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Herbal Extract as Hepatoprotective-A Review

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ABSTRACT
Medicinal practitioners have prescribed Ayurveda and drug from herbal origin as a system of medicine in India over centuries. Popularity of herbal is increasing globally. 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 plants. Hepatic disease stand as one of the foremost health troubles worldwide with liver cirrhosis and drug induced liver injury accounting 9th leading cause of death in western and developing countries.
In this review article attempt has been made to compile reported hepatoprotective plants from India and aboard and may be useful to health professional's scientists' scholar working in the field of pharmacology, therapeutics and pharmacognosy to develop evidence based alternative medicine to cure different kinds of liver disease in man and animals.

Keywords: Hepatoprotective activity, extract, hepatotoxicity, CCL_4.

1. Introduction
Many of the modern drug mainly based on synthetic chemical compounds however have been found to have harmful .side effects on human system. This has triggered off extensive research and development in the field of herbal medicine. In fact there is a growing demand for herbal medicine in most of the developed and developing countries of the world today [1].
The predominant type of liver diseases varies according to country and may be influenced by local factors. The causative factors of liver disorders include virus infection exposure to our consumption of certain chemicals. The substance that injures the liver cells in some people and results serious harm to the liver caused by drugs and by the combination of drugs and other substances is an important health problem.
Treatment options for common liver diseases such as cirrhosis, fatty liver and chronic hepatitis are problematic. The effectiveness of treatment such as interferon colchicine, penicillamine and corticosteroid are inconsistent at best and incidence of side effect is profound through the treatment is worse than the disease.
Physician and patients are in need of effective therapeutic agents with low incidents of side effect. There are few effective therapeutic agents with low incident of side effects. There are few effective plants that cure liver diseases so considerable interest has developed in the examination of these numerous plants remedies which are useful in liver diseases [3].
The present review is aimed at compiling the data on promising herbal extract from plant that have been tested in hepatotoxicity model using modern scientific system.

1.1 *Capparis decidua*
Hepatoprotective effect of aqueous and methanolic extract of *Capparis decidua* stems were evaluated against carbon tetrachloride induced liver damage in rats. Simultaneous oral administration of both extracts (200,400 nig $kg^{"1}$) with CCl_4 in paraffin oil (1:9 v/v) at a dose of 0.2 ml kg"' for 10 days recovered the liver fatty changes induced by the hepatotoxic compound observed in the intoxicated control rats. Slight to mild changes in hepatocytes were observed in rats dosed by aqueous extract of *C. decidua* stems and higher dose of methanolic extract, whereas the lower dose of methanolic extract revealed more severe lesions than the higher dose. The results were compared with the hepatoprotective effect of the standard drug silymarin [4].

1.2 *Ixora coccinea* (Rubiaceae), *Rhinacanthus nasuta* (Acanthaceae) and *Spilanthes ciliata* (Asteraceae)

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 been investigated scientifically using the liver toxin, aflatoxin. This study reports on the protective effects of these three herbal ethanolic extracts on the aflatoxin Bi (AFBI) - intoxicated livers of albino male Wistar rats. It was concluded that the hepatoprotective effects of the three plant extracts observed in this study might results from their potent antioxidative properties [5, 6, 7].

1.3 *Launaea intybacea*

Hepatoprotective activity of ethyl acetate extract of aerial parts of *Launaea intybacea* are evaluated in paracetamol induced hepatotoxicity in albino rats. Silymarin (200 mg/kg) was given as reference standard. The ethyl acetate extract of aerial parts of *Launaea intybacea* have shown very significant hepatoprotection against paracetamol-induced hepatotoxicity in albino rats in reducing serum total bilirubin, SALP, SGPT, SCOT levels and liver homogenates LPO, SOD, CAT, GPX, GST and GSH levels [8].

1.4 *Piper longum*

Piper longum Linn. (Piperaceae) (Fruits and roots powder) is given with boiled milk in the Indian traditional system of medicine for the treatment of liver ailments and jaundice. However, the biochemical basis and mechanism of hepatoprotective action of *Piper longum* milk extract, is not scientifically studied. Thus, the present study was designed to investigate the hepatoprotective activity of Piper longum milk extract. Carbon tetrachloride (CCU) was used as a hepatotoxin at a dose of 0.5 ml/kg p. o. with olive oil (1:1) thrice a week for 21 days to produce the chronic reversible type of liver necrosis. Following treatment with *Piper longum* milk extract (200 mg/day p. o. for 21 days), a significant hepatoprotective effect was observed in CCU induced hepatic damage as evident from decreased level of serum enzymes, total bilirubin and direct bilirubin. The hepatoprotective effect of Piper longum is comparable to the standard drug silymarin (25 mg/kg/day p. o. for 21 days) [9].

1.5 *Argemone mexicana*

The protective effects of the aqueous extracts of *Argemone mexicana* (Linn.) whole plant, against CCU induced hepatic failure in male albino rats (wistar strain) was investigated. For acute and massive invasion of hepatopathy, CCU (i.p. injection of CCU + Olive oil in 1:1 ratio; 2 ml/.kg) was used and the insidious intoxication was evidenced by significant turmoil of various biochemical parameters followed by significant (p< 0.004) weight loss in toxic control group (-12.83±1.13). The administration of aqueous extracts (250 mg/kg and 150 mg/kg of body weight) for 7 days , elicited protective action since the elevated levels of marker enzymes (AST, ALT, ALP) of liver function were found to decreasing progressively in dose dependent manner with net weight gain. In the aqueous extract 250 mg/ kg treated rat group all the market enzymes were analyzed to be decreasing significantly (p<0.001), (AST, 272.77±24.08; ALT, 189±7.16; ALP, 97.15±6.54) and the final body weight was also significantly (p O.001) increased (6.16±1.01) when compared with the toxic control group. The serum total protein and the serum albumin were also approaching normal values. The results found in aqueous extract 250 mg/kg treated rat were quite promising and were comparable with a standard polyherbal drug Liv-52. The statistically processed results support the conclusion, that the aqueous extract of *Argemone mexicana* (Linn.) whole plant (250 mg/kg and 150 mg/kg) possesses dose dependent, significant protective activity against CCl_4 induced hepatotoxicity [10].

1.6 *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 [12].

1.7 *Baliospermum montanum*

Rats and primary cultures of rat hepatocytes were used as the *in vivo* and *in vitro* models to evaluate the hepatoprotective activity of sub-fractions from total methanol extract of *Baliospermum montanum*. Carbon tetrachloride was selected as hepatotoxin. Silymarin was the reference hepatoprotective agent. In the *in vivo* study, serum transaminases, alkaline phosphatase, total bilirubin, total cholesterol, albumin together with total protein and histopathological examination were the criteria for the evidence of liver injury. Carbon tetrachloride caused the alterations in all the biochemical parameters and centrilobular necrosis. Among the Ethyl methyl ketone and methanol sub-fractions tested (50,100 and 150 mg/lg), methanol sub-fraction (150 mg/kg) of the bio-active total methanol extract and silymarin (100 mg/kg) enhanced liver cell recovery by restoring all the altered biochemical parameters back to normal. In the *in vitro* study, release of transaminases, total protein together and hepatocyte viability were the criteria. Primary cultures of hepatocytes were treated with carbon tetra chloride (l0 ul/ml) and various concentrations (100,500 and 1000jig/ml) of ethyl methyl ketone and methanol sub- tractions of total methane) extract and silymarin (100 u g/ml). Carbon tetrachloride reduced hepatocyte viability and also altered the biochemical parameters, which were the restored significantly (PO.05) by ethyl methyl ketone (1000 (ig/ml) and methanol (500 and 1000 ug/ml) sub-fractions. These results suggest that *Baliospermum montanum* possess the hepatoprotective activity against carbon tetrachloride induced liver injury in both rats and primary cultures of rat's hepatocytes [13].

1.8 *Casuarina equisetifolia*

The methanol extract of plant material of some plant like *Casuarina equisetifolia*, *Cajanus cajan*, *Glycosmis pentaphylla*, *Bixa orellana*, *Argemone mexicana*, *Physalis minima*, *Caesalpinia bonduc* belonging to different family were studied for hepatoprotective activity against Swiss albino rats with liver damage induced by $CC1_4$. It was found that the methanol extract of *B. orellana*, *C. cajan*, *G. pentaphylla* and *C. equisetifolia* at a dose

of 500 mg/kg body with exhibited moderate protective effect by lowering the serum level of ALT, SGPT AST, SCOT and cholesterol to a significant extent. The hepatoprotective activity was also supported by histopathological studies of liver tissue [14].

1.9 Tubers of *Amorphophallus campanulatus* Roxb.

Ethanolic and aqueous extract of *Amorphophallus campanulatus* tubers were evaluated against CCl_4 induced hepatic damage in rats. The extracts at a dose of 500 mg/kg. Were administered orally once daily. The substantially elevated serum enzymatic level were significantly restored towards normalization by the extracts. The biochemical observation were supplemented with histopathological examination of rat liver section. The result shows that ethanol extract was found more potent hepatoprotective than aqueous extract [15, 16].

1.10 *Orthosiphon stamineus*

Methanol extract of the (leaves of "*Orthosiphon stamineus*" was assessed in paracetamol induced hepatotoxicity in rats. Alteration in the levels of biochemical markers of hepatic damage like SCOT, SGPT, ALP and lipid peroxides were tested in both parasitical treated and untreated groups. Paracetamol (2 gm/kg) has enhanced the SOOT, SGPT, ALP and lipid peroxides in liver. Treatment of methanol extract of *O. stamineus* leaves (200 mg/kg.) has brought back the altered levels of biochemical markers to the near normal levels in the dose dependent manner [17].

1.11 *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 [18].

1.12 *Vitex trifolia*

Aqueous and ethanol extract of leaf of *Vitex trifolia* was investigated for hepatoprotective activity against carbon tetrachloride induced liver damage. To assess the hepatoprotective activity of the extracts, various biochemical parameters *viz*. total bilirubin, total protein, alanine transaminase, aspartate transaminase and alkaline phosphatase activities were determined. Results of the serum biochemical estimations revealed significant reduction in total bilirubin and serum marker enzymes and increase in total protein in the animals treated with ethanol and aqueous extracts. However significant rise in these serum enzymes and decrease in total protein level was noticed in $CC1_4$ treated group indicating the hepatic damage. The hepatoprotective activity also supported by histological studies of liver tissue. Histology of the liver tissue treated with ethanol and aqueous extracts showed normal hepatic architecture with few fatty lobules. Hence the present study revealed that Vitex trifolia could afford significant protection against CCU induced hepatocellular injury [19].

1.13 *Thuja occidentalis*

Thuja occidentalis (Cupressaceae), commonly known as Arbor vitae or white cedar has been used in folk medicine to treat bronchial catarrh, enuresis, cystitis, psoriasis, uterine carcinomas, amenorrhea and rheumatism and is mainly used in homeopathy as mother tincture. Extract of this plant has shown anti-oxidant, anti-viral, anti-diarrhoeal activity. The hepatoprotective potential effect of ethanolic fraction of *Thuja occidentalis* has been assessed against CCl_4 induced liver damage in rats. A dose of EFTO 400 mg/kg p.o. exhibited significant protection from liver damage in acute and chronic CCl_4 induced liver damage model. Histopathological examination was carried out after the treatment to evaluate hepatoprotection. The fraction was found to possess good hepatoprotective property [20].

1.14 *Aerva lanata*

The study was conducted to evaluate the hepatoprotective activity of hydroalcoholic extract of *Aerva lanata* against paracetamol induced liver damage in rats. The hydroalcoholic extract of *Aerva lanata* (600 mg/kg) was administered orally to the animals with hepatotoxicity induced by paracetamol (3 gm/kg). Silymarin (25 mg/kg) was given as reference standard. All the test drugs were administered orally by suspending in 0.5 % Carboxymethyl cellulose solution. The plant extract was effective in protecting the liver against the injury induced by paracetamol in rats. This was evident from significant reduction in serum enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin. It was concluded from the result that the hydroalcoholic extract of *Aerva lanata* possesses hepatoprotective activity against paracetamol induced hepatotoxicity in rats.

1.15 *Alocasia indica* Linn

Oral administration of hydroalcoholic extract of *A. indica* (250 and 500 mg/kg) effectively inhibited CCU and paracetamol induced changes in the serum marker enzymes, cholesterol, serum protein and albumin in a dose-dependent manner as compared to the normal and standard drug silymarin-treated groups. Hepatic steatosis, fatty infiltration, hydropic degeneration and necrosis observed in CCL_4 and paracetamol- treated groups were completely absent in histology of the liver sections of the animals treated with the extracts. The result suggests that the hydroalcoholic extract of leaves of an indica possess significant potential as hepatoprotective agent.

1.16 *Aegle marmelos*

Aegle marmelos leaves (Bael, family: 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 Bale leaves has excellent hepatoprotective effects.

1.17 *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^+-K^+-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 [23].

1.18 *Pterocarpus santalinus*

The aqueous (45 mg/ml.) and ethanol (30 mg/ml) extracts of stem bark in 1 % gum tragacanth was administered orally for 14 days and hepatoprotective activity studied in $CC1_4$ induced hepatic damage model. The hepatoprotective activity was assessed using various biochemical parameters like serum bilirubin, protein alanine transaminase, aspartate transaminase and alkaline phosphatase along with histopathological studies of the liver tissue. There was a significant increase in the serum levels of bilirubin ALT, as aspartate transaminase and alkaline phosphatase with decrease in total protein level in the $CC1_4$ treated animals, reflecting liver injury. Histological study of fatty lobules and cellular necrosis.

1.19 *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 CCI_4 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 [2s].

1.20 *Polygala arvensis*

The suspensions of chloroform extract of leaves in 0.3 % Carboxymethyl cellulose (CMC) was evaluated for hepatoprotective activity in Wistar albino rats by inducing hepatic injury with D- galactosamine (400 mg/kg). The chloroform extract of Polygala arvensis at an oral dose of 200 mg/kg and 400 mg/kg exhibited a significant (P<0.001, P<0.01 and P<0.05) protection effect by normalizing the levels of aspartate aminotransferase (ASAT, GOT), alanine aminotransferase (ALAT, GPT), alkaline phosphatase (ALP), total bilirubin (TB), lactate dehydrogenase (LDH), total cholesterol (TC), triglycerides (TGL), albumin, total protein (TP) which were significantly (PO.OOI) increased in rats by treatment with 400 mg/kg i.p of D-galactosamine. Silymarin (25 mg/kg) ft known hepatoprotective drug used for comparison exhibited significant activity (P<0.001) [26].

1.21 *Cichorium intybus*

The effects of different concentrations of the hydroalcoholic extract of dried powdered leaves of *Cichorium intybus* L, on CCU induced hepatotoxicity *in vivo* in rats and CCL_4 induced cytotoxicity in isolated rat hepatocytes were investigated. Rats received different concentrations of the extract by i.p. injection for 3 consecutive days before the injection of (3 ml/kg) CCU (i.p.). Twenty four h after CCL_4 injection the animals were sacrificed and the livers were dissected for biochemical and histopathological studies. The results showed that the *Cichorium intybus* extract could protect the liver from CCl_4 induced damages with doses of 50 and 100 mg/kg, but concentrations higher than 200 mg/kg were less effective. For *in vitro* studies, the extract were added to the suspension of freshly isolated rat hepatocytes incubated in Krebs-Henseleit buffer under a gas flow of 95 % O_2 and 5 % CO_2, 20 minutes before the addition of l0 mM of CCl_4. The extract with concentration of 60 to 600 ug/ml protected the cells against CCL_4 induced cytotoxicity, but concentrations of >1.5 mg/ml and higher increased the CCL_4 induced cytotoxicity. The Cichorium intybus extract itself was toxic towards isolated hepatocytes in concentrations above 3.6 mg/ml. The results of the present study therefore supported the traditional believes on hepatoprotective effect of the Cichorium intybus extract, however, the concentrations were hepatotoxic [27, 28].

1.22 *Calotropis procera*

Hydro- ethanolic extract (70 %) of *Calotropis procera* flowers was prepared and tested for its hepatoprotective effect against paracetamol-induced hepatitis in rats. Alternation 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 [29].

1.23 *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 studies 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 [30].

1.24 *Luffa echinata*

The different extracts of fruits of *Luffa echinata* Roxb (Cucurbitaceae) were tested for their hepatoprotective activity against CCU induced hepatotoxicity in albino rats. The degree of protection was measured by using biochemical parameters like SGOT, SGPT, alkaline phosphatase and total protein and total albumin. The petroleum ether, methanolic extract showed a significant activity comparable with those of silymarin [3l].

1.25 *Apium graveolens* and *Hygrophila auriculata*

Seeds of *Apium graveolens* L (Apiaceae) and *Hygrophila auriculata* are used in Indian systems of medicine for the treatment of liver ailments. The antihepatotoxic effect of methanolic extracts of the seeds of these two plants was studied on rat liver damage induced by a single dose of paracetamol (3 g/kg p.o.) or thioacetamide (l00 mg/kg, s.c.) by monitoring several liver function tests, *viz* serum transaminases (SGOT and SGPT), alkaline phosphatase, sorbitol dehydrogenase, glutamate

dehydrogenase and bilirubin in serum. Furthermore, hepatic tissues were processed for assay of triglycerides and histopathological alterations simultaneously. A significant hepatoprotective activity of the methanolic extract of the seeds of the both the plants was reported [32].

2. Results and Discussion

Popularity of herbal 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 (o vigorous preclinical studies followed by clinical trial, 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 [33]. 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 for the herbal formulations cannot be recommended for the treatment of liver diseases.

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.

3. Conclusions

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, therapeutics, and pharmacognosy to develop evidence based alternative medicine to cure different kinds of liver diseases in man and animals.

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