Review Article

LIVER TOXICITY AND HEPATOPROTECTIVE HERBS

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ABSTRACT

The liver is the largest solid organ in the upper abdomen that aids in digestion and removes waste products and worn out cells from the blood. 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_4), thioacetamide (TAA) etc.), excessive alcohol consumption and microbes. The synthetic drugs which are used 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 wide spread. 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_4), Hepatotoxicity.

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. Hepatotoxicity implies chemical driven liver damage.[1] Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g. microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. Some of the inorganic compounds producing hepatotoxicity are arsenic, phosphorus, copper and iron. The organic agents include certain naturally occurring plant toxins such as pyrrolizidine alkaloids, mycotoxins and bacterial toxins. In addition, exposure to hepatotoxic compounds may be occupational, environmental or domestic that could be accidental, homicidal or suicidal ingestion. Hepatoprotective agents are those compounds, which mitigate the liver injury caused by hepatotoxic agents. Hepatoprotective effects of plant drugs and herbal formulations are studied against chemicals (alcohol, CCl_4, alcohol CCl_4, beta galactosamine, thioacetamide) and drugs (paracetamol, nimusalide, antitubercular drugs like isoniazid, rifampicin etc.) induced hepatotoxicity in rats and mice as they virtually mimic any form of naturally occurring liver disease. In the absence of reliable liver protective drugs in allopathic medical practices herbs play important role in the management of various liver disorders. However, in ayurveda many indigenous plants have been used as hepatoprotective agents. 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 medicinal 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.[2,3]

CCl_4 induced hepatotoxicity

Liver injury due to carbontetrachloride in rats was first reported in 1936 and has been widely and successfully used by many investigators. Carbontetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl_3O^-, a reactive oxidative free radical, which initiate lipid peroxidation. Administration of a single dose of CCl_4 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_4 left in the liver. The development of necrosis is associated with leakage of hepatic enzymes into serum.[4-9]

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 uridylate 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 it's content i.e. bile salts, cholic acid and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption.[10]

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 it's content i.e. bile salts, cholic acid and deoxycholic acid.[10]

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 ¡-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.[11,12]

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 sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver.[12,5]

Nonsteroidal antiinflammatory 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.[13]

Glucocorticoids

Glucocorticoids are so named due to their effect on carbohydrate mechanism. They promote glycogen storage in liver. Enlarged liver is a rare side effect of long term steroid use in childrens. The classical effect of prolonged use both in adult and paediatric population is steatosis.[13]

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. 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.

Aegle marmelos

Aegle marmelos leaves 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 on rats using essential marker biochemical parameters. The results indicated that, the *Bael* leaves have excellent hepatoprotective effect.[14]

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.

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.[15]

Cassia roxburghii

Seeds of *Cassia roxburghii* DC have been used in ethnomedicine for various liver disorders for its hepato-protective activity. The methanolic extract of *Cassia roxburghii* reversed the toxicity produced by ethanol CCl_4 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 hepatoprotective formulation against hepatotoxins.[16]

Chamomile capitula

The effect of ethanolic extract of *Chamomile recutita* capitula on blood and liver glutathione, Na+ K+- ATPase activity, serum marker enzymes, serum bilirubin, glycogen and thiobarbutiric acid reactive substances against paracetamol induced liver damage in rats have been studied to find out the possible mechanism of hepatoprotection. It was observed that extract of *Chamomile recutita* has reversal effects on the levels of above mentioned parameters in paracetamol hepatotoxicity suggesting its hepatoprotective and/or hepato stimulant activity.[17]

Cichorium intybus

Cichorium intybus is a popular Ayurvedic remedy for the treatment of liver diseases. It is commonly known as kasni and is part of polyherbal formulations used in the treatment of liver diseases. In mice, liver protection was observed at various doses of *Cichorium intybus* but optimum protection was seen with a dose of 75 mg/kg given 30 minutes after CCl_4 intoxication. In preclinical studies an alcoholic extract of the *Cichorium intybus* was found to be effective against chlorpromazine induced hepatic damage in adult albino rats. A bitter glucoside, Cichorin has been reported to be the active constituent of the herb.[18]

Coccinia grandis

Alcoholic extract of the fruits of *Coccinia grandis* was evaluated in CCl_4 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 revealing its hepatoprotective effect.[19]

Curcuma longa

Like silymarin, turmeric has been found to protect animal livers from a variety of hepatotoxic substances, including carbon tetrachloride, galactosamine, pentobarbitol, 1-chloro-2,4-dinitrobenzene, 7 4-hydroxy-nonenal, and paracetamol. Diarylhepatonoids including Curcumin is the active constituent of the plant which is responsible for hepatoprotective activity.[20]

Ficus carica

The methanolic extract of the leaves of *Ficus carica* was evaluated for hepatoprotective activity in CCl_4 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.[21]

Flacourtia indica

The extracts of the aerial parts of *Flacourtia indica*, were evaluated for hepatoprotective 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 of 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. But, in this study the dose they have used is to high and it is not successful or rationale for human dose.[22,23]

Glychyrrhiza glabra

Glychyrrhiza glabra, commonly known as licorice contains triterpene saponin, known as glycyrrhizin, which has potential hepatotprotective activity. It belongs to a group of compounds known as sulfated polysaccharides. Several studies carried out by Japanese researchers have shown glycyrrhizin to be for antiviral and it has potential for therapeutic use in liver disease.

Experimental hepatitis and cirrhosis studies on rats found that it can promote the regeneration of liver cells and at the same time inhibit fibrosis. Glycyrrhizin can alleviate histological disorder due to inflammation and restore the liver structure and function from the damage due to carbon tetrachloride. The effects including: lowering the SGPT, reducing the degeneration and necrosis and recovering the glycogen and RNA of liver cells. Effects of glycyrrhizin have been studied on free radical generation and lipid peroxidation in primary cultured rat hepatocytes. Favorable results have been reported in children suffering from cytomegalovirus after treating with glycyrrhizin.[24]

Lepidium sativum

The hepatoprotective role of methanolic extract of *Lepidium sativum* at a dose of 200 and 400 mg/kg was investigated in CCl_4 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_4 were insignificant in the *Lepidium sativum* treated groups.[25]

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 profile in the dose dependent manner.[26]

Prostechea michuacana

Methanol, hexane and chloroform extracts of *Prostechea michuacana* (PM) were studied against CCl_4 induced hepatic injury in albino rats. Pretreatment with methanolic extract reduced biochemical markers of hepatic injury levels demonstrated dose-dependant reduction in the *in vivo* peroxidation induced by CCl_4. 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 hepatoprotective activity was comparable with sylmarin. 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.[27]

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 nonenzymatic antioxidant defense system at near normal. The antihepatotoxic potential of *S. polycystum* might possibly due to its anti-oxidant property and membrane stabilizing action.[28]

Silybum marianum

The protective effects of polyphenolic extracts of *Silybum marianum* on thioacetamide induced hepatotoxicity in rat were investigated. The extracts were injected to the rats, at a dose of 25 mg/kg 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+, K+ and liver weight between different groups was not significantly altered. These findings suggested the hepatoprotective effect of *Silybum marianum* extracts on liver cells due to the presence of flavonoids and their antioxidant effects.[29]

Solanum nigrum

In Ayurveda, the drug is known as kakamachi. Aromatic water extracted from the drug is widely prescribed by herbal vendors for liver disorders. Although clinical documentation is scare as far as hepatoprotective activity is concerned, but some traditional practitioners have reported favorable results with powdered extract of the plant.[30]

Tephrosia purpurea

In Ayurveda, the plant is known as sharpunkha. Alkali preparation of the drug is commonly used in treatment of liver and spleen diseases. In animal models, it offered protective action against carbon tetrachloride and D-galalactosamine poisoning. The roots, leaves and seeds contain tephrosin, deguelin and quercetin. The hepatotprotective constituent of the drug is still to be proved.[30]

Wedelia calendulacea

The hepatoprotective activity of ethanolic extract of *Wedelia calendulacea* was studied against CCl_4 induced acute hepatotoxicity in rats. The treatment with ethanolic extract of *Wedelia calendulacea* showed a dose dependent reduction in CCl_4 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_4 induced hepatic damaged animals that received ethanolic extract of *Wedelia calen dulacea* showed an increase over CCl_4 treated control group. [31]

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 preclinical 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. 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 hepatoprotective/curative effects that warrants their clinical testing. Due to lack of scientific based pharmacological data, most of the herbal formulations cannot be recommended for the treatment of liver diseases.[34]

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 antioxidative, antilipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating and liver regenerative. *Glycyrrhiza glabra* has been

shown to be hepatoprotective and capable of inducing an endogenous interferon. *Picrorhiza kurroa* is proved to be antiinflammatory, hepatoprotective and immunomodulatory. Extensive studies on *Phyllanthus amarus* have confirmed this plant preparation possessed antiviral against hepatitis B and C viruses, hepatoprotective and immunomodulating effects, besides antiinflammatory properties.[36]

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 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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