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## Herbal approaches on Hepatotoxic models– a Review

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### ABSTRACT

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. The present review focused on different types of herbs which are traditionally used as hepatoprotective. These herbal drugs have shown the ability to maintain the normal functional statuses of the liver with or without fewer side effects and medicinal plants may offer new alternatives to the limited therapeutic options that exist at present in the treatment of liver diseases or their symptoms, and they should be considered for future studies.

**Key words:** Hepatotoxicity, Hepatoprotection, Herbs.

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## INTRODUCTION

Herbal medicine has its roots in every culture around the world, from the Greeks, to the Celts, the Romans to Arabs, and Chinese to the Indians. There are thousands of herbs with thousand of different uses, many of which are used in conventional medicine as well as for natural remedies. The herbs are also used in many traditions as a preventive action to boost immune function and promote general well being before any disease occurs. Crude herbals and the pharmaceutical substances from the herbal origin are widely used in the pharmaceutical formulations. They are not only used as the active ingredients but also as pharmaceutical additives. In recent years, interest in herbal medicine has skyrocketed, leading to a greater scientific interest in the medicinal use of plants. Many international studies have been shown the plants are capable of treating disease and improving health, often without any significant side effects.

### **Liver**

Liver is considered to be one of the most vital organs that functions as a center of metabolism of nutrients such as carbohydrates, proteins, lipids and excretion of waste metabolites. Hepatic disease is a term that affects the cells, tissues, structures, or functions of the liver. Liver has a wide range of functions, including detoxification, protein synthesis, and production of biochemical necessary for digestion and synthesis as well as breakdown of small and complex molecules, many of which are necessary for normal vital functions. Herbal drugs are more widely used than allopathic drugs as hepatoprotective because of them are inexpensive, better cultural acceptability, better compatibility, with the human body and minimal side effects. These herbal drugs have shown the ability to maintain the normal functional statues of the liver with or without fewer side effects. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide etc., chronic alcohol consumption and microbes is well-studied. Liver protective plants contain a variety of chemical constituents like phenols, Coumarins, Lignans, essential oil, monoterpenes, carotinoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes. Therefore a large number of plants and formulations have been claimed to have hepatoprotective activity so the development of plant based hepatoprotective protective drugs has been given importance in the global market.<sup>1</sup> 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.

### **Experimental models**

The following are the various common hepatotoxic models which are utilized in the evaluation of

various hepatoprotective elements.

### **Carbon tetra chloride induced hepatotoxicity**

Liver injury due to carbon tetrachloride in rats was first reported in 1936 and has been widely and successfully used by many investigators. Carbon tetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl<sub>3</sub>O<sup>-</sup>, a reactive oxidative free radical, which initiate lipid peroxidation. Administration of a single dose of CCl<sub>4</sub> to a rat produces a centrilobular necrosis and fatty changes within 24 hrs. The poison reaches its maximum concentration in the liver within 3 hrs of administration. Thereafter, the level falls and by 24 hrs there is no CCl<sub>4</sub> left in the liver. The development of necrosis is associated with leakage of hepatic enzymes into serum. <sup>2,3</sup>

### **Galactosamine induced hepatotoxicity**

D-Galactosamine induced liver damage has been extensively used as an experimental model. Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylyate nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. Galactosamine decreases the bile flow and its content i.e. bile salts, cholic acid and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption. <sup>4</sup>

### **Thioacetamide induced hepatotoxicity**

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and its content i.e. bile salts, cholic acid and deoxycholic acid. <sup>4</sup>

### **Alcohol induced hepatotoxicity**

Among the organs liver is most susceptible to the toxic effects of ethanol. Alcohol consumption is known to cause fatty infiltration, hepatitis and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Hepatitis and cirrhosis may occur because of enhanced lipid peroxidative reaction during the microsomal metabolism of ethanol. It is generally accepted that alcohol can induce *in vivo* changes in membrane lipid composition and fluidity, which may eventually affect cellular functions. Among the mechanisms

responsible for effects of alcohol, an increase in hepatic lipid peroxidation leads to alteration in membrane phospholipid composition. The effects of ethanol have been suggested to be a result of the enhanced generation of oxyfree radicals during its oxidation in liver. The peroxidation of membrane lipids results in loss of membrane structure and integrity. This result in elevated levels of  $\gamma$ -glutamyl transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decrease the activity of catalase, superoxide dismutase, along with increase in levels of glutathione in liver. The decrease in activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol.<sup>5,6</sup>

### **Paracetamol induced hepatotoxicity**

Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl- P-benzoquinoneimine, an oxidative product of paracetamol to sulphhydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver.<sup>6</sup>

### **Nonsteroidal anti-inflammatory drugs**

Although individual analgesics rarely induce liver damage due to their widespread use, NSAIDS have emerged as a major group of drugs exhibiting hepatotoxicity. Both dose dependent and idiosyncratic reactions have been documented. Aspirin and phenylbutazone are associated with intrinsic hepatotoxicity and idiosyncratic reaction has been associated with ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac and indomethacin.<sup>7</sup>

### **Herbal approaches on Various Models**

Herbal medicine is use of plants for medicinal purposes, and the study of such use. Plants have been the basis for medicinal treatment through much of human history, and such traditional medicine is still widely practiced today. Modern medicine recognize herbalism as a form of alternative medicine, as the practice of herbalism is not strictly based on evidence gathered using the scientific method. Modern medicine does, however, make use of many plant –derived compounds. As the basis for evidence-tested pharmaceutical drugs, and phytotherapy works to apply modern standards of effectiveness of testing to herbs and medicine that are derived from natural sources. The Indian Traditional Medicine like Ayurvedha, 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. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their derivatives are still used all over the world are in one form or the other for this purpose. Scientific evaluation of plants has often shown that active principles in these are responsible for therapeutic success. A large number of medicinal plants have been tested and found to contain active principles with curative properties against a variety of diseases.

### **Aerva lanata**

The hepatoprotective activity of hydroalcoholic extract of *Aerva lanata* against paracetamol induced liver damage in rats. The hydroalcoholic extract of *Aerva lanata* (600mg/kg) was administered orally to the animals with hepatotoxicity induced by paracetamol (3gm/kg). Silymarin (25mg/kg) was given as reference standard. All the test drugs were administered orally by suspending in 0.5% Carboxy methyl cellulose solution. The plant extract was effective in protecting the liver against the injury induced by paracetamol in rats <sup>8</sup>

### **Andrographis paniculata**

The hepatoprotective activity of methanolic extracts of *Andrographis paniculata* was evaluated against paracetamol induced (500 mg/kg) hepatic damage in mice. The extracts at doses of 10 mg/kg and 100 mg/kg were orally administered at 24 and 72 hours time interval in each group. The results of the present study indicated that *Andrographis paniculata* possess hepatoprotective effects which could compromise the medicinal use of this plant in folk medicine. <sup>9</sup>

### **Occimum sanctum**

Effect of *Ocimum sanctum* leaf extract was studied on paracetamol induced hepatic damage in rats. *O. Sanctum* was found to protect the rats from hepatotoxic action of paracetamol as evidenced by significant reduction in the elevated serum enzyme levels. Histopathological studies showed marked reduction in fatty degeneration in animals receiving *O. sanctum* along with paracetamol as compared to the control group. <sup>10</sup>

### **Butea monosperma**

The methanolic extract of stem bark of *Butea monosperma* Lam (MEBM) was studied for the hepatoprotective and antipyretic activities. Carbontetrachloride (1ml/kg, i.p) induced hepatotoxicity and Brewer's yeast (10ml/kg, s.c) induced pyrexia rat models were used. The 10 days treatment of MEBM (200 mg/kg and 400 mg/kg, p.o) showed significant hepatoprotective effect by dose dependent manner. <sup>11</sup>

**Ixora parviflora**

*Ixora parviflora*, a species of the Rubiaceae, is rich in polyphenols and flavonoids, and has been traditionally used as a folk medicine. An *I. parviflora* extract (IPE) has great antioxidant activity *in vitro*, including a scavenging effect on superoxide radicals, reducing power, and ferrous ion-chelating ability. However, whether IPE is efficacious against oxidative damage *in vivo* is not known. The purpose of this study was to determine the protective effects of IPE treatment on hepatic oxidative stress and antioxidant defenses after exhaustive exercise in mice. After a single bout of exhaustive swimming exercise challenge, levels of blood ammonia and creatine kinase (CK), and hepatic superoxide dismutase (SOD) protein expression, thiobarbituric acid-reactive substance (TBARS), and gp91phox, p22phox, and p47phox subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expressions in the IPE0 group were significantly affected compared to those of the C group, but they were all significantly inhibited by the IPE treatments. Results of the present *in vivo* study in mice indicate that *I. parviflora* extract possesses antioxidative and hepatoprotective potential following exhaustive exercise.<sup>12</sup>

**Beta vulgaris**

The study was undertaken to investigate the hepatoprotective action of *Beta vulgaris* Linn. (BV, Chenopodiaceae) leaves against ethanol-mediated hepatotoxicity. Rat hepatocyte culture and rats were used as *in vitro* and *in vivo* screening models, respectively. In the *in vitro* studies, different extracts (i.e., petroleum ether, ethanol and aqueous) and fractions derived from ethanol extract (i.e., chloroform, ethyl acetate and n-butanol) of BV leaves were screened. *In vivo* hepatoprotective activity was assessed in rats intoxicated with ethanol. Levels of serum markers enzymes together with antioxidants were measured to evaluate the extent of hepatic protection. Silymarin was taken as reference drug. In the *in vitro* studies, n-butanol fraction of BV leaves (BVBF) was found to be more potent than others. Moreover, in the *in vivo* evaluation, BVBF at doses of 50, 100 and 200 mg/kg showed marked protective action against ethanol-induced hepatic toxicity as evident by restoration of biochemical changes caused by ethanol. The present study concluded that BVBF possess potent hepatoprotective effect against ethanol-induced hepatic toxicity and it may have a great potential role in the management of alcoholic liver disease.<sup>13</sup>

**Paeoniae Rubra**

In the present study the capacity of *Radix Paeoniae Rubra* aqueous extract (RPRAE) as an antioxidant to protect against carbon tetrachloride (CCl<sub>4</sub>)-induced oxidative stress and hepatotoxicity in Wistar rats was investigated. Six groups of rats were used. *Radix Paeoniae Rubra* aqueous extract (100 or 200 or 300 mg/kg of bw) or bifendate (100 mg/kg of bw) were given daily

by gavage to the animals on 28 consecutive days to elucidate the protective effects against CCl<sub>4</sub>-induced hepatotoxicity. The 20% CCl<sub>4</sub>/olive oil was gavage of gastric tube twice a week (on the third and seventh days of each week). The animals of normal control group were given only vehicle. The animals of CCl<sub>4</sub>-treated group were administered with CCl<sub>4</sub> twice a week (on the third and seventh days of each week) and with vehicle on rest of the days. The test materials were found effective as hepatoprotective agents, as evidenced by plasma and liver biochemical parameters. Therefore, the results of this study show that Radix Paeoniae Rubra aqueous extract can protect the liver against CCl<sub>4</sub>-induced oxidative damage in rats, and the hepatoprotective effects might be correlated with its antioxidant and free radical scavenger effects.<sup>14</sup>

### **Cichorium endivia**

The objective of the study was to investigate the *in vitro* and *in vivo* hepatoprotective properties of Cichorium endivia L. extract (CEE), and to identify its chemical constituents. CEE significantly blocked the oxidative stress and cytotoxicity induced by tert-butyl hydroperoxide (t-BHP) in HepG2 cells. Meanwhile, oral administration of CEE to mice before the treatment of t-BHP exhibited a markedly protective effect by lowering serum levels of ALT and AST, inhibiting the changes in liver biochemistry including MDA, SOD, GSH and GST, as well as ameliorating the liver injuries according to the histopathological observations. CEE protects hepatic tissue from oxidative damage *in vitro* and *in vivo*, potentially due to its phenolic substances, and does not cause acute oral toxicity, which suggests that CEE may be a valid and safe remedy to cure liver disease.<sup>15</sup>

### **Aframomum melegueta**

In recent years there have been remarkable developments in the prevention of diseases, especially with regards to the role of free radicals and antioxidants. Ethanol- induced oxidative stress appears to be one mechanism by which ethanol causes liver injury. The protective effect of aqueous plant extract of Aframomum melegueta on ethanol-induced toxicity was investigated in male Wistar rats. The rats were treated with 45 % ethanol (4.8 g/kg b.w.t.) for 16 days to induce alcoholic diseases in the liver. The activities of alanine aminotransferase, aspartate aminotransferase and triglyceride were monitored and the histological changes in liver examined in order to evaluate the protective effects of the plant extract. The results highlight the ability of Aframomum melegueta to ameliorate oxidative damage in the liver and the observed effects are associated with its antioxidant activities.<sup>16</sup>

### **Ixora coccinea ,Rhinacanthus nasuta and Spilanthes ciliata**

Roots of *Ixora coccinea* (Rubiaceae), and *Rhinacanthus nasuta* (Acanthaceae) and whole plants of *Spilanthes ciliata* (Asteraceae) are extensively used by tribal communities in South India to treat liver diseases. However, the veracity of these tribal claims has not been investigated scientifically using the liver toxin, aflatoxin. This study reports on the protective effects of these three herbal ethanolic extracts on the aflatoxin B1 (AFB1) -intoxicated livers of albino male Wistar rats. Biochemical parameters, including serum hepatic enzymes significant lowering of the activity of the serum enzymes and enhanced hepatic reduced GSH status. Pathological examination of the liver tissues supported the biochemical findings. It was concluded that the hepatoprotective effects of the three plant extracts observed in this study might result from their potent antioxidative properties.<sup>17</sup>

### ***Coccinia grandis***

The present study was conducted to evaluate the hepatoprotective effects of an aqueous leaf extract of *Coccinia grandis* on carbon tetrachloride (CCl<sub>4</sub>) induced liver damage in albino rats. Wistar albino rats weighing around 180-200g were used. Toxicity was induced by using 30% CCl<sub>4</sub> suspended in olive oil (1.0 ml/kg body wt intraperitoneal) after every 72 hrs for 3doses. The aqueous leaf extract at a dose of 250mg/kg was administered orally by intragastric tube for 10 days. Blood and liver tissue were collected for the assessment of serum marker enzymes such as ALT, AST and ALP. The liver tissue was used for histopathological assessment.<sup>18</sup>

### ***Silybum marianum***

The protective effects of polyphenolic extracts of *Silybum marianum* and *Cichorium intybus* on thioacetamide- induced hepatotoxicity in rat was investigated. 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 aminotransferase, 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 hepatoprotective effect of *Silybum marianum* and *Cichorium intybus* extracts on liver cells due to the presence of flavonoids and their antioxidant effects<sup>19</sup>

### ***Tylophora indica***

The methanolic extract of *Tylophora indica* leaves was screened for hepatoprotective activity in carbon tetrachloride induced hepatotoxicity in albino rats. The degree of protection was measured by estimating biochemical parameters like Serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, total protein and level of serum bilirubin (both total and direct).

Hepatoprotective activity of methanolic extract at a dose of 200 mg/kg and 300 mg/kg body weight, i.p. was compared with Silymarin (25 mg/kg,i.p.) treated animals. *Tylophora indica* leaves (200 and 300 mg/kg) exhibited significant reduction in serum hepatic enzymes when compared to rats treated with carbon tetrachloride alone. Furthermore, histopathological studies were also done to support the study<sup>20</sup>

### ***Embelia ribes***

*Embelia ribes* commonly known as Vidanga has been reported to be useful in jaundice. It is constituent of various formulation marketed for liver ailments. The protective effects of *Embelia ribes* on paracetamol induced liver cell damage was studied using mice as experimental animals. Paracetamol was administered orally in a dose of 500 mg/kg. Body wt. 48 hrs. Before administration of drugs. The mice treated with *Embelia ribes* extract (50, 100, 200 mg/100 gm/day) showed a dose dependent fall of 41 % 47 % and 66 % to respectively in the serum SGPT level as compared to the elevated levels in the mice receiving paracetamol only. Histopathology of liver mice revealed 67 %, 70 % and 80 % normal liver respectively in the mice receiving the dose of E-ribs, the result suggest that extract of E. ribs possesses hepatoprotective activity against paracetamol induced acute hepatocellular damage in the mice<sup>21</sup>

### ***Pterocarpus marsupium***

Hepatoprotective effects of the methanol and aqueous extracts of *P. marsupium* stem bark was evaluated by assay of liver function biochemical parameters (Total bilirubin, serum protein alanine aminotransaminase, aspartate aminotransaminase, and alkaline phosphatase activity) and histopathological studies of the liver. In methanol extract treated animals the toxic effects of CCl<sub>4</sub> was controlled significantly by restoration of levels of serum bilirubin protein, and enzyme as compared to the normal and standard drug Silymarin treated group. Histology of liver sections of the animals treated with extract showed the presence of the normal hepatic cords, absence of necrosis and fatty infiltration which further evidenced the hepatoprotective activity<sup>22</sup>

### ***Ficus carica***

Shade dried leaves of *Ficus carica* were extracted using petroleum ether (60-80 °C) and tested for antihepatotoxic activity on rats treated with 50 mg/ kg of rifampicin orally. The parameters assessed were serum levels of glutamic oxaloacetate transaminase, glutamic pyruvic transaminase, bilirubin and histological changes in liver. Liver weights and pentobarbitone sleeping time as a functional parameter were also monitored. There was significant reversal of biochemical, histological and functional changes induced by rifampicin treatment in rats by petroleum ether extract treatment, indicating promising hepatoprotective activity<sup>23</sup>

**Calotropis procera**

Hydro-ethanolic extract (70 %) of *Calotropis procera* flowers was prepared and tested for its hepatoprotective effect against paracetamol-induced hepatitis in rats. Alteration in the levels of biochemical markers of hepatic damage like SGPT, SCOT, and ALP, bilirubin, cholesterol, HDL and tissue GSH were tested in both treated and untreated groups. Paracetamol (2 g/kg) has enhanced the SGPT, SGOT, ALP, bilirubin and cholesterol levels and reduced the serum levels of HDL and tissue level of GSH. Treatment with hydro-ethanolic extract of *C. procera* flowers (200 mg/kg and 400 mg/kg) has brought back the altered levels of biochemical markers to the near normal levels in the dose dependent manner<sup>24</sup>.

**Chamomilla recutita**

Hepatoprotective activity of aqueous ethanol extract of *Chamomilla recutita capitula* against paracetamol induced hepatic damage in albino rat was observed the effect of aqueous ethanol extract of *Chamomilla recutita capitula* on blood and liver glutathione Na<sup>+</sup>-K<sup>+</sup>-ATPase activity, serums marker enzyme, serums bilirubin glycogen and thiobarbituric acid reactive substances against paracetamol induced damage in the rats have been studied to find out the possible mechanism of hepatoprotective. It was observed that extract of chamomile has reversal effect on the levels of above mentioned parameter in paracetamol hepatotoxicity. The extract of *Chamomilla recutita* function as hepatoprotective agent and this hepatoprotective activity of chamomile may be due to normalization of impaired membrane function activity.<sup>25</sup>

**Crataegus songarica**

The protective activity of the methanolic extract of the *Crataegus songarica* leaves was investigated against CCl<sub>4</sub>- and paracetamol-induced liver damage. On folklore levels, this plant is popularly used to treat various toxicological diseases. We evaluated both in vitro and ex vivo antioxidant activity of *C. songarica*. At higher concentration of plant extract (700 µg/ml), 88.106% inhibition on DPPH radical scavenging activity was observed and reducing power of extract was increased in a concentration-dependent manner. We also observed its inhibition on Fe<sup>2+</sup>/ascorbic acid-induced lipid peroxidation on rat liver microsomes in vitro. In addition, *C. songarica* extract exhibited antioxidant effects on calf thymus DNA damage induced by Fenton reaction. Hepatotoxicity was induced by challenging the animals with CCl<sub>4</sub> (1 ml/kg body weight, i.p.) and paracetamol (500 mg/kg body weight) and the extract was administered at three concentrations (100, 200, and 300 mg/kg body weight). Hepatoprotection was evaluated by determining the activities of liver function marker enzymes and antioxidant status of liver. Administration of CCl<sub>4</sub> elevated the levels of liver function enzymes, SGOT, SGPT, and LDH. We also observed a

dramatic increase in ALT, AST, bilirubin, and alkaline phosphatase levels in rats administered 500 mg/kg body weight of paracetamol. Therefore, *C. songarica* methanol extract may be an effective hepatic protective agent and viable candidate for treating hepatic disorders and other oxidative stress-related diseases.<sup>26</sup>

### **Cichorium glandulosum**

*Cichorium glandulosum* Boiss. et Huet is a traditional Uygur herbal medicine that has been used as a cholagogic and diuretic agent to improve liver function. However, the mechanism is not known for the liver-protective function. We investigated the antioxidant effects of plant extraction (CGE60) *in vitro* and *in vivo*, and find the mechanism of liver protection in Bacille Calmette-Guerin vaccine (BCG)+Lipopolysaccharides (LPS) induced liver injury in mice. CGE60 exhibited strong antioxidant ability *in vitro*. With oral administration, CGE60 significantly increased the activity of CAT, SOD, GSH-PX, and decreased the level of NO, NO synthase, hydroxyproline, ALP and lipid peroxidation liver of in the BDG+ LPS model. This study suggests that CGE60 possesses antioxidant activity and this activity associates with hepatoprotective effect in the mice of BCG +LPS model, and the mechanisms underlying these effects may involve antioxidant actions and anti-inflammation activities.<sup>27</sup>

### **Maackia amurensis**

Hepatoprotective properties of ethanol extract from the roots of *Maackia amurensis* Ruper et Maxim have been studied on the model of toxic hepatitis induced by carbon tetrachloride damage. It is established that the extract contains daidzein, 7-O-gentobiosides of isoflavonoids genistein, formononetin, pseudobabtin, and 5-O-methylgenistein, and 3-O-gentobiosides of pterocarpans (6aR, 11aR)-maackiain and (6aR, 11aR)-medicarpin. The administration of extract facilitates the restoration of antioxidant protection enzymes activity and reduced glutathione level, decreases the formation of toxic peroxidation products, produces normalizing impact on liver phospholipid pattern, and improves the erythrocyte tolerance to hemolytic agents. The action of isoflavonoids from *Maackia amurensis* in restoration of metabolic pathways of the liver and removal of toxic stress was more effective as compared to that of the reference hepatoprotector legalon.<sup>28</sup>

### **Mucuna pruriens**

This study investigated the hepatoprotective and *in vivo* antioxidant activities of the hydroethanolic extract of *Mucuna pruriens* leaves in antitubercular and alcohol-induced hepatotoxicity assays in rats. The hepatotoxicants significantly increased the levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), bilirubin, and malondialdehyde

(MDA); and reduced the levels of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and reduced glutathione GSH compared to control. *M. pruriens* significantly reversed the elevation in the level of ALT, AST, ALP, and bilirubin caused by the hepatotoxicants. *M. pruriens* (100-400 mg·kg<sup>-1</sup>) elicited significant reduction in the level of MDA compared to the alcohol group. The hydroethanolic extract of *Mucuna pruriens* leaves possesses hepatoprotective activity with enhancement of in vivo antioxidants as a possible mechanism of action.<sup>29</sup>

### **Wheatgrass**

The study aimed to analyze the effect of wheatgrass extract on alcohol and thermally oxidized PUFA ( $\Delta$ PUFA) induced oxidative stress in male albino Wistar rats. The levels of marker enzymes gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lipid peroxidative markers; thiobarbitric acid reactive substances (TBARS) and lipid hydroperoxides (LH), the levels of enzymatic (catalase [CAT], superoxide dismutase [SOD], glutathione peroxidase [GPx]) and nonenzymatic (reduced glutathione [GSH], vitamin E, vitamin C) antioxidants were analyzed in liver to evaluate the effects of wheatgrass. The levels of TBARS and LH were significantly ( $p \leq .05$ ) increased in alcohol +  $\Delta$ PUFA group, which were found to be reduced on treatment with wheatgrass. The levels of both enzymatic and nonenzymatic antioxidants were significantly decreased in alcohol +  $\Delta$ PUFA group, which were found to be restored on treatment with wheatgrass. From the results obtained, we conclude that wheatgrass protects the liver against alcohol and  $\Delta$ PUFA induced oxidative stress.<sup>30</sup>

### **Entada pursaetha**

The alcoholic extract of stem of *E. pursaetha* (PSE, 30, 100, 300 mg/kg body weight, po for 7 days) showed hepatoprotective activity against CCl<sub>4</sub> (2 mL/kg body weight, ip)-induced hepatotoxicity. The extract exhibited a significant dose-dependent hepatoprotective effect comparable to standard drug silymarin, by preventing increase in serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, and total bilirubin, lactate dehydrogenase; by lowering hepatic levels of malonaldehyde, nitrate-nitrite, myeloperoxidase activity; enhancing activities of antioxidant enzymes, superoxide dismutase, catalase and increasing reduced glutathione levels in liver, which suggests the antioxidant property of PSE. Histopathological studies also supported the above biochemical parameters. The results suggested that alcoholic extract of *E. pursaetha* possesses significant hepatoprotective activity in CCl<sub>4</sub>-induced acute hepatotoxicity in rats and this is likely to be mediated through its antioxidant activities.<sup>31</sup>

**Phragmites australis**

The rhizome of *Phragmites australis* has long been used for the treatment of hepatitis in traditional Chinese medicine. In this study, the hepatoprotective and antioxidant activities of an aqueous extract from the rhizome of *P. australis* (AE-PA) were evaluated. The oral administration of AE-PA to rats for 5 days before CCl<sub>4</sub> intoxication caused a significant decrease in the CCl<sub>4</sub>-induced elevation of hepatic enzymes activities in serum, such as aspartate aminotransferase, alanine aminotransferase, and lactic acid dehydrogenase. This suggested that AE-PA had good hepatoprotective activity against CCl<sub>4</sub>-induced liver injury, which was confirmed by pathomorphological examination of the liver. Through evaluation of hydroxyl radical and superoxide anion radical scavenging activities, respectively, it was demonstrated that AE-PA had good antioxidant activity, which possibly contributed to its hepatoprotective activity. More research is needed to study the bio-active compounds in *P. australis* and to identify the potential hepatoprotective and antioxidant agents.<sup>32</sup>

**Curcuma longa and Zingiber officinale**

The hepatoprotective effects of oils from *Zingiber officinale* (ginger) and *Curcuma longa* (turmeric) on acute ethanol-induced fatty liver in male Wistar rats were evaluated. Ferric reducing antioxidant power activity and oxygen radical absorbance capacity of the oils were evaluated *ex vivo*. Rats were pretreated for 28 days with standard drug (Livolin Forte) and oils from *Z. officinale* and *C. longa* before they were exposed to 45% ethanol (4.8 g/kg) to induce acute fatty liver. Histological changes were observed and the degree of protection was measured by using biochemical parameters such as alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase activities. Serum triglyceride (TG) level, total cholesterol (TC) level and the effects of both oils on reduced glutathione (GSH), glutathione-S-transferase (GST), superoxide dismutase (SOD) and hepatic malondialdehyde (MDA) levels were estimated. Oils from *Z. officinale* and *C. longa* at a dose of 200 mg/kg showed hepatoprotection by decreasing the activities of serum enzymes, serum TG, serum TC and hepatic MDA, while they significantly restored the level of GSH as well as GST and SOD activities. Histological examination of rats tissues was related to the obtained results.<sup>33</sup>

**Caesalpinia gilliesii and Cajanus cajan**

This study aims to evaluate two proteins derived from the seeds of the plants *Cajanus cajan* (Leguminosae) and *Caesalpinia gilliesii* (Leguminosae) for their abilities to ameliorate the toxic effects of chronic doses of acetoaminphen (APAP) through the determination of certain biochemical parameters including liver marker enzymes: alanine aminotransferase, aspartate

aminotransferase, alkaline phosphatase, and total bilirubin. Also, total protein content and hepatic marker enzyme, lactate dehydrogenase were studied. Moreover, liver antioxidants, glutathione (GSH), nitric oxide, and lipid peroxides were determined in this study. Hepatic adenosine triphosphatase (ATPase), adenylate energy charge (ATP, adenosine diphosphate, adenosine monophosphate, and inorganic phosphate), and phosphate potential, serum interleukin-6, tumor necrosis factor- $\alpha$ , and myeloperoxidase were also examined in the present study. On the other hand, histopathological examination of intoxicated and liver treated with both proteins was taken into consideration. Improvement in all biochemical parameters studied was noticed as a result of treatment intoxicated liver with *C. gilliesii* and *C. cajan* proteins either paracetamol with or post paracetamol treatment. These results were documented by the amelioration signs in rat's hepatic architecture. Thus, both plant protein extracts can upregulate and counteract the inflammatory process, minimize damage of the liver, delay disease progression, and reduce its complications.<sup>34</sup>

### **Zingiber officinale**

*Zingiber officinale* is a traditional medicine against various disorders including liver diseases. The aim of this study was to assess the hepatoprotective activity of the ethanolic extract of rhizomes of *Z. officinale* (ERZO) against thioacetamide-induced hepatotoxicity in rats. Five groups of male Sprague Dawley have been used. In group 1 rats received intraperitoneal (i.p.) injection of normal saline while groups 2-5 received thioacetamide (TAA, 200 mg/kg; i.p.) for induction of liver cirrhosis, thrice weekly for eight weeks. Group 3 received 50 mg/kg of silymarin. The rats in groups 4 and 5 received 250 and 500 mg/kg of ERZO (dissolved in 10% Tween), respectively. Hepatic damage was assessed grossly and microscopically for all of the groups. Results confirmed the induction of liver cirrhosis in group 2 whilst administration of silymarin or ERZO significantly reduced the impact of thioacetamide toxicity. Moreover, fractions of the ERZO extract were tested on Hep-G2 cells and showed antiproliferative activity. This study showed hepatoprotective effect of ERZO.<sup>35</sup>

### **Melastoma malabathricum**

*Melastoma malabathricum* L. (Melastomaceae) is a small shrub with various medicinal uses. The present study was carried out to determine the hepatoprotective activity of methanol extract of *M. malabathricum* leaves (MEMM) against the paracetamol-induced liver toxicity in rats model. MEMM exerted significant ( $p < 0.05$ ) and high antioxidant activity in which high TPC was recorded; while in the hepatotoxicity study, the extract exhibited significant hepatoprotective effects against the paracetamol-induced hepatotoxic model. The results observed for serum liver enzymes (ALT, ALP and AST) as well as the microscopic

observations and microscopic scoring supported the hepatoprotective potential of MEMM. The phytochemical and HPLC analysis of MEMM demonstrated the presence of flavonoids as its major constituents. The MEMM-induced hepatoprotective activity could be allied partly to its antioxidant activity and the presence of flavonoids.<sup>36</sup>

### **Penthorum chinense**

This research was to figure out the hepatoprotective constituents of *Penthorum chinense* Pursh, a typical species both for food and medicine, using carbon tetrachloride-induced chronic hepatotoxicity in HL-7702 cells. Cell viability, levels of microsomal enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the concentration of malondialdehyde (MDA) were determined in homogenates of the liver cells. Results showed that the cell viability increased significantly in all test groups in a concentration-dependent manner and the content of the peroxidation product MDA decreased significantly, similar to the serum levels of hepatic enzyme biomarkers (ALT and AST). The effects of 70% ethanol extracts and Vc were better than 95% ethanol and water extracts, and the ethyl acetate extracts further obtained from 70% ethanol fraction showed the highest hepatoprotective activity, even better than Vc. The ethyl acetate fraction from 70% ethanol extracts is responsible for the hepatoprotective function of *P. chinense*.<sup>37</sup>

### **Camellia sinensis**

This study was designed to investigate the hepatoprotective effects of the tea polysaccharides (ZTPs) extracted from a selenium-enriched Ziyang green tea (*Camellia sinensis*). ZTPs were identified as the heteropolysaccharides with glucose (31.4%), arabinose (23.5%) and galactose (21.8%) being the main constitutive monosaccharides. ZTPs displayed noteworthy scavenging effects against DPPH, OH and O<sub>2</sub>(-), and high antioxidant effects in vitro, and the effects were further verified by suppressing CCl<sub>4</sub>-induced oxidative liver damage in mice at 100, 200 and 400mg/kg BW. Administration of ZTPs in mice prior to CCl<sub>4</sub> significantly prevented the CCl<sub>4</sub>-induced increases in serum alanine aminotransferase, aspartate aminotransferase and lactic dehydrogenase, as well as hepatic malondialdehyde level. Mice treated with ZTPs showed normal glutathione peroxidase and superoxide dismutase activities, relative to CCl<sub>4</sub>-treated group. ZTPs also prevented the CCl<sub>4</sub>-caused liver histological alteration, as indicated by histopathological evaluation. These findings demonstrate that ZTPs have protective effects against acute CCl<sub>4</sub>-induced oxidative liver damage.<sup>38</sup>

### **Juniperus phoenicea**

Different fraction obtained from the aerial parts of *Juniperus phoenicea* showed significant activity as hepatoprotective when investigated against carbon tetrachloride induced liver injury. The hepatoprotective activity was evaluated through the quantification of biochemical parameters and confirmed using histopathology study. Phytochemical investigation of the petroleum ether, chloroform and methanol fractions utilizing different chromatographic techniques resulted in the isolation of five known diterpenoids namely: 13-epicupressic acid (1), imbricatolic acid (2), 7 $\alpha$ -hydroxysandaracopimaric acid (3), 3 $\beta$ -hydroxysandaracopimaric acid (4), isopimaric acid (5), four flavonoid derivatives: cupressuflavone (6), hinokiflavone (7), hypolaetin-7-O- $\beta$ -xylopyranoside (9), (-) catechin (10), in addition to sucrose (8). Both physical and spectral data were used for structure determination and all isolates were evaluated for their hepatoprotective activity. Compounds 2 and 6 were effective, however; 7 was the most active. Hepatoprotective activity of 7 is comparable with the standard drug silymarin in reducing the elevated liver enzymes and restoring normal appearance of hepatocytes. Hepatoprotective effect of combination of 6, 7 and silymarin with the diterpene sugiol was also explored.<sup>39</sup>

### ***Eucommia ulmoides***

A comparison of analysis in evaluating the hepatoprotective action of fractional ethanolic (F0), ethyl acetic (F1), n-butanol (F2) and aqueous (F3) extracts of *E. ulmoides* Oliv. (EUO) against thioacetamide (TAA) induced hepatic damage was studied in mice. The extract (453 mg/kg-F0, 104 mg/kg-F1, 95 mg/kg-F2 and 237 mg/kg-F3 body weight, po, once daily for 15 days) restored serum marker enzymes levels to normal in TAA treated mice. The biochemical biomarkers viz., total protein, albumin and total bilirubin were also restored forward normal level expression pattern of liver protein profile of mice by using sodium dodecyl sulfate polyacrylamide gel electrophoresis and two-dimensional gel electrophoresis showed 144 spots in TAA administered group which were significantly reduced in EUO extracts treated group. Among the four extracts ethyl acetate (F1) and n-butanol (F2) extracts showed more significant liver protection. TAA induced injury can be correlated with its high phenolic content in these extracts which may have hepatoprotective effects in regulating liver proteins by scavenging free radicals.<sup>40</sup>

### ***Orthosiphon diffusus***

Preparations of *Orthosiphon diffusus* (Benth.) have been used by folk medicinal practitioners in the Western Ghats of India for treating inflammation, hepatitis and jaundice for many years and their effectiveness is widely acclaimed among the tribal communities. The mechanisms behind the antioxidant and hepatoprotective potential of *Orthosiphon diffusus* methanol active fraction (MAF) using in vivo (rat) and in vitro (cell culture) models was evaluated. Neutralization of CCl<sub>4</sub>-induced

hepatotoxicity by MAF was evaluated in rats. Towards this, serum levels of hepatic injury markers (lactate dehydrogenase and alkaline phosphatase), antioxidant enzymes in the liver homogenates, and histological examination were performed. In *in vitro* studies, mechanisms of neutralization of H<sub>2</sub>O<sub>2</sub>-induced toxicity by MAF using MTT, Comet assay and up-regulation of antioxidant enzymes at genetic level (RT-PCR) was performed in HepG2 cells. *Orthosiphon diffusus* MAF demonstrated significant hepatoprotection against CCl<sub>4</sub>-induced hepatotoxicity by antioxidant mechanisms comparable to silymarin. H<sub>2</sub>O<sub>2</sub>-induced oxidative stress was completely neutralized by MAF through enhanced expression of genes for antioxidant enzymes. Therefore, this study validates the use of *Orthosiphon diffusus* by folk medicinal practitioners in India. Further, MAF of *Orthosiphon diffusus* can serve as a strong candidate for the development of herbal hepatoprotective agents.<sup>41</sup>

### **Calotropis gigantea**

Ethanol extract of *Calotropis gigantea* flowers (CGFE) was evaluated for its antioxidant and hepatoprotective activity to validate its use in traditional therapeutic indications. This CGFE exhibited significant antioxidant activity (at 20, 40, 60, 80 and 100 µg/ml *in vitro*) as evidenced by its hydroxyl, nitric oxide and hydrogen peroxide anion radical scavenging activities. This *in vitro* antioxidant activity was reinforced by a significant hepatoprotection (at 250 and 500 mg/kg dose) by decreasing the activity of serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase. The hepatoprotective activity of the CGFE was comparable with standard drug silymarin (100 mg/kg, *p.o.*). The results obtained from present study indicate the presence of natural antioxidants and hepatoprotective constituents. Hence, the above finding confirms *in vitro* antioxidant and hepatoprotective potential of CGFE in mice.<sup>42</sup>

### **Astragalus kahiricus**

The hepatoprotective activity of the ethanol extract of *Astragalus kahiricus* (Fabaceae) roots against ethanol-induced liver apoptosis was evaluated and it showed very promising hepatoprotective actions through different mechanisms. The extract counteracted the ethanol-induced liver enzymes leakage and glutathione depletion. In addition, it demonstrated anti-apoptotic effects against caspase-3 activation and DNA fragmentation that were confirmed by liver histopathological examination. Moreover, the phytochemical study of this extract led to the isolation of four cycloartane-type triterpenes identified as astrasieversianin II (1), astramembrannin II (2), astrasieversianin XIV (3), and cycloastragenol (4). The structures of these isolates were established by HRESI-MS and 1D and 2D NMR experiments. The antimicrobial, antimalarial, and cytotoxic activities of the isolates were further evaluated, but none of them showed any activity.<sup>43</sup>

**Cassia singueana**

The vivo antioxidant and hepatoprotective activities of the methanolic extract of the root of *Cassia singueana* in rats following acute and chronic carbon tetrachloride intoxication was evaluated. Malondialdehyde (MDA), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin as indices of liver damage and lipid peroxidation were detected in rats after intraperitoneal administration of extract (5 mg/kg). The liver, kidney and heart showed significant reduction ( $P < 0.05$ ) in the levels of MDA. Similarly, compared to the CCl<sub>4</sub> control, significant reduction ( $P < 0.05$ ) in serum AST, ALT and bilirubin as well as in level of total cholesterol and MDA with concomitant increase in HDL cholesterol, superoxide dismutase and catalase levels when CCl<sub>4</sub>-intoxicated rats were treated with *Cassia singueana* root extract for two weeks. These results suggest that methanolic extract of *Cassia singueana* contain potent antioxidant compounds that can offer significant protection against hepatic and oxidative injuries.<sup>44</sup>

**Melochia corchorifolia**

The hepato protective and antioxidant capacity of *Melochia corchorifolia* aerial part extracts were evaluated. Antioxidant activity was evaluated by using three free radicals (Superoxide, Hydroxyl and DPPH) and hepatoprotective activity was assessed against CCl<sub>4</sub> induced liver intoxication in rats. The extracts produced concentration dependent percentage protection in decrease of serum enzymes and percentage inhibition on free radicals. Among all extracts methanol extract showed better activity with percentage protection of SGOT (78.98%), SGPT (79.65%), ALP (82.48%) and total bilirubin (80.0%) levels against CCl<sub>4</sub> liver intoxication and also methanolic extract showed better activity with IC<sub>50</sub> values on superoxide, hydroxyl and DPPH radicals. From the results obtained during the study it could be concluded that *M. corchorifolia* aerial part extracts have antioxidant and hepatoprotective components.<sup>45</sup>

**Meconopsis integrifolia**

*Meconopsis integrifolia* (Maxim.) Franch is a high mountain endemic species used as a traditional Tibetan and Mongolian herb to treat hepatitis, pneumonia, and edema. This study aims to investigate the hepatoprotective and antioxidant effects of *Meconopsis integrifolia* ethanolic extract (MIE) *in vitro* and *in vivo*. The *in vitro* antioxidant property of MIE was investigated by employing various established systems. Rats with carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury were used to assess the hepato protective and antioxidant effect of MIE *in vivo*. The level or activity of alkaline phosphatase (ALP), glutamate pyruvate transaminase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB) in the blood serum and thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT), and glutathione

(GSH) in the liver and kidney of the rats were assayed using standard procedures. MIE exhibited strong antioxidant ability *in vitro*. In the rats with CCl<sub>4</sub>-induced liver injury, the groups treated with MIE and silymarin showed significantly lower levels of ALT, AST, ALP, and TB. MIE demonstrated good antioxidant activities in both the liver and kidney of the rats *in vivo*. MIE exhibits excellent hepatoprotective effects and antioxidant activities *in vitro* and *in vivo*, supporting the traditional use of *Meconopsis integrifolia* in the treatment of hepatitis.<sup>46</sup>

## CONCLUSION

Development of herbal medicines with standards of safety and efficacy can revitalise treatment of the liver disorders and hepatoprotective activity. In this review, an attempt has been made to compile the reported hepatoprotective plants which 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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