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Review

Hepatoprotective leads from plants

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Abstract

Liver has a surprising role in the maintenance, performance and regulation of homeostasis of the body. It is involved with almost all the biochemical pathways responsible for growth, fight against disease, nutrient supply, energy provision and reproduction. In the same time, hepatic diseases stand as one of the leading health quandary worldwide. Therapies developed along the principles of western medicine are often limited in efficacy, leads to serious adverse effects which eventually cause hepatic damage, and are often costly. In the absence of reliable liver protective drugs in modern medicine, there exists a challenge for pharmaceutical scientists to explore the potential of hepatoprotective activity of plants based on traditional use. Study of many traditional plants used for liver problems led to the discovery of active compounds yet developed to successful drugs. The effectiveness of most of these phytochemicals were scientifically validated. The present review is a compilation of data on promising hepatoprotective compounds of plant origin.

Key words: Liver diseases, hepatoprotective agents, phytochemicals, silymarin, hepatocellular carcinoma

1. Introduction

Liver diseases are one of the fatal diseases in the world and over 10% of the world population afflicted liver diseases (Mishra and Tiwari, 2011). It includes chronic hepatitis, alcoholic steatosis, fibrosis, cirrhosis and hepatocellular carcinoma, are the most health threatening conditions, drawing considerable attention from medical professionals and scientists (Zhang *et al.*, 2013). Modern medicines have little to offer for alleviation of hepatic diseases and it is chiefly the plant based preparations which are employed for the treatment of liver disorders. The current options for the treatment of liver disease include pharmacotherapy, surgery as well as liver transplantation, all of which have shown limited therapeutic benefits and are associated with serious complications (Muriel and Rivera-Espinoza, 2008; Duvoux, 2001).

The use of natural products to prevent and/or treat various liver diseases, dates back to several thousand years in many countries. The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy (Thyagarajan *et al.*, 2002).

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Therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly. Some liver protective medicines and their adverse effects are depicted in Table 1.

2. Hepatoprotective phytochemicals

Phytochemicals that are found in vegetables, fruits, plant extracts, herbs, *etc*., have been traditionally used for treating liver diseases. Many phytochemicals have been clinically available as potent hepatoprotective agents against commonly occurring liver diseases. This review summarizes the current progress in the phytochemicals used in treatment of various liver diseases. The compounds described herein are silymarin, andrographolide, curcumin, glycyrrhizin, berberine, ursolic acid, picroside and kutkoside, resveratrol, wogonin, phyllanthin, emodin, thymoquinon, *etc*.

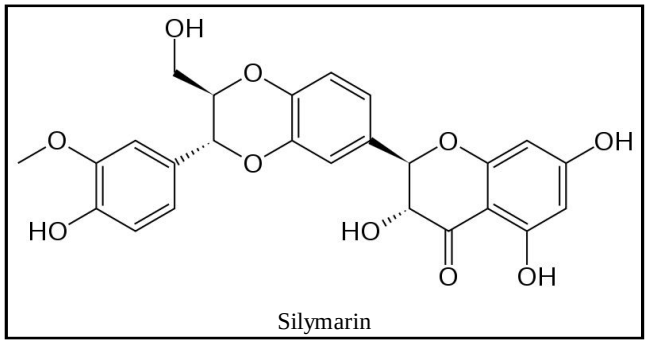
2.1 Silymarin

Silybum marianum (L.) Gaertn. (Fam. Asteraceae) is commonly known as 'milk thistle' and is one of the oldest, thoroughly investigated plant in the treatment of liver diseases. The extracts of milk thistle are being used as a general medicinal herb from as early as 4th century B.C. and first reported by Theophrastus. In the 1st century A.D., Dioskurides used this plant as emetic as well as a general medicinal herb. It became a favoured medicine for hepatobiliary diseases in 16th century and the drug was revived again in 1960 in central Europe (Luper, 1998; Schuppan *et al.*, 1999; Pradhan and Girish, 2006).

2.1.1 Chemistry

Silymarin is a mixture of flavonolignans (Wagner and Seligmann, 1985). The principal components of silymarin are silybin A,

silybin B, isosilybin A, isosilybin B, silychristin A, silychristin B and silydianin. The first six compounds exist as equimolar mixtures as trans diastereoisomers. These diastereomers have very similar ^{1}H and ^{13}C NMR spectra and have no characteristic signals for facile identification of the individual isomers (Lee and Liu, 2003).



Silymarin

2.1.2 Pharmacology

Hepatoprotective activity of silymarin has been demonstrated by researchers from all over the world against partial hepatectomy models (Sonnenbitchler *et al.*, 1986; Srivastava *et al.*,1996) and toxic models like carbon tetrachloride (Subramoniam and Pushpangadan, 1999; Sherlock and Dooley; 2002), acetaminophen (Neuman *et al.*, 1999; Renganathan, 1999), ethanol (Wang *et al.*, 1996), galactosamine (Datta *et al.*, 1999), iron (Bhattacharya *et al.*, 2000) and *Amanita phalloides* toxin (Vogel *et al.*, 1984) induced hepatotoxicity.

2.1.3 Mechanism of action

Preclinical studies showed that silymarin has multiple actions in liver protection. The antioxidant property (Kosina *et al.*, 2002) and cell-regenerating functions as a result of increased protein synthesis (Sonnenbichler and Zetl, 1986) are considered as most important. Action of silibinin in isolated Kupffer cells indicated a strong inhibitory effect on LTB4 formation (Dehmlow *et al.*, 1996). Silymarin is found to suppress both NF-κB DNA binding activity and its dependent gene expression induced by okadaic acid in the hepatoma cell line HEPG2 (Saliou *et al.*, 1998). It has also a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against xenobiotic injury (Munter *et al.*, 1986; Pradhan and Girish, 2006).

2.1.4 Clinical trials

Silymarin significantly decrease ALT and AST levels in patients with alcoholic liver disease (Salmi and Sarna, 1982). In chronic alcoholic liver disease, a dose of 420 mg/day of silymarin resulted in normalization of serum transaminases (AST, ALT and ν-GT), total bilirubin, significant decrease in procollagen III peptides and an improvement in the histological examination of liver biopsies (Feher *et al.*, 1989). In patients with alcoholic cirrhosis, the survival rate was 58 per cent in silymarin group and 39 per cent in placebo, indicated that the treatment was effective (Ferenci *et al.*, 1989). Trials performed against *Amanita* mushroom poisoning showed positive result (Carducci *et al.*, 1996). Coadministration of silymarin with tacrine (an anticholinesterase drug) showed improvement in tolerability in the initial phase of treatment (Allain *et al.*, 1999).

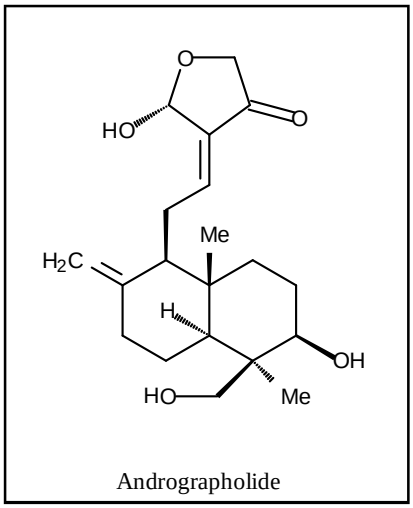
The major causes of liver related deaths were upper gastrointestinal bleeding (UGB), hepatic failure, or primary liver cell carcinoma (Khan *et al.*, 2000). The data showed that the incidence of hepato cellular carcinoma was lower in the silymarin treated patients (Saller *et al.*, 2001). The reduction in lipid peroxidation produced by silymarin can improve metabolic control and reduce requirements for endogenous insulin in such patients. Silymarin treatment produced significant reduction in daily and fasting blood glucose, daily glucosuria, glycosylated haemoglobin values, malondialdehyde values and a drop in insulin requirement and fasting insulinaemia (Velussi *et al.*, 1997; Pradhan and Girish, 2006).

2.1.5 Toxicity and drug interaction

Silymarin is reported to have a very good safety profile (Saller *et al.*, 2001). Both animal and human studies showed that silymarin is non-toxic even when given at high doses (>1500 mg/day). However, a laxative effect is noted at these doses may be due to increased bile secretion and bile flow (Luper, 1998). Few reports of associated occurrence of adverse effects related to gastrointestinal tract like bloating, dyspepsia, nausea, irregular stool, diarrhoea (Jacobs *et al.*, 2002), pruritus, headache, exanthema, malaise, asthenia and vertigo (Saller *et al.*, 2001). *In vitro* studies showed that in higher concentrations, silymarin has an inhibitory effect on both phase I and phase II drug metabolizing enzymes such as CYP3A4, CYP2D6 and CYP2C9 (Sridar *et al.*, 2004).

2.2 Andrographolide

Andrographis paniculata (Burm.f.) Wall. ex Nees (Fam. Acanthaceae) is a herbaceous medicinal plant, often cultivated in India, China, Taiwan, Thailand and many other countries. Due to its extreme bitter taste, it is often referred to as the “king of bitters”. The main components of the herb are diterpene lactones. Andrographolide was the first diterpene lactone identified. Later, four more diterpene lactones, *i.e.*, neoandrographolide, deoxy-didehydroandrographolide,deoxy-oxoandrographolide and deoxy-andrographolide were isolated (Zhu, 1998). Andrographolide, structurally a labdane diterpenoid, is quantitatively the major bitter tasting secondary metabolite of the plant and it is now often considered to be the major bioactive constituent of the plant involved in its observed therapeutically interesting bioactivities (Lim *et al.*, 2012; Hidalgo *et al.*, 2013).

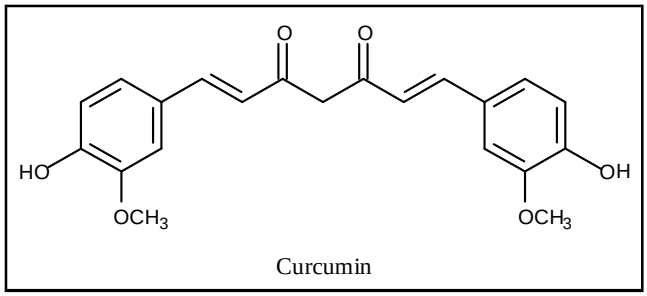


Andrographolide

A crude extract of *A. paniculata* induce mouse hepatic cytochrome P450 isoforms CYP1A1 and CYP2B *via* increases in ethoxyresorufin-*O*-dealkylase and pentoxyresorufin-*O*-dealkylase activities (Jarukamjorn *et al.,* 2006). Further, it is demonstrated that andrographolide significantly upregulate the CYP1A1, CYP1A2 (Jaruchotikamol *et al.,* 2007) and CYP1B1 (Chatuphonprasert *et al.,* 2009) mRNA expression. 14-deoxy-11, 12-didehydro andro grapholide and andrographolide have been shown to inhibit CYP1A2, CYP2D6 and CYP3A4 expressions in HepG2 cells (Jarukamjorn *et al.,* 2010). In contrast, neoandrographolide suppressed BNF induced CYP1A1 expression (Chatuphonprasert *et al.,* 2011). Interaction with GSH significantly enhanced the BNF inducible CYP1A1 mRNA expression in C57BL/6 mouse hepatocytes (Kondo *et al.,* 2011). Qiu *et al.* (2012) demonstrated that andrographolide (1, 10, 100 μM) significantly down regulates the mRNA level and protein level of CYP3A4 in Caco-2 cells in a combination therapy study. In addition, the *A. paniculata* 60% ethanol extract or andrographolide may cause herb-drug interactions through CYP3A and CYP2C9 inhibition *in vitro* or CYP2C11 inhibition *in vivo* (Pekthong *et al.,* 2008, 2009).

2.3 Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a bright yellow-colored phenolic compound that was initially isolated from *Curcuma longa* L. (Fam. Zingiberaceae) rhizomes in 1815 (Gupta *et al.,* 2013). Curcumin attenuates liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis and acute, subchronic and chronic carbon tetrachloride intoxication; moreover, it reverses CCl_4 cirrhosis to some extent. The curcumin has the ability to inhibit several factors like NF-κB, which modulates several proinflammatory and profibrotic cytokines as well as its antioxidant properties, provide a rational molecular basis to use it in hepatic disorders (Rivera-Espinoza and Muriel, 2009). Numerous studies demonstrated decreased hepatic expression of NF-κB and its downstream targets by curcumin (Bisht *et al.,* 2011; Tu *et al.,* 2012b; Xu *et al.,* 2014). It has also been shown that curcumin could decrease the expression of TLR2 and TLR4 and their ligand molecule HMGB1 in the rat model of fibrogenesis (Tu *et al.,* 2012b) and T-cell-mediated hepatitis in concanavalin A-challenged mice (Tu *et al.,* 2012a, 2013), suggesting a potential to attenuate inflammatory processes in the liver. Curcumin could ameliorate LPS/D-GalN-induced liver injury through reduction of hepatic mRNA levels of SIRT1 (Zhang *et al.,* 2014a). Over expression and hyperactivity of hepatic protein tyrosine phosphatase 1B (PTP1B) was reduced by curcumin, with subsequent improvement of insulin and leptin signaling. Moreover, it decreased the hepatic gene expression of inflammatory cytokines, procollagen I and TIMP-1 in experimental steatohepatitis in mice (Vizzutti *et al.,* 2010; Domitrovic and Potocnjak, 2015).



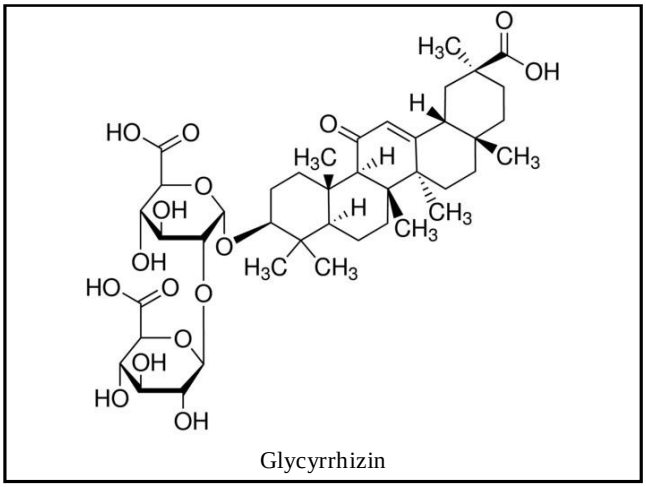
Curcumin

Curcumin down-regulated Patched (Ptch) and Smoothened (Smo), two key elements in Hedgehog (Hh) signaling, simultaneously restoring Hhip (a gene known to be downregulated upon HSC activation) expression in fibrotic rat livers and cultured HSCs (Lian *et al.,* 2015). Curcumin also impaired production of ECM proteins in alcohol-stimulated HSCs and CCl_4 induced liver by suppressing the TGF-α/Smad 2/3 signaling and inducing Smad7 (Chen *et al.,* 2014). Curcumin could also inhibit HBV and HCV replication *via* down-regulation of metabolic coactivator PGC-1α and the Akt/SREBP-1 pathway, respectively (Kim *et al.,* 2010; Rechtman *et al.,* 2010). However, another study demonstrated inhibition of HCV replication through suppression of PI3K/Akt and induction of HO-1 (Chen *et al.,* 2012). Administration of curcumin has been shown to decrease activity of CYP2B1/2 and CYP1A1 in mice liver (Sehgal *et al.,* 2013) and inhibit activation of CYP2E1 in chronic alcohol and high-fat diet-induced liver injury in mice (Lee *et al.,* 2013). Similarly, microsomal CYP2C and CYP3A activities in bovine hepatocytes were inhibited by treatment with curcumin (Lemley and Wilson, 2010; Domitrovic and Potocnjak, 2015).

Curcumin has shown beneficial effects in clinical trials in patients with arsenic-induced genotoxicity (Biswas *et al.,* 2010; Roy *et al.,* 2011a). More than 84 clinical studies, including randomized blind placebo-controlled, non-randomized phase II/III trials, and so on (www.ClinicalTrials.gov), are investigating the effects of curcumin on human disorders (Nabavi *et al.,* 2014). The FAO and WHO Expert Committee on Food Additives in 1996 reported that the acceptable daily intake (ADI) of curcumin is up to 3 mg/kg body weight. It is well known that curcumin is a natural product with a long history of consumption in the human diet, but there appear to be few scientific studies on its toxicity to both animals and humans, especially at high doses (Rivera Espinoza and Muriel, 2009; Nabavi *et al.,* 2014).

2.4 Glycyrrhizin

Glycyrrhizin, a triterpenoid glycoside isolated from the roots of the plant, *Glycyrrhiza glabra* L. (Fam. Fabaceae), has been shown to increase antioxidant defence in the liver (Rahman and Sultana, 2006; Orazizadeh *et al.,* 2014). Glycyrrhizin and its metabolite, glycyrrhetinic acid, inhibited collagen αI(I) gene expression and progression of liver fibrosis induced by CCl_4 (Moro *et al.,* 2008). The compounds significantly decreased mRNA expression of TGF-β1, Smad2/3 and specificity protein-1 (SP-1) in the liver (Qu *et al.,* 2015).



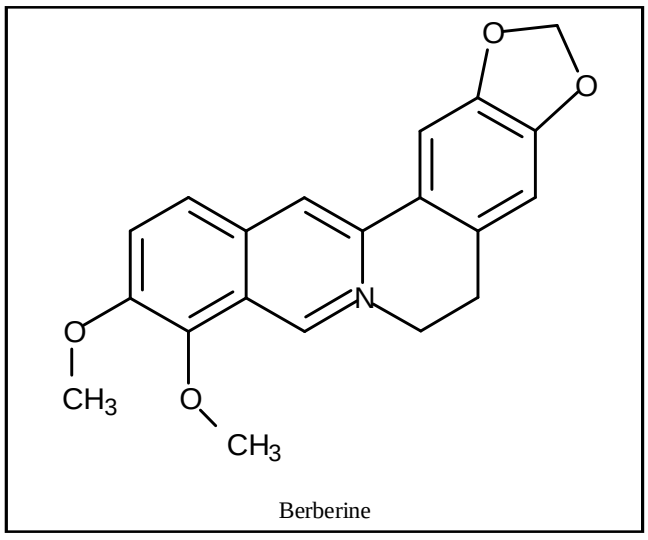
Glycyrrhizin

The potential of this compound to accelerate recovery from hepatic injury has been demonstrated *in vitro*. Glycyrrhizin suppressed activation of HSCs and induced their apoptosis by blocking nuclear translocation of NF-κB (Qu *et al.,* 2012). Importantly, glycyrrhizin and its metabolites may induce growth of hepatocytes by binding to EGFR and stimulating ERK2-mediated hepatocyte DNA synthesis and proliferation (Kimura *et al.,* 2001), which could contribute to acceleration of liver regeneration. Glycyrrhizin treatment of HCV-infected hepatic cells resulted in reduced release of infectious HCV particles through inhibitory effect on (PLA2), whereas a cotreatment with glycyrrhizin augmented antiviral effect of IFN-α (Matsumoto *et al.,* 2013). Moreover, glycyrrhizin modified the intracellular transport and suppressed sialylation of HBsAg *in vitro* (Takahara *et al.,* 1994), which was also observed in patients with chronic HBV infection (Sato *et al.,* 1996; Domitrovic and Potocnjak, 2015).

In patients who failed previous IFN-α-based therapy, intravenous administration of glycyrrhizin significantly reduced serum alanine transaminase (ALT) level after 12 weeks of therapy and improved necroinflammation and fibrosis after 52-week treatment (Manns *et al.,* 2012). In another study, a 6-month cotreatment with IFN-α2b and glycyrrhizin was less effective in reducing ALT levels compared to IFN-α2b and ribavirin coadministration. Similar effect of this compound was observed in another study on 1093 patients nonresponding to IFN (Veldt *et al.,* 2006). Importantly, usage of the suppositories of glycyrrhizin improved quality of life for chronic hepatitis C patients similarly to intravenously treated patients, with greater benefit in those who did not respond to IFN therapy (Fujioka *et al.,* 2003; Domitrovic and Potocnjak, 2015).

2.5 Berberine

Berberine is a plant alkaloid present in many medicinal herbs, such as *Hydrastis canadensis*, *Rhizoma coptidis* (Fam. Ranunculaceae), *Berberis aquifolium, B. aristata* and *B. vulgaris* (Fam. Berberidaceae) (Ye *et al.,* 2009; Tang *et al.,* 2009). Berberine possesses antioxidant properties which could suppress oxidative stress in the liver (Li *et al.,* 2014; Othman *et al.,* 2014).



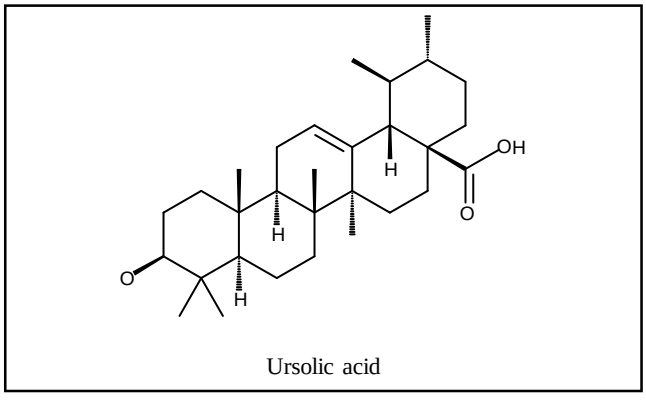
Berberine

Berberine alone or in combination with S-allyl-cysteine diminished these effects and induced apoptosis by stimulating protein phosphatase 2A (PP2A) and inhibiting JNK activation (Sengupta *et al.,* 2014). Furthermore, amelioration of the early phase of DEN and phenobarbital-induced hepatocarcinogenesis by berberine was accompanied by suppression of iNOS expression and inhibition of CYP2E1 and CYP1A2 activities (Zhao *et al.,* 2008). Berberine also ameliorated apoptosis in ischemia-/reperfusion-injured rat livers by increasing the Bcl-2/Bax ratio and inhibiting caspase-3 cleavage. The mechanism of its action involved up-regulation of Akt, with concomitant inhibition of mTOR expression (Sheng *et al.,* 2015). Moreover, berberine protected against ethanol-induced steatosis in mice by restoring PPARα/PGC-1α and hepatocyte nuclear factor 4 alpha (HNF4α)/microsomal triglyceride transfer protein (MTTP) pathways, involved in secretion of lipoproteins (Zhang *et al.,* 2014b).

Berberine pretreatment in LPS-induced inflammation in mice reduced the expression of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9), a cholesterol homeostasis regulator, and decreased IFN-γ, TNF-α, IL-1α and 8-isoprostane levels (Xiao *et al.,* 2012). CCl_4-induced acute liver injury was ameliorated by berberine through suppression of TNF-α, COX-2 and iNOS expression, with concomitant attenuation of oxidative/nitrosative stress (Domitrovic *et al.,* 2011). In experimental liver fibrosis, berberine decreased TGF-β1 expression, increased MMP-2 levels and stimulated elimination of fibrous deposits (Domitrovic *et al.,* 2013). Moreover, berberine treatment attenuated liver fibrosis *via* activation of AMPK and decreased expression of NOX4 and phosphorylated Akt (Li *et al.,* 2014a). In hyperlipidemic patients with HBV, HCV and liver cirrhosis, treatment with 500 mg of berberine hydrochloride orally twice a day for 3 months has been shown to markedly improve serum indicators of liver injury and lipid parameters (Zhao *et al.,* 2008), suggesting its beneficial potential in hepatic viral infections.

2.6 Ursolic acid

Ursolic acid is a triterpenoid that exists as a major component of some traditional medicinal herbs like *Ocimum sanctum* (Fam. Lamiaceae), *Vaccinum myrtillus* (Fam. Vacciniaceae), *Boerhavia diffusa* (Fam. Nytaginaceae), *Harpagophytum procumbens* (Fam. Pedaliaceae), *Sambucus nigra* (Fam. Caprifoliaceae), *Mentha piperita* (Fam. Lamiaceae), *Vinca minor* (Fam. Apocynaceae), *Lavandula augustifolia* (Fam. Lamiaceae), *Origanum vulgare* (Fam. Lamiaceae), *Thymus vulgaris* (Fam. Lamiaceae), *Crataegus laevigata* (Fam. Rosaceae), *Prunus laurocerasus* (Fam. Rosaceae), *etc*.



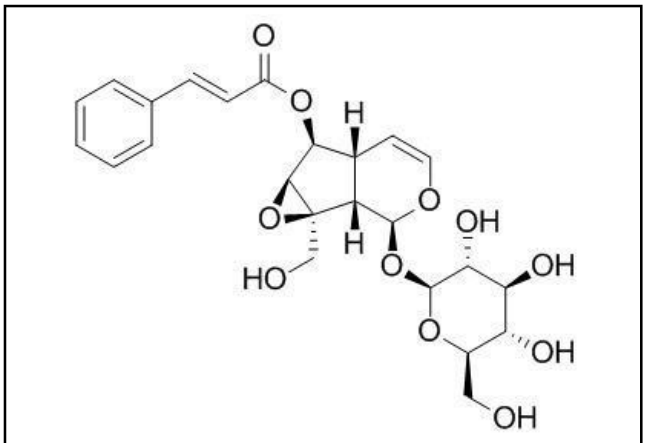
Ursolic acid

Ursolic acid was shown to activate autophagy in mice model of hepatic steatosis in the NAFLD model in rodents, by inducing the expression of LC3-II and beclin 1 (Jia *et al.,* 2015). Ursolic acid treatment significantly decreased hepatic steatosis in db/db mice by

modulating β-oxidation and ER stress in the liver (Li *et al.,* 2015a). Mechanistically, it reduced expression of the unfolded protein response sensor inositol-requiring enzyme-1alpha (IRE-1α) expression and activation of ERK, JNK and CHOP, while increasing PPARα levels. In addition, ursolic acid decreased palmitic acid-induced intracellular lipid accumulation in L02 cells, with concomitant inhibition of ATF6, IRE-1α and CHOP gene expression. In culture-activated HSCs, ursolic acid activated caspase-3 and caspase-9, decreased phosphorylation of Akt and diminished nuclear localization of NF-κB (Wang *et al.,* 2011), suggesting their apoptosis and suppression of survival mechanisms. Treatment of hepatocytes with ursolic acid in the presence of LPS dose-dependently inhibited ROS production and NF-κB activation. Ursolic acid also prevented CCl_4-induced hepatotoxicity and fibrosis in mice, at least in part, through modulation of the Nrf2/ARE signaling pathway (Ma *et al.,* 2015; Domitrovic and Potocnjak, 2015).

2.7 Picroside and kutkoside

The underground parts of *Picrorhiza kurrooa* Royle ex Benth (Fam. Scrophulariaceae) have been found to yield a crystalline product "Kutkin" or "Picroliv", which usually is a mixture of two major C9 – iridoid glycosides, *i.e.,* picroside I (6-*O*- trans cinnamoylcatalpol) and kutkoside (10-*O*-vanilloylcatalpol) in the ratio of 1:2 (Singh *et al.,* 1992). The plant grows in Himalayan region in moist, rocky slopes as well as in organic soils, Garhwal to Bhutan, southeast Tibet, north Burma and west China.



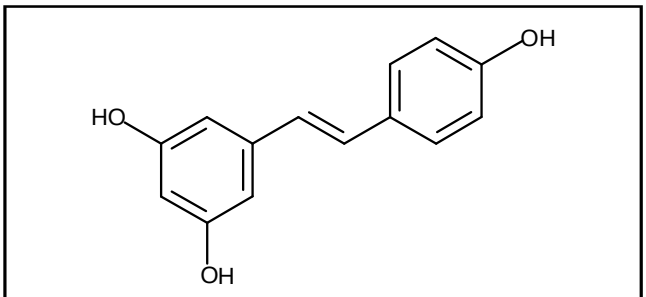
Picroside

P. kurroa forms a major ingredient of many indigenous medical preparations, especially useful for the treatment of diseases of liver, such as hepatitis (Mittal *et al.,* 1978; Ansari *et al.,* 1988) and jaundice (Handa *et al.,* 1986). Picroliv antagonizes paracetamol-induced decrease in LDL receptor cell-surface expression and increase in conjugated di-enes in hepatocytes (Singh *et al.,* 1992). In rats, infected with *Plasmodium berghei,* picroliv reduced the increased levels of lipid peroxidation products in the liver and brain and normalized glutathione metabolism (Chander *et al.,* 1992). Picroliv has been found to be a potent inhibitor of hepato-carcinogenesis induced by N-nitrosodiethylamine (NEDA) in male wistar rats. Picroliv was found to increase the life span of tumor bearing animals (Kumar and Kuttan, 2000). Aqueous extact of *P. kurroa* root may have potential as feed additives to increase the efficiency of utilization of energy and nitrogen in ruminant diet (Alexander *et al.,* 2008).

In another experimental study, the investigations were carried out on the effect of oral administration of picroliv, obtained from total alcohol extractable rhizome of *P. kurroa* concurrently with toxication of rats for two weeks with CCl_4 and the results showed that administration of carbon tetra chloride to normal rats increased activities of hepatic 5'-nucleotidase, acid phospahatase, acid ribonuclease while the activities of succinate dehydrogenase, glucose 6-phosphatse, superoxide dismutase and cytochrome p450 were decreased. Picroliv in doses of 6 and 12 mg / Kg provided a significant protection against most of the biochemical alterations produced by CCl_4 (Diwedi *et al.,* 1990; Pandey and Verma, 2013).

2.8 Resveratrol

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene), a natural phytoalexin present in peanuts, grapes and red wine, possesses several beneficial actions including antioxidant and anti-inflammatory properties, prevention of cancer and modulation of lipid metabolism (Fremont, 2000; Dong, 2003; Aggarwal *et al.,* 2004).



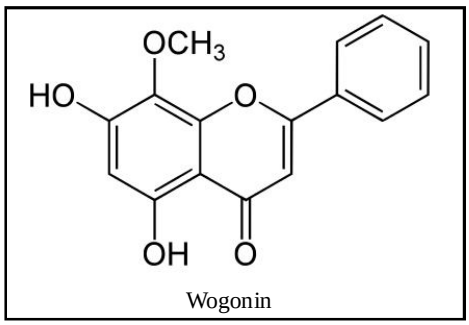
Resveratrol

Resveratrol could significantly reduced TNF-α and IL-6 mRNA and decreased the number of Kupffer cells recruited in the injured liver. It decreased fibrosis and promoted hepatocyte regeneration, which increased the survival of BDL mice. Resveratrol was beneficial for the treatment of cholestatic liver injury (Chan *et al.,* 2011). The histopathological, immunohistochemical, and apoptotic analysis were used to assess the effect of resveratrol on morphological, oxidative status in CCl_4-challenged liver tissue (Roy *et al.,* 2011b). The administration of resveratrol either at the early or advanced stages of hepato-carcinogenesis is equally effective and involves the activation of the apoptotic pathway in male wistar rats (Rajasekaran *et al.,* 2011). The inhibitory effect of resveratrol on vascular endothelial growth factor activity and angiogenesis in hepatocellular carcinoma may occur partly through suppression of the activation of NF-kappa B in HepG2 cells (Yu *et al.,* 2010). Resveratrol showed not only reduced mRNA expression of fibrosis related genes such as transforming growth factor beta1, collagen type I, and alpha-smooth muscle actin, but also a significant decrease of hydroxyproline in rats with DMN-induced liver fibrosis (Hong *et al.,* 2010). Resveratrol exhibited *in vivo* hepatoprotective and antifibrogenic effects against DMN-induced liver injury, suggesting that resveratrol could be used to treat liver injury and fibrosis and be useful in preventing the development of liver fibrosis and cirrhosis (Zhang *et al.,* 2013).

2.9 Wogonin

Wogonin is a monoflavonoid isolated from *Scutellaria radix* L. (Fam. Lamiaceae) which has been used for thousands of years in Asia for inflammatory diseases and also for hepatitis (Guo *et al.,* 2007). The

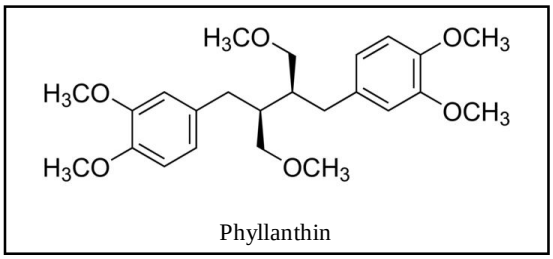
anti-HBV activity of wogonin demonstrates its ability to suppress hepatitis B surface antigen (HBsAg) secretion in cell culture. Plasma HBsAg level was significantly reduced in ducks treated with wogonin, and an additional histopathological evaluation of their liver showed considerable improvement. Wogonin had effective cytotoxic effects through apoptosis induction in hepatocellular carcinoma cells SK-HEP-1; activation of caspase-3 cascade, induction of p53 protein and alternative expression of p21 protein were involved (Chen *et al.*, 2002). Furthermore, immunohistological staining of human HBV-transgenic mouse livers confirmed the potential of wogonin in HBsAg reduction (Zhang *et al.*, 2013).



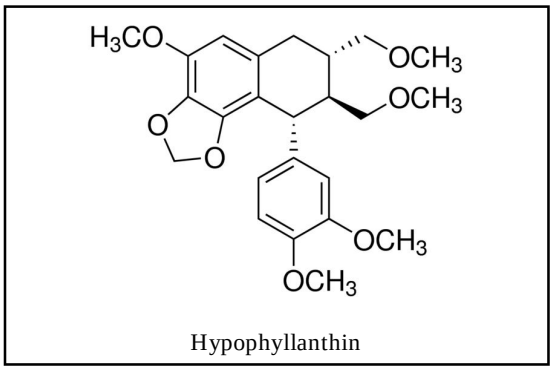
Wogonin

2.10 Phyllanthin and hypophyllanthin

Phyllanthin and hypophyllanthin are potent hepatoprotective phytochemicals found in *Phyllanthus* sp. (Fam. Euphorbiacea). Chemically, both phyllanthin and hypophyllanthin are lignans (Krishnamurthi and Seshandri, 1946; Row *et al.*, 1966). Phyllanthin is linked through C_8-C_{80} of phenyl propanoid units, while hypophyllanthin is additionally linked through C_2-C_{70} to make a tetrahydronaphthalene ring system (Row *et al.*, 1967).



Phyllanthin

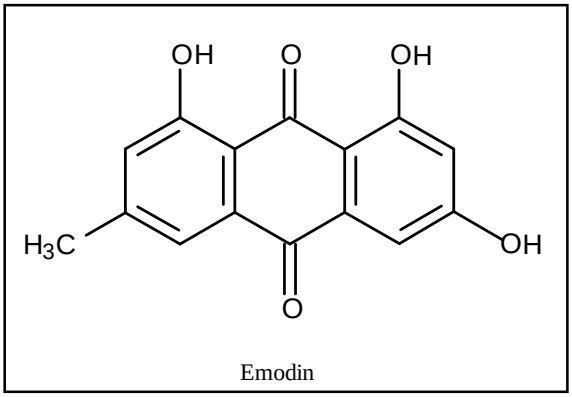


Hypophyllanthin

In India, it is used as a single drug in the treatment of jaundice in children (Dixit and Achar, 1983), and British researchers showed that children treated with *Phyllanthus* extract for acute hepatitis could return the liver function to normal within 5 days. Using a rat hepatocyte primary culture, Shamasundar *et al.* (1985) have shown that phyllanthin and hypophyllanthin protected cells against carbon tetrachloride cytotoxicity. *P. niruri* is used as one of the components of a multiherbal preparation for treating liver ailments (Kapur *et al.*, 1994). However, a hepatoprotective effect of *P. niruri* has not been demonstrated *in vivo*. Several studies have shown that the hepatoprotective effect is associated with antioxidant rich plant extracts (Emmanuel *et al.*, 2001; Harish and Shivanandappa, 2006). Phyllanthin and hypophyllanthin compounds present in *P. amarus* have been shown to have hepatoprotective effect against CCl_4, galactosamine and ethanol induced hepatotoxicity in primary cultured rat hepatocytes and HepG2 cells (Shamsunder *et al.*, 1985; Krithika *et al.*, 2009; Chirdchupunseree and Pramyothin, 2010).

2.11 Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone), is an active ingredient in the root and rhizome of *Rheum palmatum* L. (Fam. Polygonaceae) (Wang *et al.*, 2011) and several other plant species like *Rheum officinale, Ventilago madraspatana, Polygonum multiflorum, Polygonum cuspidatum, Rumex patientia, Rhamnus catharticus, Rhamnus orbiculatus, Aloe vera, Acorus tatarinowii, Cassia obtusifolia, Cassia occidentalis, Eriocaulon buergerianum, etc.*

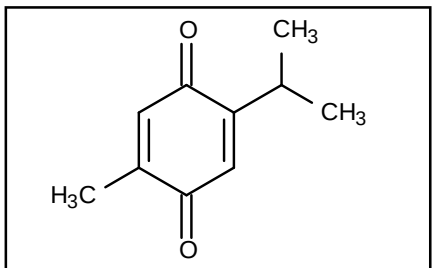


Emodin

Emodin protected against acetaminophen and CCl_4-induced oxidative stress and acute liver injury in rats (Dang *et al.*, 2008; Bhadauria, 2010). Emodin also alleviated alcohol-mediated oxidative stress and liver steatosis in mice by down-regulating hepatic CYP2E1 expression (Liu *et al.*, 2014d). Emodin also ameliorated NAFLD in rats induced with a high caloric diet by suppressing GRP78-mediated SREBP-1c pathway in the liver and restoring reduced expression of PPARγ gene expression (Dong *et al.*, 2005; Li *et al.*, 2015b). In steatotic hepatic cells, emodin down-regulated HMGCR and diacylgycerol acyltransferase 1 (DGAT1), key enzymes in the synthesis of cholesterol and triglycerides, while upregulating expression of CYP7A, involved in hepatic bile acid biosynthesis (Wang *et al.*, 2014). Protection against CCl_4-induced fibrogenesis by emodin was mediated by the reduction of the mRNA levels of TGF-β1 and Smad4 and inhibition of myofibroblastic differentiation (Dong *et al.*, 2009). Another study by Lin *et al.* (1996) showed emodin exhibited hepatoprotective effects on CCl_4 as well as D-galactosamine induced liver damage. The histopathological examination also clearly showed that emodin reduced lymphocyte cells, Kupffer cells, ballooning degeneration, cell necrosis and hyaline degeneration on CCl_4 and D-galactosamine induced tests.

2.12 Thymoquinone

Thymoquinone, a monoterpenoid quinone, the major active compound derived from the *Nigella sativa* L. (Fam. Ranunculaceae) seeds, has been reported to protect experimental animals against oxidative hepatic injury by improving hepatic antioxidant status (Sayed-Ahmed *et al.,* 2010; Prabhakar *et al.,* 2014). In addition, thymoquinone treatment has been shown to significantly suppress CYP1A2, CYP3A4 but not CYP2E1 activity in rabbits (Elbarbry *et al.,* 2012). Chemically induced hepatic fibrosis and inflammation in mice were attenuated by thymoquinone through suppression of protein and mRNA expression of collagen I and TIMP-1 and reduction of ECM accumulation (Bai *et al.,* 2014; Ghazwani *et al.,* 2014). Thymoquinone down-regulated the expression of TLR4 and decreased proinflammatory cytokine levels (Bai *et al.,* 2014). In addition, it also inhibited PI3K phosphorylation, enhanced the phosphorylation AMPK and liver kinase B (LKB)-1. In rats, injected with cisplatin, thymoquinone reduced the expression of NF-κB and proinflammatory proteins TNF-α, IL-1β (Al-Malki and Sayed, 2014). Investigating the mechanism of antifibrotic activity in several HSC lines, Ghazwani *et al*. (2014) showed that the inhibition of LPS-induced mRNA expression of IL-6 and MCP-1 was associated with the inactivation of NF-κB pathway and down-regulation of mRNA expression of several fibrosis-related genes. This quinone also showed the inhibitory potential toward TLR4 and PI3K/Akt signaling pathways in activated HSCs and proapoptotic activity, as shown by decreased XIAP and c-FLIP expression (Bai *et al.,* 2013). Moreover, thymoquinone administration in rats fed high-fat diet (HFD) diminished metabolic syndrome by preventing reduction in hepatic mRNA levels of PPAR-α and PPAR-γ (Prabhakar *et al.,* 2014).



Thymoquinone

3. Some other reports on hepatoprotective phytochemicals

There have been several other reports regarding various hepatoprotective agents isolated from plants**:** Cliv-92 (a mixture of three structurally similar coumarinolignoids) isolated from *Cleome viscosa* (Ray *et al.,* 1985), oleanolic acid from *Lantana camara* (Misra *et al.,* 1997), β amyrin and α amyrin from *Protium heptaphyllum* (Oliveira *et al.,* 2005), anastatin A and anastatin B from *Anastatica hierochuntica* (Yoshikawa *et al.,* 2003b), genistein, orobol and 5,7,4' trihydroxy 3' methoxyisoflavone from *Erycibe expansa* (Matsuda *et al.,* 2004), γ amyrin, γ amyrone, 18β hydroperoxy olean 12 en 3 one and 3 epi γ amyrin from *Sedum sarmentosum* (Amin *et al.,* 1998), rutin from *Artemisia scoparia* (Janbaz *et al.,* 2002), rubiadin from *Rubia cordifolia* (Rao *et al.,* 2006), myristin from *Myristica fragrans* (Morita *et al.,* 2003), naringenin and wighteone from *Cudrania cochinchinensis* (Lin *et al.,* 2003), kaempferol and salidroside from *Rhodiola sachalinensis* (Song *et al.,* 2003), gentiopicroside and sweroside from *Swertia japonica* (Hase *et al.,* 1997a), tetrahydroswertianolin from *Swertia japonica* (Hase *et al.,* 1997b), mangiferin from *Salacia reticulata* (Yoshikawa *et al.,* 2003a), torilin and torilolone from *Cnidium monnieri* (Oh *et al.,* 2002), acanthoic acid from *Acanthopanax koreanum* (Park *et al.,* 2004), 18β glycyrrhetinic acid from *Glycyrrhiza uralensis* (Shim *et al.,* 2000), lithospermate B from *Salvia miltorhiza* (Hase *et al.,* 1997b), corilagin from *Terminalia catappa* (Kinoshita *et al.,* 2007), neoandrographolide from *Andrographis paniculata* (Chander *et al.,* 1995), scropolioside A from *Scrophularia koelzii* (Garg *et al.,* 1994), schisandrin B from *Schisandra chinensis* (Ip *et al.,* 1995), kahweol and cafestol from *Coffea arabica* and *C. robustica* (Lee *et al.,* 2007), quercetin from *Oenothera biennis*, *Podophyllum* spp., *etc.* (Molina *et al.,* 2003), lupeol from *Crataeva nurvala* (Preetha *et al.,* 2006), caffeic acid from *Ipomoea purga*, *Ocimum basilicum*, *etc.* (Janbaz *et al.,* 2004), bergenin from *Mallotus japonicas* (Kim *et al.,* 2000), tiliroside from *Magnolia fargesii* (Matsuda *et al.,* 2002), kolaviron from *Garcinia kola* (Iwu *et al.,* 1987), thymoquinon from *Nigelle sativa* (Daba and Abdel-Rahman, 1998), bupleurosides III, VI, IX, and XIII from *Bupleurum scorzonerifolium* (Matsude *et al.,* 1997), trans-tetracos-15-enoic acid from *Indigofera tinctoria* (Singh *et al.,* 2006), gomishins, schisandrin A and wuweizisu C from *Schizandra chinensis*, saikosaponins from *Bupleurum falcatum*, sarmentosins fom *Sedum sarmetosum*, fumaric acid from *Sida cordifolia* (Valan *et al.,* 2010), helioxanthin from *Taiwania cryptomerioides* (Tseng *et al.,* 2008), matrine and oxymatrine from *Sophora japonica* (Zhang *et al.,* 2001; Ma *et al.,* 2013), nobiletin from *Citrus unshiu* (Suzuki *et al.,* 2005; Yoshigai *et al.,* 2013), genistein from *Hydrocotyle sibthorpioides* (Huang *et al.,* 2013), salvianic acid A from *Salvia miltiorrhiza* (Zhang *et al.,* 2012), betulin and betulinic acid from *Betula platyphylla* (Szuster-Ciesielska and Kandefer-Szerszen, 2005; Szuster-Ciesielska *et al.,* 2011), rosmarinic acid, baicalin (Yang *et al.,* 2012) and paeoniflorin from *Moutan cortex* (Li *et al.,* 2010; Li *et al.,* 2011), β-caryophyllene identified in the essential oil of numerous plants and fruits (Calleja *et al.,* 2013), *etc.*

Some of the traditionally used plants for liver disorders provided useful therapeutic agents. A large number of such plants lack the scientific evidences supporting their effectiveness. Many groups of researchers worldwide were involved in studying the protective effects of plant extracts against experimentally induced liver toxicity. These results can be a helpful guide for researchers to explore the constituents of the most promising plants and molecular mechanisms in liver protection in order to discover new useful natural drugs for the management of liver disorders.

3.1 Indian systems of medicine and liver diseases

Due to the high prevalence of chronic hepatic diseases in South Asia, Indian systems of medicine has generated extensive empirical knowledge in their treatment over several centuries (Patel *et al.,* 2015). There are more than 300 preparations in the Indian systems of medicine for the treatment of jaundice and chronic liver diseases (Table 2) (Thyagarajan *et al.,* 2002). In India, more than 87 medicinal plants are used in different combinations as herbal drugs for liver diseases (Handa *et al.,* 1989; Sharma *et al.,* 1991b). However, not all the plants have been evaluated for their pharmacological and antiviral efficacy.

Table 1: Clinical relevance of modern medicine

Sl. No.	Modern medicine	Disease condition	Clinical application	Reference
1.	Corticosteroids	Reduce cytokine production Antifibrotic	Most studies show no important effects. Now -a-days, it is considered that corticosteroids have a poor future in the treatment of liver diseases.	Kashaw *et al.*, 2011
2.	Interferons	Antiviral Antifibrotic	Effective in hepatitis B and C Not tested directly as antifibrotic in humans. Several side effects attherapeutic doses includes as depression, anxiety, agitation, suicidal ideation and even suicide.	Muriel and Rivera-Espinoza, 2008
3.	Lamivudine	Hepatitis B and cirrhosis	Continuous usage leads to emergence of a resistant hepatitis B virus mutant.	Yun-Fan *et al.*, 2004
4.	Propylthiouracil	Alcoholic hepatic diseases	Render metabolically-compromised patients hypothyroid.	Arteel *et al.*, 2003
5.	Colchicine	Against gout Antifibrotic	No beneficial properties were recently demonstrated. Very toxic at high doses.	Muriel and Rivera-Espinoza, 2008
6.	Pentoxifylline	Severe alcoholic hepatitis	Protective effects against hepatorenal syndrome and its excellent safety profile. Patients with xanthine hypersensitivity should avoid use of pentoxifylline.	http://livertox.nih.gov/
7.	Ursodeoxycholic acid	Non-alcoholic fatty hepatic disease	Improves hepatic enzymes and hepatic histology in patients with various hepatobiliary diseases and improves oxidative stress. In human patients that taurine depletion may be potentiated by chronic treatment with ursodeoxycholic acid.	Federico *et al.*, 2006
8.	Rosiglitazone	Non-alcoholic fatty hepatic disease	Increase risk of heart attack.	Xiao *et al.*, 2013

Table 2 : Herbal formulations approved by Indian medicinal practitioner's co-operative pharmacy and stores

Sl No.	Ayurvedic preparation	Siddha preparation	Unani preparations
1.	Bhringarajasava	Arumuga chendooram	Jawarish-e-Amilasada
2.	Chandraprabhavati	Annabedhi chendooram no. 1 and 2	Jawarish-e-Amila luluvi
3.	Drakahadi rasayam	Ayakantha chendooram	Jawarish-e-Tabashir
4.	Guduchi satwam	Mandooradi kudineer	Kurs-e-gul
5.	Jambeeradi panakam	Ayabringaraja karpam	Rue-e-amila
6.	Panchatiktakwatha churnam	Karisalai lehyam	Sherbeth-e-anarshreen
7.	Dhathri loham	Kantha chendooram	Sherbeth-e-deenar
8.	Tapyadi loham	Loha mandooram	Muffarah-e-Ahmedi
9.	Pipilyadi loham		Gul-e-Nilofer
10.	Saptamiruda loham		Bhoi-Amla

4. Conclusion

Liver diseases are one of the foremost health troubles worldwide, with liver cirrhosis and drug induced liver injury accounting to ninth leading cause of death in Western and developing countries. There are numerous plants and traditional formulations available for the treatment of liver diseases. About 600 commercial herbal formulations with claimed hepatoprotective activity are being sold all over the world. In India, more than 93 medicinal plants are used in different combinations in the preparations of 40 patented herbal formulations. However, only a small proportion of hepatoprotective plants as well as formulations used in traditional medicine are pharmacologically evaluated for their safety and efficacy. Development of standardized, safe and effective herbal formulations

with proven scientific evidence can augment the existing arsenal of herbal drugs to combat liver diseases. A regulated research policy to highlight the advantages of hepatoprotective herbal medicine with respect to their safety and efficacy could result in a better utilisation of these complementary systems of medicine. Thus, plants have the potential to serve as a source of new therapeutic agents for the development of future drugs in the treatment of various hepatic diseases.

Conflicts of interest

We declare that we have no conflict of interest.

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