



## Hepatoprotective Herbs – A Review

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### ABSTRACT

Liver is a vital organ play a major role in metabolism and excretion of xenobiotics from the body. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Liver cell injury caused by various toxic chemicals (certain antibiotic, chemotherapeutic agents, carbon tetrachloride (CCL<sub>4</sub>), thioacetamide (TAA) etc.), excessive alcohol consumption and microbes is well-studied. The available synthetic drugs to treat liver disorders in this condition also cause further damage to the liver. Hence, Herbal drugs have become increasingly popular and their use is widespread. Herbal medicines have been used in the treatment of liver diseases for a long time. A number of herbal preparations are available in the market. The present review is aimed at compiling data on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models using modern scientific system.

**Keywords:** Herbal Drugs, Liver Injury, Carbon tetrachloride (CCL<sub>4</sub>), Hepatotoxicity, Serum Transaminases.

### INTRODUCTION

Liver is considered to be one of the most vital organs that functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide etc., chronic alcohol consumption and microbes is well-studied. Enhanced lipid peroxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis. Since time immemorial, mankind has made the use of plants in the treatment of various ailments. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well-documented uses of plant-products is their use as

hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent (Agarwal, 2001).

### Hepatoprotective herbs

Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are (i) lack of standardization of the herbal drugs; (ii) lack of identification of active ingredient(s)/principles(s); (iii) lack of randomized controlled clinical trials (RCTs), and (iv) lack of toxicological evaluation (Radha *et al.*, 2005). The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. The 21<sup>st</sup> 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).

A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary mul-

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ti-ingredient plant formulations (Handa *et al.*, 1986). In spite of the tremendous advances made, no significant and safe hepatoprotective agents are available in modern therapeutics. Therefore, due importance has been given globally to develop plant-based hepatoprotective drugs effective against a variety of liver disorders. The present review is aimed at compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models.

#### ***Flacourtia indica***

The extracts of the aerial parts of *Flacourtia indica* (Burm. f.) Merr., were evaluated for hepato-protective properties. In paracetamol-induced hepatic necrosis in rat models, all extracts were found to reduce serum aspartate transaminase (AST), serum alanine transaminase (ALT) and serum alkaline phosphatase (ALP). The most significant reduction of the serum level of AST and ALT were exhibited by petroleum ether and ethyl acetate extracts at a single oral dose of 1.5g/kg of body weight with a reduction of 29.0% AST & 24.0% ALT level by petroleum ether extract, and 10.57% AST & 6.7% ALT level by ethyl acetate extract compared to paracetamol (3 g/kg of body weight) treated animals. Histopathological examination also showed good recovery of paracetamol-induced necrosis by petroleum ether and ethyl acetate extracts. On the other hand, the methanol extract did not show any remarkable effect on paracetamol-induced hepatic necrosis. The hepatoprotective effects exhibited by petroleum ether and ethyl acetate extract might be mediated through the inhibition of microsomal drug metabolizing enzymes (Nazneen *et al.*, 2008). But, in this study the dose they have used is too high and it is not successful or rationale for human dose.

#### ***Annona squamosa***

The extracts of *Annona squamosa* (300 & 350 mg/kg bw) were used to study the hepatoprotective effect in isoniazid + rifampicin-induced hepatotoxic model in albino Wistar rats. There was a significant decrease in total bilirubin accompanied by significant increase in the level of total protein and also significant decrease in ALP, AST, and ALT in treatment group as compared to the hepatotoxic group. In the histopathological study, the hepatotoxic group showed hepatocytic necrosis and inflammation in the centrilobular region with portal triaditis. The treatment group showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal (Saleem *et al.*, 2008).

In another study, the protective effect was evaluated in diethylnitrosamine induced hepatotoxicity. This study revealed that the extracts of *Annona squamosa* exerted hepatoprotective effect and the plant extract could be an effective remedial for chemical-induced hepatic damage (Raj *et al.*, 2009).

#### ***Silybum marianum***

The protective effects of polyphenolic extracts of *Silybum marianum* and *Cichorium intybus* on thioacetamide-induced hepatotoxicity in rat was investigated (Madani *et al.*, 2008). The extracts were injected to the rats, at a dose of 25 mg kg<sup>-1</sup> body weight together with thioacetamide at a dose of 50 mg kg body weight. Significant decrease in the activity of aminotransferases, alkaline phosphatase and bilirubin was observed in the groups treated with extracts and thioacetamide compared with the group that was treated only with thioacetamide. The level of Na<sup>+</sup>, K<sup>+</sup> and liver weight between different groups was not significantly altered. This finding suggested the hepato-protective effect of *Silybum marianum* and *Cichorium intybus* extracts on liver cells due to the presence of flavonoids and their antioxidant effects (Madani *et al.*, 2008).

#### ***Chamomile capitula***

The effect of ethanolic extract of *Chamomile recutita* capitula (400 mg kg<sup>-1</sup>, P.O.) on blood and liver glutathione, Na<sup>+</sup> K<sup>+</sup>-ATPase activity, serum marker enzymes, serum bilirubin, glycogen and thiobarbituric acid reactive substances against paracetamol-induced liver damage in rats have been studied to find out the possible mechanism of hepato-protection. It was observed that extract of *Chamomile recutita* has reversal effects on the levels of above-mentioned parameters in paracetamol hepatotoxicity (Gupta and Misra, 2006) suggesting its hepato-protective and/or hepato-stimulant activity.

#### ***Coccinia grandis***

Alcoholic extract of the fruits of *Coccinia grandis* Linn (Curcubitaceae) was evaluated in CCl<sub>4</sub>-induced hepatotoxicity in rats and levels of AST, ALT, ALP, total proteins, total and direct bilirubin were evaluated. At a dose level of 250 mg/kg, the alcoholic extract significantly (p<0.05) decreased the activities of serum enzymes (AST, ALT and ALP) and bilirubin which were comparable to that of silymarin (Vadivu *et al.*, 2008) revealing its hepato-protective effect.

#### ***Wedelia calendulacea***

The hepatoprotective activity of ethanolic extract of *Wedelia calendulacea* L. (Family: Asteraceae) was studied against CCl<sub>4</sub>-induced acute hepatotoxicity in rats. The treatment with ethanolic extract of *Wedelia calendulacea* showed a dose-dependent reduction in CCl<sub>4</sub>-induced elevated serum enzyme activities with parallel increase in total proteins and bilirubin, indicating the extract could enhance the return of normal functional status of the liver comparable to normal rats. The weight of the organs such as liver, heart, lung, spleen and kidney in CCl<sub>4</sub>-induced hepatic damaged animals that received ethanolic extract of *Wedelia calendulacea* showed an increase over CCl<sub>4</sub>-treated control group (Murugaian *et al.*, 2008).

***Prostechea michuacana***

Methanol, hexane and chloroform extracts of *Prostechea michuacana* (PM) were studied against CCl<sub>4</sub>-induced hepatic injury in albino rats. Pre-treatment with methanolic extract reduced biochemical markers of hepatic injury levels demonstrated dose-dependant reduction in the *in vivo* peroxidation induced by CCl<sub>4</sub>. Likewise, pretreatment with extracts of PM on paracetamol-induced hepatotoxicity and the possible mechanism involved in this protection were also investigated in rats after administering the extracts of PM at 200, 400 and 600mg/kg. The degree of protection was measured by monitoring the blood biochemical profiles. The methanolic extract of orchid produced significant hepatoprotective effect as reflected by reduction in the increased activity of serum enzymes, and bilirubin. These results suggested that methanolic extract of PM could protect paracetamol-induced lipid peroxidation thereby eliminating the deleterious effects of toxic metabolites of paracetamol. This hepato-protective activity was comparable with silymarin. Hexane and chloroform extracts did not show any apparent effect. The findings indicated that the methanolic extract of PM can be a potential source of natural hepatoprotective agent (Rosa and Rosario, 2009).

***Aegle marmelos***

*Aegle marmelos* leaves (*Bael*, family of Rutaceae) which is also called as *Bilva* in ancient Sanskrit, was used as herbal drug in the Indian System of medicine. The hepatoprotective effect of *Aegle marmelos* in alcohol-induced liver injury was evaluated rats using essential marker biochemical parameters. The results indicated that, the *Bael* leaves have excellent hepatoprotective effect. Similar findings were also reported by other workers (Singanan *et al.*, 2007).

***Cassia roxburghii***

Seeds of *Cassia roxburghii* DC had been used in ethnomedicine for various liver disorders for its hepatoprotective activity. The methanolic extract of *Cassia roxburghii* reversed the toxicity produced by ethanol-CCl<sub>4</sub> combination in dose dependent manner in rats. The extract at the doses of 250 mg/kg and 500 mg/kg are comparable to the effect produced by Liv-52®, a well established plants-based hepato-protective formulation against hepatotoxins (Arulkumaran *et al.*, 2009).

***Orthosiphon stamineus***

The hepatoprotective activity of the methanol extract of *Orthosiphon stamineus* was assessed in paracetamol-induced hepatotoxicity rat model. Change in the levels of biochemical markers such as AST, ALT, ALP and lipid peroxides were assayed in both paracetamol treated and control (untreated) groups. Treatment with the methanolic extract of *O. stamineus* leaves (200 mg/kg) has accelerated the return of the altered levels of biochemical markers to the near normal pro-

file in the dose-dependent manner (Maheswari *et al.*, 2008).

***Ficus carica***

The methanolic extract of the leaves of *Ficus carica* Linn. (Moraceae) was evaluated for hepatoprotective activity in CCl<sub>4</sub>-induced liver damaged rats. The extract at an oral dose of 500 mg/kg exhibited a significant protective effect reflected by lowering the serum levels of AST, ALT, total serum bilirubin, and malondialdehyde equivalent, an index of lipid peroxidation of the liver (Krishna *et al.*, 2007).

***Lepidium sativum***

The role hepato-protective of methanolic extract of *Lepidium sativum* at a dose of 200 and 400 mg/kg was investigated in CCl<sub>4</sub>-induced liver damage in rats. Significant reduction in all biochemical parameters were found in groups treated with *Lepidium sativum*. The severe fatty changes in the livers of rats caused by CCl<sub>4</sub> were insignificant in the *Lepidium sativum* treated groups (Afaf *et al.*, 2008).

***Sargassum polycystum***

The protective effect of ethanol extract of *Sargassum polycystum* was evaluated in D-galactosamine-induced hepatitis in rats. Prior oral administration of *S. polycystum* extract [125mg/kg bodyweight/day for 15 days] significantly attenuated (P<0.05) the D-galactosamine-induced increases in the levels of diagnostic marker enzymes (AST, ALT and ALP) in plasma of rats. It has also demonstrated antioxidant activity against D-galactosamine-induced hepatitis by inhibiting the activation of lipid peroxidation and by preserving the hepatic enzymatic and non-enzymatic antioxidant defense system at near normal. The antihepatotoxic potential of *S. polycystum* might possibly due to its antioxidant property and membrane stabilizing action (Meena *et al.*, 2008).

***Solanum nigrum***

The effects of *Solanum nigrum* extract (SNE) was evaluated on thioacetamide (TAA)-induced liver fibrosis in mice. Mice in the three TAA groups were treated daily with distilled water and SNE (0.2 or 1.0 g/kg) via gastrogavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and  $\alpha$ -smooth muscle actin protein levels in TAA-treated mice. SNE inhibited TAA-induced collagen ( $\alpha_1$ )(I), transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and mRNA levels in the liver. Histological examination also confirmed that SNE reduced the degree of fibrosis caused by TAA treatment. Oral administration of SNE significantly reduces TAA-induced hepatic fibrosis in mice, probably through the reduction of TGF- $\beta$ 1 secretion (Hsieh *et al.*, 2008).

In other study, the protective effects of aqueous extract of SN (ASNE) against liver damage were evaluated in CCl<sub>4</sub> - induced chronic hepatotoxicity in rats. The results showed that the treatment of ASNE significantly

lowered the CCl<sub>4</sub>-induced serum levels of hepatic enzyme markers, superoxide and hydroxyl radicals. Liver histopathology showed that ASNE reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, hepatic necrosis, and fibrous connective tissue proliferation induced by CCl<sub>4</sub> in rats. Therefore, the results of this study suggest that ASNE could protect liver against the CCl<sub>4</sub>-induced oxidative damage in rats, and this hepatoprotective effect might be contributed to its modulation on detoxification enzymes and its antioxidant and free radical scavenger effects (Lin *et al.*, 2008). The presence of plant extracts of *Solanum nigrum* and *Cichorium intybus* in the reaction mixture containing calf thymus DNA and free radical generating system protect DNA against oxidative damage to its deoxyribose sugar moiety. The effect was dependent on the concentration of plant extracts. However, the effect of *Cichorium intybus* was much pronounced as compared to the effect of *Solanum nigrum*. These studies suggested that the observed hepatoprotective effect of these crude plant extracts may be due to their ability to suppress the oxidative degradation of DNA in the tissue debris (Sultana *et al.*, 1995). Since these herbs are commonly known as hepatoprotective agents and have shown their efficacy in protecting against CCl<sub>4</sub>-induced hepatic injury (Karandhikar, 1963; Bardhan *et al.*, 1985), it may be proposed that their efficacy may be attributed to their free radical scavenging ability.

## DISCUSSION

Popularity of herbal remedies is increasing globally and at least one quarter of patients with liver diseases use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting to vigorous pre-clinical studies followed by clinical trials to unravel the mysteries hidden in the plants. This approach will help exploring the real therapeutic value of these natural pharmacotherapeutic agents and standardized the dosage regimen on evidence-based findings to become more than a fashionable trend (Stickel and Schuppan, 2007). Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental hepatotoxicity models in laboratory or higher animals, several herbals exerted hepato-protective/curative effects that warrants their clinical testing. Due to lack of scientific-based pharmacological data, most of the herbal formulations can not be recommended for the treatment of liver diseases (Stickel and Schuppan, 2007).

In spite of the availability of more than 300 preparations for the treatment of jaundice and chronic liver diseases in Indian Systems of Medicine (using more than 87 Indian medicinal plants,) only four terrestrial plants have been scientifically elucidated while adhering to the internationally acceptable scientific protocols. In-depth studies have proved *Sylibum marianum*

to be anti-oxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating and liver regenerative. *Glycyrrhiza glabra* has been shown to be hepatoprotective and capable of inducing an endogenous interferon. *Picrorrhiza kurroa* is proved to be anti-inflammatory, hepatoprotective and immunomodulatory. Extensive studies on *Phyllanthus amarus* have confirmed this plant preparation possessed anti-viral against hepatitis B and C viruses, hepatoprotective and immunomodulating effects, besides anti-inflammatory properties (Thyagarajan *et al.*, 2002).

## CONCLUSION

Chronic hepatic diseases stand as one of the foremost health troubles worldwide, with liver cirrhosis and drug induced liver injury accounting ninth leading cause of death in western and developing countries. Therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating liver diseases with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, an attempt has been made to compile the reported hepatoprotective plants from India and abroad and may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of liver diseases in man and animals.

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