andrographolide, andrographine, neoandrographolide, panicoline, paniculide-A, paniculide-B and paniculide-C. Chemically, andrographolide is a labdane diterpene lactone named as, 3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-naphthalenyl}ethylidene]dihydro-4-hydroxy, 2(3H)-furanone (Figures 3 and 4).

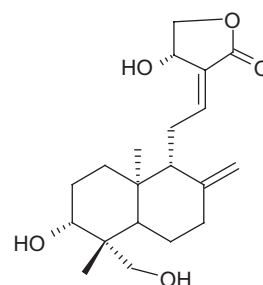


Figure 3. Structure of andrographolide.

Andrographolide, chief constituent extracted from the leaves of the plant, is a bitter water-soluble lactone and is responsible for the hepatoprotective activity of *A. paniculata* (Visen et al., 1993). Andrographolide, showed a significant dose-dependent protective activity against acetaminophen induced toxicity on isolated rat hepatocytes. It significantly increased the percentage viability of the hepatocytes as tested by Trypan blue exclusion and oxygen uptake tests. It completely antagonized the toxic effects of acetaminophen on certain enzymes (AST, ALT and ALP) in serum as well as in isolated hepatic cells. Antihepatotoxic activity of andrographolide (100 mg/kg, i.p.) was evaluated using CCl_4 intoxicated rats. Biochemical parameters like serum AST, ALT, ALP, serum bilirubin and hepatic triglycerides were estimated to assess the liver function (Handa & Sharma, 1990a). Hepatoprotective effect of andrographolide was studied on acute hepatitis induced in rats by single dose of galactosamine (800 mg/kg, i.p.). The results confirmed the *in vivo* hepatoprotective effect of andrographolide against galactosamine induced hepatotoxicity in rats (Handa and Sharma, 1990b). The protective activity of andrographolide against ethanol-induced hepatotoxicity in mice has been established (Singha et al., 2007).

The diterpenes andrographolide, andrographiside and neoandrographolide were investigated for their protective effects on hepatotoxicity induced in mice by tert-butylhydroperoxide (tBHP) intoxication. Pretreatment of mice with the diterpenes produced significant hepatoprotection in the toxin treated groups. Reduction in MDA formation and GSH depletion was observed in the animals treated with diterpenes, which suggests that antihepatotoxic activity of the diterpenes could be due to antioxidant mechanism (Kapil et al., 1993). Neoandrographolide has been reported to possess free radicals scavenging activity by donating the allylic hydrogen of the unsaturated lactone ring (Kamdem et al., 2002). Andrographolide and neoandrographolide were found to suppress NO production in LPS activated macrophages (Batkhuu et al., 2002). Also it has been found that neoandrographolide inhibits the activation of p38 MAPKs instead of JNK, ERK1/2, or

NF- κ B. These results indicated that the anti-inflammatory properties of neoandrographolide might result from the inhibition of iNOS and COX-2 expression through inhibiting p38 MAPKs activation (Liu et al., 2007).

Picrorhiza kurroa

Picrorhiza kurroa Royle Benth. (Scrophulariaceae) is a well-known herb in the Ayurvedic system of medicine and has traditionally been used to treat disorders of the liver and upper respiratory tract, reduce fevers, and to treat dyspepsia, chronic diarrhea, and scorpion sting. It is a small perennial herb from the Scrophulariaceae family, found in the Himalayan region. The active constituents are obtained from the root and rhizomes. Kutkin is the active principle of *Picrorhiza kurroa* and is comprised of kutoside and the iridoid glycoside picosides I, II, and III. Other identified active constituents are apocynin, drosin and nine cucurbitacin glycosides. Picroliv is a standardized iridoid glycoside mixture isolated from the roots and rhizomes of *Picrorhiza kurroa*. It contains at least 60% of a 1:1.5 mixture of picoside I and kutoside; the remainder (40%) is a mixture of iridoid as well as cucurbitacin glycosides and some still unidentified substances (VerMa et al., 2009). Chemically, these are iridoid glycosides with a common unit known as "catalpol." Picoside I is established as 6'-O-cinnamoylcatalpol, while kutoside is 10-vanilloylcatalpol (Figures 5 and 6).

Picroliv has been found to possess potent hepatoprotective activity against different hepatotoxins (Dwivedi et al., 1993). Hepatoprotective activity of picroliv has been established against thioacetamide (TAA) (Dwivedi

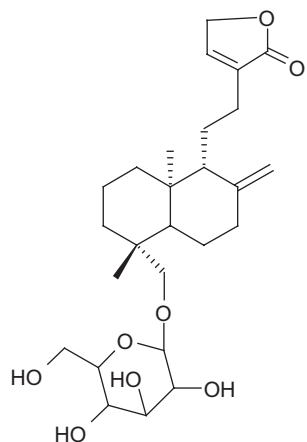


Figure 4. Structure of neoandrographolide.

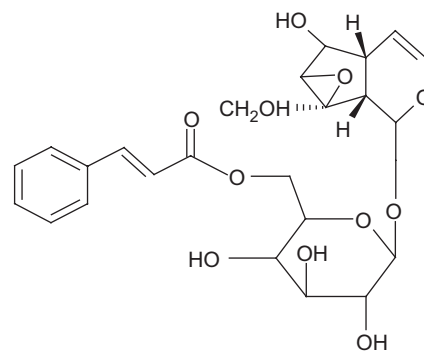


Figure 5. Structure of picoside 1.

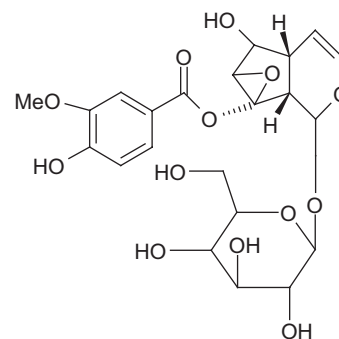


Figure 6. Structure of kutoside 1.

et al., 1991), CCl_4 (Dwivedi et al., 1990) and alcohol (Rastogi et al., 1996). CCl_4 treatment resulted in elevation of serum ALT and AST and reduction of liver GSH, G6PD, catalase and membrane-bound Na^+/K^+ ATPase which was reversed by administration of Picroliv. Thus, Picroliv offers significant protection against liver damage by CCl_4 by acting as free radical scavenger and inhibitor of LPO of liver plasma membrane (Santra et al., 1998).

Curcumin

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family, *Curcuma longa* L. (Zingiberaceae). Apart from culinary use, turmeric has been used in traditional medicine for the treatment of jaundice and other disorders of liver, parasitic infections, ulcers, inflammation of joints, various skin diseases, etc. Curcuminoids are a mixture of several structurally close phenolic compounds present in the rhizomes of turmeric. Three curcuminoids of major occurrence are curcumin (60–80%), demethoxycurcumin (10–20%), and bisdemethoxycurcumin (5–10%). Chemically, curcumin is a diferuloylmethane having a diferulic acid moiety fused with another carbon atom or methylene moiety. Thus, it has a methylene-1, 3-diketo group showing keto-enol tautomerism due to stabilization by hydrogen bonding. Curcumin exists mainly in keto-enol form rather than in a diketo form (Figure 7).

Curcumin attenuates liver injury induced by acetaminophen, CCl_4 , ethanol, TAA, iron overdose and cholestasis (Girish et al., 2009a; Bruck et al., 2007). Curcuminoids suppressed the increase of lactate dehydrogenase (LDH), ALT, and AST levels caused by D-galactosamine treatment (Miyakoshi et al., 2004). Aflatoxin B (1) is a potent hepatotoxic and hepatocarcinogenic mycotoxin. LPO and oxidative DNA damage are the principal manifestations of aflatoxin B₁ induced toxicity that could be counteracted by antioxidants. Aflatoxin B (1) administration significantly increased serum ALT, AST and γ -GT levels, LPO and reduced activities of GSH, SOD, catalase and GSH-Px. Curcumin showed a significant hepatoprotective activity by lowering the levels of serum marker enzymes, LPO and elevating the levels of GSH, SOD, catalase and GSH-Px (El-Agamy, 2010; Nayak & Sashidhar, 2010).

A study was carried out to demonstrate the potential protective effect of curcumin pretreatment against ethanol-induced hepatocytes oxidative damage, with emphasis on HO-1 induction. HO-1 is an important antioxidant enzyme (AOE) that plays a pivotal role in cytoprotection against noxious stimuli of both endogenous and exogenous origin. Ethanol exposure resulted in a sustained

MDA elevation, GSH depletion and evident release of cellular LDH and AST, which was significantly ameliorated by curcumin pretreatment. Induction of HO-1 by curcumin was dose-dependent. It was concluded that hepatoprotective activity of curcumin against ethanol involves HO-1 induction (Bao et al., 2010). It has been reported to induce expression of the AOE in various cell lines. In one study, it was found that oral administration of curcumin at 200 mg/kg dose for four consecutive days not only protected against dimethylnitrosamine (DMN)-induced hepatic injury, but also resulted in more than threefold induction of HO-1 protein expression as well as activity in rat liver. Inhibition of HO-1 activity by zinc protoporphyrin-IX abrogated the hepatoprotective effect of curcumin against DMN toxicity. NF-E2-related factor 2 (Nrf2) plays a role in the cellular protection against oxidative stress through antioxidant response element (ARE)-directed induction of several phase-2 detoxifying and AOE including HO-1. Curcumin administration resulted in enhanced nuclear translocation and ARE-binding of Nrf2. These findings suggest that ARE-driven induction of HO-1 expression by curcumin is involved in protection against DMN-induced hepatotoxicity (Farombi et al., 2008).

One study used liver slice culture model to demonstrate hepatoprotective activity of curcumin *in vitro*. Ethanol was used as hepatotoxin and the cytotoxicity of ethanol was estimated by quantization of the release of LDH. Ethanol induced increased release of LDH from the liver cells and twice the amount of LPO as compared to the cells from untreated liver tissue and this was significantly reduced in presence of curcumin (5 μM). The activity of AOE namely SOD, catalase and peroxidase was measured and found that in ethanol treated cells activity of all three enzymes was elevated. However, when curcumin was added along with ethanol their levels were kept low. The fact that release of LDH is significantly reduced along with LPO and the activity of AOE is kept low indicates that curcumin by its antioxidant activity reduced the oxidative stress induced by ethanol and protected the liver cells *in vitro* (Naik et al., 2004). Curcumin is capable of preventing NF- κB activation and therefore to prevent the secretion of proinflammatory cytokines (Reyes-Gordillo et al., 2007). CCl_4 administration in rats resulted in increased TNF- α , IL-1 β and IL-6 production, while curcumin remarkably suppressed these mediators of inflammation in liver damage. Administration of CCl_4 -induced the translocation of NF- κB to the nucleus, which was blocked by curcumin treatment (Rivera-Espinoza & Muriel, 2009). Thus, curcumin prevents acute liver damage by acting as an antioxidant and by inhibiting NF- κB activation and thus reducing production of proinflammatory cytokines.

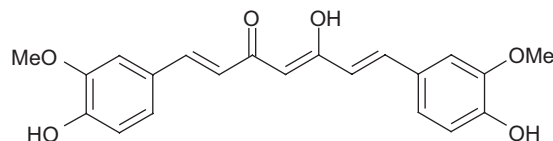


Figure 7. Structure of curcumin.

Phyllanthin

Phyllanthin is a lignan obtained from *Phyllanthus niruri* L. (Euphorbiaceae). It is a well-known Ayurvedic plant

used in folk remedy for jaundice and other liver disorders. The main plant constituents include alkaloids, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, phyllanthusiin D gallo catechins, geraniin, hypophyllanthin, lignans, lintetralins, lupeols, nirurin, phyllanthin, phyllanthine and phyllanthenol. Phyllanthin and hypophyllanthin have been established as the hepatoprotective agents (Harish & Shivanandappa, 2006). Chemically, both phyllanthin and hypophyllanthin are lignans (Figures 8 and 9). Whole plant, fresh leaves and fruits are used to treat various ailments, particularly hepatitis. This herb has shown potent antioxidant activity and hepatoprotective activity (Harish & Shivanandappa, 2006). Methanol and aqueous extract of leaves and fruits of *P. niruri* showed inhibition of membrane LPO, scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and inhibition of reactive oxygen species (ROS) *in vitro*. Antioxidant activities of the extracts were also demonstrable *in vivo* by the inhibition of CCl_4 -induced formation of lipid peroxides in liver of rats by pretreatment with the extracts. CCl_4 -induced hepatotoxicity in rats was prevented by pretreatment with the extracts, demonstrating the hepatoprotective action of *P. niruri*. Treatment with protein isolates of *P. niruri* significantly increase SOD and catalase which were reduced due to CCl_4 administration (Bhattacharjee & Sil, 2007).

In a study, the hepatoprotective potential of aqueous extract of the herb *P. niruri* on nimesulide induced hepatotoxicity by antioxidant activity was evaluated in mice. Nimesulide administration (8 mg/kg) for 7 days caused significant depletion of the levels of SOD, CAT and GSH, along with the increased levels of LPO. Intraperitoneal administration of the extract at a dose of 50 mg/kg body weight for 7 days, prior to nimesulide treatment, significantly increased levels of SOD, CAT, GSH and decreased MDA levels suggesting beneficial effect of the aqueous

extract of *P. niruri* could be due to its antioxidant property (Chatterjee & Sil, 2006). A study investigated the hepatoprotective and antioxidative property of phyllanthin using CCl_4 -induced toxicity in human hepatoma HepG2 cell line. Free radical scavenging activity of phyllanthin was examined using DPPH assay. CCl_4 treatment caused a significant decrease in cell viability, initiated LPO and caused leakage of ALT and LDH with a significant decrease in GSH levels. It was observed that phyllanthin effectively alleviated the changes induced by CCl_4 in a concentration-dependent manner (Krithika et al., 2009). The protective effect of phyllanthin on ethanol-induced rat liver cell injury has been investigated. Primary cultures of rat hepatocytes were pretreated with phyllanthin (1, 2, 3 and 4 $\mu\text{g}/\text{ml}$) for 24 h. After 24 h pretreatment, cells were treated with ethanol (80 $\mu\text{l}/\text{ml}$) for 2 h. Ethanol decreased %MTT, increased the release of ALT and AST with the increase in the production of intracellular ROS and LPO. Phyllanthin demonstrated its role in protection by antagonizing the above effect induced by ethanol. Phyllanthin also restored the antioxidant capability of rat hepatocytes including level of total glutathione, and activities of SOD and glutathione reductase (GR) which were reduced by ethanol. These results suggest the hepatoprotective effect of phyllanthin against ethanol-induced hepatotoxicity is through its antioxidant activity (Chirdchupunseree & Pramyothin, 2010). The antioxidant activity of some of the principal constituents of *Phyllanthus* namely Amariin, 1-galloyl-2-,3-dehydrohexahydroxydiphenyl-glucose, repandusinic acid, geraniin, corilagin, phyllanthusiin D, rutin and quercetin 3-*O*-glucoside were examined for their ability to scavenge free radicals in a range of systems including DPPH, ABTS, ferric reducing antioxidant power and pulse radiolysis. In addition, their ability to protect rat liver mitochondria against oxidative damage was determined by measuring the $\text{ROO}^\bullet$ radical induced damage to proteins and lipids and $^\bullet\text{OH}$ radical induced damage to plasmid DNA. The compounds showed significant antioxidant activities with differing efficacy depending on the assays employed. The ellagitannins Amariin, repandusinic acid and phyllanthusiin D showed higher antioxidant activity (Londhe et al., 2008).

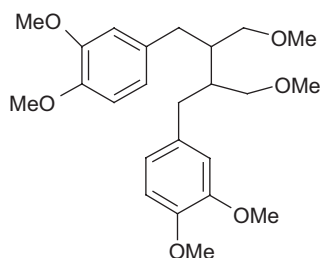


Figure 8. Structure of phyllanthin.

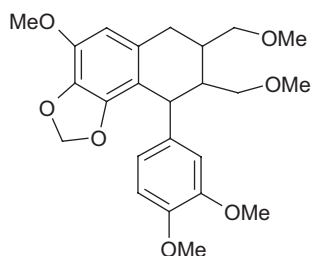


Figure 9. Structure of hypophyllanthin.

Berberine

Berberine is an alkaloid obtained from *Berberis aristata* L. (Berberidaceae). It is an edible plant employed in the South Asian Traditional Medicine, particularly its fruits being used as a tonic remedy for liver and heart. *Berberis aristata* is rich in alkaloids like berberine, oxyberberine, berbamine, aromoline, karachine, and oxycanthine. The isoquinoline alkaloid, berberine, is the major active constituent (Figure 10). Berberine has experimentally established hepatoprotective activity (Janbaza & Gilanib, 2000). Pretreatment of animals with berberine (4 mg/kg; orally twice daily for 2 days) prevented acetaminophen induced rise in serum levels of ALP, AST and ALT, suggestive of hepatoprotection. Pretreatment of animals with

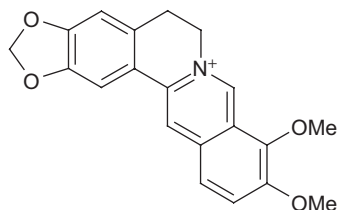


Figure 10. Structure of berberine.

a single oral dose of berberine (4 mg/kg) induced prolongation of the pentobarbital (60 mg/kg, i.p.) induced sleeping time as well as increased strychnine (0.3 mg/kg; i.p.)-induced toxicity, suggestive of inhibitory effect on microsomal drug metabolizing enzymes, cytochrome P450s (CYPs). The effects of berberine on ion channels of isolated rat hepatocytes have been studied. Berberine 1–300 $\mu\text{mol/l}$ reduced delayed outward potassium currents and Ca^{++} release-activated Ca^{++} currents in a concentration-dependent manner. Thus it was concluded that berberine has inhibitory effects on potassium and calcium currents in isolated rat hepatocytes, which may be involved in hepatoprotection (Wang et al., 2004).

One study investigated the effect of berberine on the early phase of hepatocarcinogenesis stimulated by diethylnitrosamine (DENa, 150 mg/kg, 4 weeks) plus phenobarbital (PB, 75 mg/kg, 7 days) in rats. The expressions of proliferating cell nuclear antigen (PCNA) and iNOS were evaluated by immunohistochemistry. Results showed that expressions of PCNA and iNOS were induced by DENa + PB in liver tissues. Oral administration of berberine (50 mg/kg) inhibited the hepatocyte proliferation and iNOS expression, decreased cytochrome P450 content and inhibited activities of CYP2E1 and CYP1A2 in DENa + PB treated rats *in vivo*. Also, berberine (10, 50 and 100 μM) inhibited activities of CYP2E1 and CYP1A2 in microsomes isolated from DENa + PB treated rats *in vitro*, suggesting that anti-hepatocarcinogenetic potential of berberine might be due to inhibiting oxidative metabolic activities of CYP 2E1 and CYP1A2, and decreasing NO production in rats (Zhao et al., 2008).

Embelin

Embelia ribes Burm.f. (Myrsinaceae) is a large scandent shrub with slender branches and elliptic-lanceolate and gland dotted leaves. The plant contains embelin, christembine, quercitol and resins. It is a widely used herb for its anthelmintic, analgesic, antifertility, hepatoprotective and antitumour properties. Embelin is the major active constituent and is responsible for the antioxidant and hepatoprotective activity (Mukherjee et al., 2007). Chemically embelin is 2,5-dihydroxy-3-undecyl-1,4-benzoquinone (Figure 11).

Free radical scavenging activity and LPO studies have been conducted using embelin to elucidate the hepatoprotective activity of embelin. After the induction of liver damage by CCl_4 intoxication to rats, the concentration of LPO was significantly higher in liver and serum, along with concomitant decrease in the levels of antioxidants

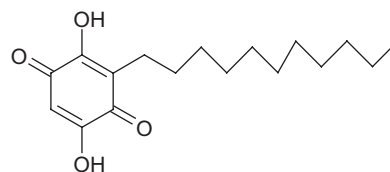


Figure 11. Structure of embelin.

and CYP450 enzyme in liver as compared to vehicle controls. The activities of marker enzymes-AST, ALT, ALP, γ -glutamyl transpeptidase, LDH, total bilirubin and total protein levels were altered significantly in the serum of CCl_4 treated rats. Treatment with embelin (oral, 25 mg/kg), significantly reduced hepatopathy, and results were comparable to silymarin. The study concluded that embelin acts as a natural antioxidant against hepatotoxicity induced in rats (Singh et al., 2009). The free radical scavenging reactions and antioxidant activity of embelin have been studied. It has been found to scavenge DPPH radical and inhibit hydroxyl radical induced deoxyribose degradation. It has been also found to inhibit LPO and restore impaired Mn-SOD in rat liver mitochondria. Further, kinetics and mechanism of the reactions of embelin with hydroxyl, one-electron oxidizing, organo-haloperoxyl and thiyl radicals have been studied using nanosecond pulse radiolysis technique. Its redox potential has been also evaluated with cyclic voltammetry. These studies suggest that embelin can act as a competitive antioxidant in physiological conditions (Joshi et al., 2007).

X-Linked inhibitor of apoptosis protein (XIAP) is a promising molecular target for the design of new anticancer drugs aiming at promoting apoptosis in cancer cells (Chen et al., 2006). Embelin has been recognized as a fairly potent, nonpeptidic, cell-permeable, small-molecule inhibitor of XIAP. The effects of embelin (50 mg/kg/day) against *N*-nitrosodiethylamine (DENa)-initiated and PB-promoted hepatocarcinogenesis were studied in Wistar rats. It was able to prevent the induction of hepatic hyperplastic nodules, body weight loss, increase in the levels of hepatic diagnostic markers, and hypoproteinemia induced by DENa + PB treatment indicating possible chemopreventive effects of embelin against DENa + PB-induced hepatocarcinogenesis in Wistar rats (Sreepriya & Bali, 2005). In a further study of effects of administration of embelin on LPO, hepatic glutathione antioxidant defense were examined during DENa + PB promoted hepatocarcinogenesis in rats. DENa + PB-induced hepatic damage was manifested by a significant drop in the hepatic glutathione antioxidant defense, increased LPO and histological alterations like dysplasia, and atypical cells with abnormal chromatin pattern. Treatment with embelin (50 mg/kg) prevented the drop in hepatic glutathione antioxidant defense, decreased LPO, and minimized the histological alterations induced by DENa + PB. Results indicate beneficial effects of embelin against oxidative tissue damage during chemically induced hepatocarcinogenesis in rats (Sreepriya & Bali, 2006).

Resveratrol

Resveratrol is a naturally occurring polyphenol which shows pleiotropic health beneficial effects, including antioxidant, anti-inflammatory, anti-aging, cardioprotective and neuroprotective activities. Resveratrol is a phytoalexin which is produced when plants are under attack from bacteria or fungi. Resveratrol is present in many plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts and giant knotweed. Also red wine is an abundant source of it. Chemically it is trans-3,5,4'-trihydroxystilbene (Figure 12).

It is a very potent antioxidant and this property has implications in anticarcinogenic, antidiabetic, neuroprotective and cardioprotective benefits. In order to investigate protective antioxidant action of resveratrol, primary rat hepatocyte cultures were exposed to 300 μ M tBHP and various concentrations of resveratrol (25, 50, 75 μ M). Necrosis was evaluated by LDH liberation to the medium. Resveratrol inhibited necrosis induced by tBHP. It also was effective in eliminating ROS. Results show that resveratrol protects primary rat hepatocytes in culture from oxidative stress induced cell death (Rubiolo and Vega, 2008). In order to elucidate the molecular mechanism of resveratrol in protecting liver cells from oxidative stress induced damage the activation of Nrf2 transcription factor that regulates the expression of antioxidant and phase II detoxifying enzymes was studied. Resveratrol pretreatment effectively protected hepatocytes in culture exposed to oxidative stress, increasing the activities of catalase, SOD, GPx, NADPH quinone oxidoreductase and GST. Resveratrol increases the level of Nrf2 and induces its translocation to the nucleus. Also, it increases the concentration of the mRNA for Nrf2. These results suggest that resveratrol could enhance the antioxidant status of hepatic cells and could be a useful drug for the protection of liver cells from oxidative stress induced damage (Rubiolo et al., 2008). In one study, the effect of subacute pretreatment with this natural compound on LPS-induced hepatotoxicity was investigated. Resveratrol counteracted LPS-induced lipoperoxidation and depletion of AOE activities as SOD and catalase. The polyphenol also abrogated LPS-induced liver and plasma NO elevation and attenuated endotoxemia-induced hepatic tissue injury. Resveratrol treatment abolished LPS-induced iron sequestration from plasma to liver. The results suggest that mode of action of resveratrol responsible for alleviating LPS-induced hepatotoxicity involves differential iron compartmentalization via iron shuttling proteins (Sebai et al., 2010).

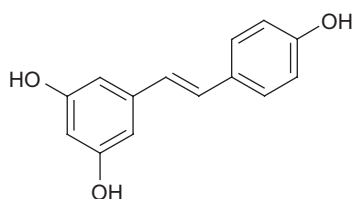


Figure 12. Structure of resveratrol.

A study was conducted to evaluate the preventive effect of resveratrol on ethanol-induced oxidative stress in rat liver. Rats were treated daily with 35% ethanol solution for 6 weeks. Chronic ethanol administration leads to hepatotoxicity as monitored by the increase in the level of hepatic marker enzymes and the appearance of fatty change, necrosis, fibrosis and inflammation in liver sections. Ethanol also enhanced the formation of MDA in the liver and decreased the activities of hepatic SOD, GPx and catalase. Dietary supplementation with resveratrol during ethanol treatment inhibited hepatic LPO and ameliorated SOD, GPx and CAT activities in the liver, indicating that resveratrol could have a beneficial effect in inhibiting the oxidative damage induced by chronic ethanol administration (Kasdallah-Grissa et al., 2007). The effects of resveratrol pretreatment on LPS (0.5 μ g/kg) induced hepatitis in D-galactosamine (800 mg/kg) sensitized rats has been investigated. Effect of resveratrol on iNOS and inducible HO-1 were studied. Resveratrol administration ameliorates liver damage induced by LPS plus D-galactosamine. Effects of resveratrol include reduction in NO, downregulation of NOS-2 and modulation of HO-1 which led to overall improvement in hepatotoxic markers and morphology after the hepatic insult (Farghali et al., 2009).

One study investigated the bioavailability of resveratrol from dietary sources and its effect on CCl₄-induced liver LPO. Ten rats were intragastrically administered for 14 days with a grape-stalk extract determining a daily dosage of resveratrol (3 mg/kg). After 1 week, the induction of liver LPO by CCl₄ was carried out. Serum and liver samples, at different time intervals, were collected to evaluate resveratrol content. Liver MDA as marker of oxidative stress was measured. Significant accumulation of resveratrol in liver was found after 14 days. The increase of MDA liver concentration due to CCl₄ injection after 1 week was reduced by 63% by treatment with resveratrol. Thus it was concluded that consumption of resveratrol from a dietary source resulted in a time-dose-dependent liver accumulation, which was able to counteract CCl₄-induced liver LPO thus demonstrating the hepatoprotective property of resveratrol (Vitaglione et al., 2009). Resveratrol inhibits NF- κ B, which regulates the transcription of several genes including cytokines such as the profibrogenic TGF- β . To elucidate the antifibrogenic mechanism of resveratrol, the activation of NF- κ B and the production of TGF- β were measured in CCl₄-induced cirrhosis in the rats. CCl₄ increased levels of NF- κ B and TGF- β along with increased fibrosis. Resveratrol administration decreased levels of NF- κ B and TGF- β and fibrosis. Results indicate that resveratrol possesses a strong antifibrogenic effect which is associated with its ability to reduce NF- κ B activation and TGF- β (Chávez et al., 2008). Resveratrol (10 mg/kg) was found to inhibit pyrogallol (40 mg/kg) induced hepatotoxicity. Resveratrol reduced pyrogallol-mediated increase in ALT, AST, bilirubin, LPO and catalytic activity of CYP2E1 and CYP1A2. Pyrogallol-mediated decrease in GST, GPx and GSH content was

significantly attenuated in resveratrol treated animals (Upadhyay et al., 2008).

Acteoside

Acteoside is a phenylethanoid glycoside obtained from *Cistanche tubulosa* (Schrenk) Wight (Orobanchaceae) and *Syringa vulgaris* L. (Oleaceae) (Figure 13). One study investigated the protective effects of acteoside on the CCl_4 -induced hepatotoxicity as well as the possible mechanisms involved in this protection. Pretreatment with acteoside prior to the administration of CCl_4 significantly prevented the increased serum enzymatic activities of ALT and AST and hepatic MDA in a dose-dependent manner. Glutathione content in the liver of CCl_4 intoxicated mice was increased. The effects of acteoside on cytochrome P450 2E1, the major isozyme involved in CCl_4 bioactivation were also investigated. Treatment of the mice with acteoside resulted in a significant decrease in the P450 2E1-dependent *p*-nitrophenol and aniline hydroxylation in a dose-dependent manner. The level of CYP2E1 protein was reduced. Acteoside exhibited antioxidant effects on FeCl_2 -ascorbate induced LPO in a mouse liver homogenate, and on superoxide radical scavenging activity. These results suggest that the protective effects of acteoside against the CCl_4 -induced hepatotoxicity possibly involve mechanisms related to its ability to block the P450-mediated CCl_4 bioactivation and free radical scavenging effects (Lee et al., 2004). Acteoside inhibited D-galactosamine induced death of hepatocytes. Acteoside has been found to reduce TNF- α induced cytotoxicity in L929 cells, thus indicating cytoprotective activities (Morikawa et al., 2010).

Acteoside exhibited stronger free radical scavenging activities than α -tocopherol on DPPH radical and xanthine/xanthine oxidase generated superoxide anion radical (Xiong et al., 1996). In a study, acteoside, 2'-acetylacteoside and isoacteoside significantly suppressed NADPH/ CCl_4 -induced LPO in rat liver microsomes. Addition of them to primary cultured rat hepatocytes efficiently prevented cell damage induced by exposure to CCl_4 or D-galactosamine (Xiong et al., 1998). The

hepatoprotective effect of acteoside was evaluated in BCG plus LPS-induced immunological liver injury (ILI) in mice. Acteoside (50, 150, or 300 mg/kg) was administered for 12 days. The liver index, liver homogenate levels of AST and ALT, hepatic NO, MDA content, SOD activity, production of TNF- γ and IL-2, 4, 10, as well as histopathological changes of the liver were evaluated following the 12-day treatment. Moreover, the modulation influence of acteoside on the expression of Bcl-2 (hepatocyte apoptosis inhibitor) and Bcl-2 associated X protein (Bax, hepatocyte apoptosis promoter) in the mice liver with immunological hepatic injury was also studied. Acteoside (50, 150, or 300 mg/kg) effectively reduced the BCG/LPS-induced elevated liver index, liver homogenate AST and ALT levels, hepatic NO and MDA contents, restored hepatic SOD activity and reduced the degree of liver injury. The expression of Bax was decreased (vs. BCG + LPS group), while the expression of Bcl-2 increased (vs. BCG + LPS group). These results suggest that acteoside has a protective and therapeutic effect on ILI mice, which might be associated with its antioxidant properties, immunoregulatory function and regulation of hepatic apoptosis (Zhao et al., 2009).

The effect of acteoside on hepatic apoptosis and the subsequent liver failure induced by D-GalN and LPS was assessed. A co-administration of D-GalN (700 mg/kg) and LPS (35 $\mu\text{g/kg}$) in mice evoked typical hepatic apoptosis characterized by DNA fragmentation and apoptotic body formation, resulting in fulminant hepatitis. Pre-administration of acteoside at 10 or 50 mg/kg subcutaneously at 12 and 1 h prior to D-GalN/LPS intoxication significantly inhibited hepatic apoptosis, hepatitis and lethality. TNF- α secreted from LPS-stimulated macrophages is an important mediator of apoptosis. Acteoside prevented *in vitro* TNF- α (100 ng/ml) induced cell death in D-GalN (0.5 mM)-sensitized hepatocytes at the concentrations of 50, 100 and 200 μM . These results indicated that D-GalN/LPS-induced hepatic apoptosis can be blocked by acteoside suggesting its antiapoptotic activity (Xiong et al., 1999).

Saichinone

Saururus chinensis (Lour.) Bail. (Saururaceae) has been used in Chinese folk medicine for treatment of various diseases, such as edema, jaundice, gonorrhea, antipyretic, diuretic, and anti-inflammatory agents. The diastereomeric lignan saichinone which is the active constituent of *Saururus chinensis* has cytoprotective and antioxidant activities (Figure 14). The hepatoprotective and antifibrotic effects of *Saururus chinensis* extract in CCl_4 -induced liver fibrosis rats has been evaluated (Wang et al., 2009). *Saururus chinensis* extract effectively reduced the elevated levels of serum ALT, AST, and hepatic MDA contents, enhance the reduced hepatic SOD activity in CCl_4 treated rats. The histopathological analysis suggested that *Saururus* extract alleviated the degree of liver fibrosis induced by CCl_4 . One study

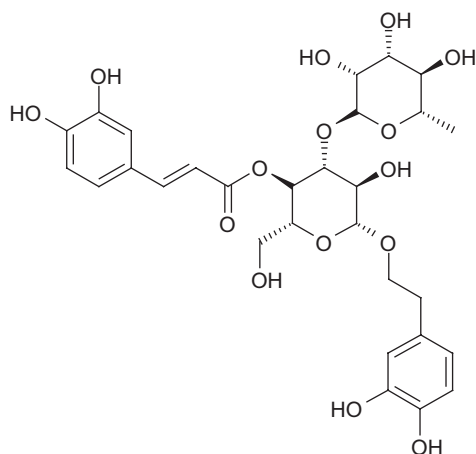


Figure 13. Structure of acteoside.

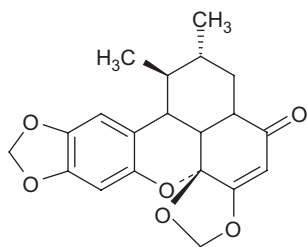


Figure 14. Structure of sauchinone.

investigated the potency of sauchinone as a hepatic HO-1 inducer and its protective effects in HepG2 cells (Sung et al., 2000). Treatment of the cells with sauchinone induced HO-1 expression and increased HO activity in a concentration and time-dependent manner. This expression conferred cytoprotection against oxidative injury induced by tBHP. HO-1 expression by sauchinone also suppressed tBHP induced ROS generation in HepG2 cells. Moreover, sauchinone promoted the nuclear accumulation of Nrf2, and increased the activity of ARE. Furthermore, treatment of the cells with a p38 MAPK inhibitor (SB203580) reduced sauchinone-induced HO-1 expression and its protective effects (Jeong et al., 2010). These results suggest that sauchinone increases the cellular resistance of HepG2 cells to tBHP induced oxidative injury, presumably through the p38 MAPK pathway-Nrf2/ARE-dependent HO-1 expression. At a concentration of 50 μ M, sauchinone significantly reduced the release into the culture medium of GPT from CCl₄ damaged cultures of rat hepatocytes. Sauchinone protects primary cultured rat hepatocytes exposed to CCl₄ from significant drops in the levels of glutathione, SOD and GPx. Sauchinone also seemed to ameliorate LPO as demonstrated by a reduction in the production of MDA. These results suggest that sauchinone may exert hepatoprotective activity through antioxidant activity (Sung & Kim, 2000).

Asiatic acid

Asiatic acid (AA) is one of the triterpenoid components of *Terminalia catappa* L. (Combretaceae) which has anti-oxidative, anti-inflammatory and hepatoprotective activity. The effect of the chloroform extract of *T. catappa* on CCl₄-induced acute liver damage and D-GalN induced hepatocyte injury has been evaluated. The effects of AA on mitochondria and free radicals were investigated to determine the mechanism underlying the action of *Terminalia* on hepatotoxicity. Hepatotoxicity induced by CCl₄ was reversed with pretreatment with 50 and 100 mg/kg extract of *T. catappa* (Tang et al., 2006). The increased ALT and AST levels in the medium of primary cultured hepatocytes induced by D-GalN were blocked by pretreatment with 0.05, 0.1, 0.5 g/l *T. catappa* extract. In addition, Ca²⁺ induced mitochondrial swelling was inhibited by AA. AA at concentrations ranging from 50 to 500 μ M, showed dose-dependent superoxide anion and hydroxyl radical scavenging activity (Gao et al., 2004). Also the disruption of mitochondrial membrane potential, intramitochondrial Ca²⁺ overload and suppression of mitochondrial

Ca²⁺-ATPase activity in the liver of CCl₄ insulted mice were effectively prevented by pretreatment with *T. catappa* extract. Thus it could be concluded that the hepatoprotective activity of *T. catappa* extract is related to protection of liver mitochondria and the scavenging action on free radicals. It was also found to markedly suppress the CCl₄-induced over-transcription of IL-6 gene. As a result, the expression of IL-6 protein was blocked by it in CCl₄ stimulated mice. Mitochondrial protection of AA against acute liver injury induced by LPS and D-GalN in mice has been studied. It was found that pretreatment with 25, 50 or 100 mg/kg AA significantly blocked the LPS + D-GalN-induced increase in both serum ALT and AST levels. Different doses of AA decreased the synthesis of voltage-dependent anion channels (VDACs), and blocked the translocation of cytochrome c from mitochondria to cytosol. Also pre-incubation with 25, 50 and 100 μ g/ml AA inhibited the Ca²⁺ induced mitochondrial permeability transition (MPT), including mitochondrial swelling, membrane potential dissipation and releasing of matrix Ca²⁺ in liver mitochondria separated from normal mice, indicating the direct role of AA on mitochondria. Results suggest that AA could protect liver from damage and the mechanism might be related to upregulating mitochondrial VDACs and inhibiting the process of MPT (Gao et al., 2006).

The protective effects of AA and the relative mechanism in the D-GalN + LPS induced hepatotoxicity in hepatocytes and kupffer cells co-cultured system have been explored. The cultures were pretreated with AA for 12h, followed by D-GalN + LPS exposure for 12h. AA reduced AST and LDH generation and increased cell viability in a concentration-dependent manner. The effects of AA in leukotriene C₄ synthase (LTC₄S) expression and cellular redox status including ROS and GSH content were detected. The results showed that D-GalN + LPS induced the increase of ROS followed by extracellular signal-regulated kinase 1/2 (ERK 1/2) and NF- κ B activation. Treatment with ERK 1/2 specific inhibitor 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene (U0126) abolished the ERK1/2 protein phosphorylation and blunted LTC₄S expression. ROS signaling pathway inhibitor pyrrolidine dithiocarbamate (PDTC) inhibited ROS generation and NF- κ B activation, which in turn blocked LTC₄S expression and attenuated the injury. Thus AA protects against D-GalN + LPS-induced hepatotoxicity partly via redox-regulated LTC₄S expression pathway (Ma et al., 2009). Two AA derivatives, 3 β ,23-dihydroxyurs-2-oxo-12-ene-28-oic acid (AS-10) and 3 β ,23-dihydroxyurs-12-ene-28-oic acid (AS-14) exhibited significant protective activity against CCl₄-induced hepatotoxicity in primary cultures of rat hepatocytes. AS-10 and AS-14 preserved the level of glutathione and the activities of AOE's such as GR, GPx, SOD and catalase. In addition, these compounds ameliorated LPO, as demonstrated by a reduction in the production of MDA. Results suggest that both AS-10 and AS-14 exerted their hepatoprotective activities against CCl₄-induced injury

by preserving the cellular antioxidative defense system (Lee et al., 2009).

***Solanum nigrum* (Solanaceae)**

Solanum nigrum L. has been widely used as hepatoprotective and anti-inflammation agent. The principal constituents are solamargine-A, solamargine-B, solasodine and solasodine. Its hepatoprotective and antioxidant activity has been established experimentally (Lin et al., 2008) in CCl₄-induced chronic hepatotoxicity in rats. *Solanum nigrum* extract was orally administered which reversed hepatotoxicity caused by CCl₄. This hepatoprotective effect could be contributed to its antioxidant effects as the reduced hepatic content and activities of GSH, SOD and GST were restored by *Solanum* extract. The effects of *Solanum* extract on TAA induced liver fibrosis (0.2 g/kg, i.p., 3 times/week for 12 weeks) in mice have been investigated. Treatment with *Solanum* extract reduced the hepatic hydroxyproline levels of TAA-treated mice and TAA induced TGF- β 1 mRNA levels in the liver (Hsieh et al., 2008). One 150 kDa glycoprotein isolated from *S. nigrum* produced significant increases in the activities of AOE. The activities of SOD, catalase and GPx were increased after treatment with the glycoprotein (Lee et al., 2005). In one study Lin et al., 2007 demonstrated the cytotoxic effect of *Solanum* extracts on HepG2 cells. High doses of *Solanum* extract (2 and 5 mg/ml) induced apoptotic cell death in HepG2 cells, as evidenced by increases in the expressions of p-JNK and Bax, mitochondrial release of cytochrome c, and caspase activation. On the other hand, cells treated with low concentrations of *Solanum* (50–1000 μ g/ml) induced autophagocytic death evidenced by increased levels of autophagic vacuoles and LC3-I and LC3-II proteins, which are specific markers of autophagy. This study suggests that *Solanum* could be important in treatment of liver cancers (Lin et al., 2007).

Current clinical status of some hepatoprotective medicines

Many herbal preparations which demonstrated significant hepatoprotective activity in preclinical studies have been successfully evaluated in clinical studies on patients suffering from dysfunctional hepatic system. To determine the effect of silymarin on the outcome of patients with cirrhosis, a double blind, prospective, randomized study was performed in 170 patients with cirrhosis. 87 patients received 140 mg silymarin three times daily whereas 83 received placebo. All patients received the treatment for 2 years. The 4-year survival rate was 58% in silymarin-treated patients and 39% in the placebo group indicating effectiveness of silymarin treatment (Ferenci et al., 1989). In a 6-month double blind clinical trial the effects of silymarin therapy on liver function tests, serum procollagen III peptide level and liver histology was studied in 36 patients with chronic alcoholic liver disease. During silymarin treatment serum bilirubin, ALT and AST values normalized, while procollagen III peptide

level decreased. The histological alterations showed an improvement in the silymarin group, while remained unchanged in the placebo group. These results indicated that silymarin improves liver functions in alcoholic patients (Fehér et al., 1989). In a different randomized, placebo-controlled trial efficacy of silymarin treatment in patients with acute clinical hepatitis was evaluated. The intervention consisted of daily administration of 140 mg of silymarin. Patients randomized to the silymarin group had quicker resolution of symptoms related to biliary retention, viz., dark urine, jaundice and scleral icterus. There was a reduction in indirect bilirubin among those assigned to silymarin (El-Kamary et al., 2009). Efforts have been made to study the effect of silymarin treatment in patients with chronic hepatitis C. In one study patients aged 21–65 years old with a diagnosis of chronic hepatitis C who were not using antiviral therapy were asked to participate. Patients were randomized to treatment with silymarin 160 mg orally three times a week for 4 weeks or to no-treatment. The percent change for ALT, AST and viral load were compared between the treated and control group demonstrating a statistically significance difference for ALT and AST, but not for viral load. These results suggest that silymarin may have a protective effect in the inflammatory response to HCV (Torres et al., 2004).

SNMC is a drug with glycyrrhizin as the principal ingredient. The therapeutic effects of administration of SNMC three times a week for 12 weeks in patients with chronic viral hepatitis were evaluated in a randomized clinical trial in which SNMC administration suppressed ALT levels in a dose-dependent manner (Miyake et al., 2002). The efficacy and safety of SNMC were evaluated on 194 patients with chronic hepatitis B in nine hospitals in China. All patients received oral SNMC tablets. SNMC was efficacious in normalizing ALT levels (Zhang and Wang, 2002). In a multicenter double blind study, ALT levels decreased in the patients who received 40 ml/day of SNMC for 4 weeks. Furthermore, SNMC 100 ml/day for 8 weeks improved liver histology in 40 patients with chronic hepatitis, in correlation with improved ALT levels in serum. Liver cirrhosis occurred less frequently in 178 patients on long-term SNMC than in 100 controls. Finally, hepatocellular carcinoma (HCC) developed less frequently in the 84 patients on long-term SNMC than in the 109 controls (Kumada, 2002). Long term administration of SNMC in the treatment of chronic hepatitis C was effective in preventing liver carcinogenesis (Arase et al., 1997).

To validate the claims of Liv-52 being a potent hepatoprotective several clinical studies have been conducted. The efficacy of Liv-52 was determined on liver cirrhotic patients, a randomized, double blind, placebo-controlled study was conducted in 36 cirrhotic patients in Tehran Hepatic Center. The efficacy of Liv-52 on liver cirrhosis outcomes was compared with the placebo for 6 months. The results demonstrated that the patients treated with Liv-52 for 6 months had significantly better child-pugh score, decreased ascites, decreased serum

ALT and AST, whereas no such effect was observed in placebo administered patients. Results of this study conclude that Liv-52 possess hepatoprotective effect in cirrhotic patients (Huseini et al., 2005). In one retrospective study, effect of Liv-52 on 19 patients with alcoholic liver damage was investigated. It was found that administration of Liv-52 improved the subjective condition and clinical parameters in patients with liver damage. No undesirable side-effects were detected even after one year of treatment (Kaláb & Krechler, 1997).

The effectiveness of *Phyllanthus amarus* in treatment of hepatitis has been demonstrated in a randomized study where 35 patients with chronic viral hepatitis B were treated with *P. amarus* derivative for 3 months in the treatment group while another 25 patients were treated with recombinant human IFN α -1b for 3 months as control. Effective rate in the treatment group was 83.3%. The normalization rates of ALT and bilirubin in the treatment group were significantly higher than that in the control. The negative conversion rates of HBeAg and HBV-DNA in the treatment group were 42.3 and 47.8%, showing no significant difference from the control. It is indicated that *Phyllanthus amarus* derivative has remarkable effect for chronic viral hepatitis B in recovery of liver function and inhibition of the replication of HBV (Xin-Hua et al., 2001). There are several herbal preparations which are

used as hepatoprotective drugs all over the world, some of which are listed in Table 3.

Conclusion

Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases, with large efforts being made to elucidate their modes of action. Large sections of patients with liver disease use botanicals. Future efforts will have to implement extensive methodological improvements to separate the real therapeutic value of these agents from unsubstantiated hopes associated with them. The active molecules must be isolated and tested through well designed experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. There are many such isolated lead molecules which if rigorously investigated could become hepatoprotective drugs of the future (Table 2). Sound and controlled clinical studies with herbals and especially their active ingredients in chronic liver diseases are important, with regard to discover novel antifibrotic and anti-inflammatory activities. There is a huge demand for both experimental and clinical research to validate the potential of herbal drugs and rigorous scientific testing along the principles of

Table 3. List of herbal preparations available as hepatoprotective drugs.

Herbal preparations	Names of plants	Major constituents	Therapeutic indications	References
Legalon	<i>Silybum marinum</i>	Silymarin	Liver disorders, jaundice, liver cirrhosis	Mayer et al., 2005; Pradhan & Girish, 2006; Ferenci et al., 1989
Liv-52	<i>Capparis spinosa</i> , <i>C. intybus</i> , <i>S. nigrum</i> , <i>Terminalia arjuna</i> , <i>Cassia occidentalis</i> , <i>Achillea millefolium</i> , <i>Tamarix gallica</i>	Solasodine, inulin, cichoriin, arjunolic acid, arjunine, chamazulene, tamarixin, stachydrine, achilline	Jaundice, Alcoholic liver disease, Viral hepatitis, liver cirrhosis, as adjuvant with hepatotoxic drugs	Huseini et al., 2005; Vidyashankar & Patki, 2010; Girish et al., 2009b; Vidyashankar et al., 2010
Hepatomed	<i>P. kurroa</i> , <i>A. paniculata</i> , <i>Eclipta alba</i> , <i>C. intybus</i> , <i>S. nigrum</i> , <i>Phyllanthus niruri</i>	Andrographolide, picroside, phyllanthin, hypophyllanthin, wedelolactone	Jaundice, Alcoholic liver disease, cirrhotic liver disease	Sharma et al., 1995; Ram, 2001
HD 03	<i>C. intybus</i> , <i>S. nigrum</i> , <i>P. kurroa</i> , <i>A. paniculata</i> , <i>Tephrosia purpurea</i>	Solasodine, inulin, cichoriin, picroside, tephrosin, andrographolide	Jaundice, Alcoholic liver disease, Viral hepatitis	Mitra et al., 1998, 2000, 2001
Kamilari	<i>Thespesia populnea</i> , <i>Elettaria cardamomum</i> , <i>Zingiber officinale</i> , <i>Glycyrrhiza glabra</i>	Populneol, cineole, glycyrrhizin, zingerone, gingerols	Jaundice, Alcoholic liver disease, Viral hepatitis, liver cirrhosis	Rajesh & Latha, 2004
Livfit	<i>E. alba</i> , <i>P. niruri</i> , <i>C. intybus</i> , <i>Rheum emodi</i> , <i>Tephrosia purpurea</i>	Wedelolactone, phyllanthin, emodin, aloe-emodin, rhein, tephrosin	Protects liver against various hepatotoxins, promotes appetite	Gupta et al., 2004
Stimuliv	<i>A. paniculata</i> , <i>P. niruri</i> , <i>E. alba</i> , <i>P. kurroa</i> , <i>Boerhaavia diffusa</i> , <i>Azadirachta indica</i> , <i>Berberis aristata</i> , <i>Ipomoea turpethum</i> , <i>T. purpurea</i>	Punarnavoside, liiroadendrin, picroside, berberine, nimbin, nimbinin	Liver stimulant and tonic	Dange et al., 1992; Girish et al., 2009b
Himoliv	<i>P. kurroa</i> , <i>B. diffusa</i> , <i>Tinospora cordifolia</i> , <i>A. paniculata</i> , <i>P. emblica</i>	Tinosporine, tinosporide	Ayurvedic medicine for hepatic dysfunction	Bhattacharyya et al., 2003
Tefroliv	<i>A. paniculata</i> , <i>E. alba</i> , <i>Ocimum sanctum</i> , <i>P. niruri</i> , <i>P. kurroa</i> , <i>Piper longum</i> , <i>S. nigrum</i> , <i>Tephrosia purpurea</i> , <i>Terminalia chebula</i>	Piperine, chavicine, piperidine, Solasodine, tannic acid, Chebulinic acid	Standardized liver formulation for effective hepatic regeneration	Girish et al., 2009b

evidence-based medicine will help herbal medicine to become a very justifiable scientific treatment regime.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

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