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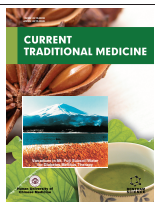
REVIEW ARTICLE

An Insight of Herbal Drugs and their Pharmaceutical Formulations Reported to have Hepatoprotective Activity



Md. Mujahid[1], Afreen Usmani[1], Md. Akhlaqur Rahman[1] and Md. Azizur Rahman[1,*]

[1]*Herbal Bioactive Research Laboratory, Faculty of Pharmacy, Integral University, Dasauli, Lucknow, Uttar Pradesh, India*

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Abstract: ***Background:*** Medicinal plants play an important role in the world's human healthcare system including folk practices as well as Ayurveda, Unani and Siddha. Approximately, 80% of the world's human population relies on the usage of traditional medicine which is primarily based on plant-derived drugs. Liver is the most important organ for the detoxification of various toxins and disposition of the endogenous substances. It is always exposed to the toxins and chemotherapeutic agents that lead to hepatotoxicity. Herbal drugs and their pharmaceutical formulations have been used in the treatment of liver diseases and hepatotoxicity for a long time.

Aims: The present review is aimed at compiling data on promising medicinal plants that have been tested in hepatotoxicity models using the modern scientific system.

Materials and Methods: Literature surveys on scientific national and international journals, books as well as electronic resources were performed.

Results: It showed several herbal drugs and their pharmaceutical formulations that have hepatoprotective activity. The herbal medicines mentioned were of an enormous value.

Conclusion: This reported insight of herbal drugs and their pharmaceutical formulations will definitely be helpful to the future researchers and the practitioners while deciding and choosing an effective drug for the treatment of liver diseases and hepatotoxicity.

Keywords: Hepatoprotective agents, medicinal plants, phytochemicals, traditional medicine, toxins, Ayurveda, Unani, Siddha.

1. INTRODUCTION

Liver is the most important organ for the detoxification of various toxins and disposition of the endogenous substances. It is always exposed to the toxins and chemotherapeutic agents that lead to hepatotoxicity. All the injuries to the liver (*e.g.* toxic, traumatic, circulatory or microbiological) lead to damage of liver cells (hepatocytes) resulting in its malfunctioning [1].

The liver is the most important organ regulating homeostasis in the body. It is concerned with nearly all the biochemical pathways associated with growth, nutrient supply, energy provision, fight against diseases and reproduction [2].

Hepatotoxicity implies liver damage due to chemicals. Sometimes, some medicinal agents taken

*Address correspondence to this author at the Herbal Bioactive Research Laboratory, Faculty of Pharmacy, Integral University, Dasauli, Lucknow, Uttar Pradesh, India;
Tel: +918896510421; E-mail: marahman@iul.ac.in

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in overdoses or introduced even within therapeutic window results in liver injury. Chemical agents like those used in laboratories and industries, natural chemicals like microcystins and even some herbal remedies can provoke hepatotoxicity. The chemicals causing liver injury are called as hepatotoxins. More than 900 drugs have been caught up that cause liver injury which is the main cause for a drug to be withdrawn from the market and to be banned. Drug induced liver injury is liable for approximately 5% of all hospital admissions and 50% of all acute liver failures. More than 75% of cases of idiosyncratic drug reactions resulted in liver transplantation or death [3].

Recent researches on hepatotoxicity study suggest that excessive alcohol consumption, xenobiotics, some diseased conditions and reactive secondary metabolites of the drugs are responsible for liver injury (Table **1**). The xenobiotics or the metabilites directly affect mitochondrial electron transport chain, mitochondrial permeability transitional pore, glutathione-S-acyltransferases and cytochromes P-450. The resulting hepatotoxicity as injury to the liver is related to the diminished liver function. The association of anti-inflammatory/ anti-oxidant herbal drugs could improve the hepatoprotective effects [4, 5]. Several herbal drugs and their pharmaceutical formulations are being used for the liver diseases in traditional systems of medicines and in ethno-medical practices in India. Conventional herbal drugs used in the cure of liver diseases are inadequate. Also, there is no drug in allopathic medicine for hepatoprotection. It is therefore needed nowadays to search for the alternative herbal drugs for the management and treatment of hepatic injury [6]. Approximately, 40 reported polyherbal commercial formulations having hepatoprotective action are being used in India. It has also been reported that approximately 160 phyto-constituents from about 101 different plants have hepatoprotective activity [7]. Silymarin, a flavonolignan extracted from the seeds and fruits of *Silybum marianum* (family Compositeae) was the miraculous hepatoprotective drug [8]. Hence, the present review is designed aiming at compiling the data based on the reported works on a large number of promising medicinal plants and the formulations claiming to have hepatoprotective activity.

2. PROMISING HEPATOPROTECTIVE MEDICINAL PLANTS

The ethanolic extract of *Aquilaria agallocha* (EEAA), family *Thymelaeaceae* commonly known as Agarwood, leaves administered at the dose of 200 mg/kg and 400 mg/kg body weight per oral for 10 days in rats with paracetamol induced hepatic damage showed significant hepatoprotective activity compared with standard silymarin at the dose of 100 mg/kg [9]. The EEAA leaves administered at the dose of 200 mg/kg and 400 mg/kg body weight per oral for 10 days in rats with CCl_4 induced hepatotoxicity showed significant reduction in serum ALT, AST and ALP levels in treated groups compared with standard drug silymarin [10].

Table 1. Commonly reported drugs associated with drug induced liver injuries.

Drug's Category	Selected Drugs Causing Liver Injuries
Non steroidal anti-inflammatory drugs	Diclofenac, ibuprofen, naproxen
Antipyretics	Paracetamol
Antituberculars	Isoniazid, rifampicin, pyrazinamide
Antibiotics	Amoxicillin+clavulanate, flucloxacillin, erythromycin, ciprofloxacin
Anti-epileptics	Phenytoin, carbamazepine, valporic acid
Immunosuppressants	Azathioprine, cyclophosphamide
Anti-retroviral drugs	Ritonavir
Anti-arrhythmic drugs	Amiodarone
Psychiatric drugs	Chlorpromazine, paroxetine

Pretreatment with the extract of *Averrhoa bilimbi* (Family Oxalidaceae, commonly known as Cucumber tree) fruit as at two different concentrations 250 and 500 mg/kg body weight in wistar albino rats which were later intoxicated by acetaminophen, inhibited the increase of liver marker enzymes Serum Gluatamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP) [11].

50% methanolic extract of *Adenanthera pavonina* administered at doses of 100 and 200 mg/kg body weight for 28 days exhibited significant hepatoprotective effects compared against INH & RIF induced hepatic damage in rats as compared to standard drug silymarin 100 mg/kg [12].

Aqueous extract of *Argemone mexicana* (*Papaveraceae*) whole plant administered at the doses of 150 and 250 mg/kg of body weight for 7 days in CCl_4 (i.p. injection with olive oil in 1:1 ratio, at dose 2ml/kg) induced hepatotoxicity in male albino rats showed significant protective effect, compared with Liv 52 (a standardpolyherbal drug). It reduced various biochemical parameters such as AST, ALP, ALT, LDH, total bilirubin; and normalized the serum albumin and total protein. It also significantly increased the final body weight as compared to toxic control group [13].

The hydroalcohalic extract of *Aerva lanata* (*Amaranthanthaceae*) (600 mg/kg) administered orally to the animals with paracetamol (3 gm/kg) induced hepatotoxicity reduced various serum enzymes which was evident of hepatoprotective activity against paracetamol induced hepatotoxicity in rats compared with silymarin 25 mg/kg, bw as standard drug [14].

The hydroalcoholic extract of *Alocasia indica* (Araceae) leaves at the doses of 250 and 500 mg/kg showed significant protective effect in paracetamol and carbon tetrachloride induced hepatic failure in rats compared with the standard drug siymarin. Hepatic necrosis, steatosis, hydropic degeneration and fatty infiltration observed in CCl_4 and paracetamol induced groups of animals were completely absent in the histology of the liver sections of the animals treated with the extracts [15].

The powdered leaves of *Aegle marmelos* (Rutaceae) at the dose of 1000 mg/kg bw p.o. for 14 days showed hepatoprotective effect in carbon tetrachloride induced liver injury in rats compared with a herbal formulation Liv 52 as a reference drug and significantly decreased the level of various hepatic marker enzymes as well as normalized the levels of total protein and albumin [16].

The ethanolic extract of *Amorphophallus campanulatus* (Araceae) tubers was found more potent hepatoprotective than the aqueous extract at the dose of 500 mg/kg against CCl4 induced hepatotoxicity in rats and it significantly restored the hepatic cords and substantially elevated the serum enzymatic levels towards normal [17].

Pre-treatment of the rats with methanol or aqueous extract of *Amorphophallus paeoniifolius* (Araceae) tubers in the dose of 300 mg/kg, p.o. for 4 days prior to paracetamol administration in the dose of 2.5 g/kg, p.o. caused a significant ($p<0.01$) reduction in the values of SGOT, SGPT, ALP and SB as compared to the toxic group which received only paracetamol (2.5 g/kg, p.o.) on the last day and it was almost comparable to the reduction done in silymarin (100 mg/kg, p.o.) or Liv-52 (5 ml/kg, p.o.) treated groups whose hepatoprotective activity was confirmed by histopathological examination of the liver tissues of control and treated groups of animals. The phytochemical investigation of the extracts also showed the presence of carbohydrates, proteins, steroids and flavonoids [18].

There was a significant decrease in total bilirubin, ALP, AST and ALT accompanied by significant increase in the level of total protein in the groups treated with the extracts of *Annona squamosa* (*Annonaceae*) in the dose of 300 & 350 mg/kg bw as compared to the hepatotoxic group with hepatotoxicity induced by isoniazid + rifampicin. In the treated groups, histopathology of liver tissues was normal in architecture showing the hepatoprotective effect of the extracts in albino Wistar rats [19].

The essential oil of *Artemisia capillaris* (*Asteraceae*) commonly known as sweet sagewort at the dose of 50 and 100 mg/kg i.p. antagonized CCl_4-induced hepatic injury, maintained the hepatic serum enzymes towards normal levels ($p<0.01$), which increased or decreased due to CCl_4-induced hepatic injury showing protection of hepatic function against CCl_4-induced liver injury in mice. It showed potent ($p<0.01$) antioxidant activity too and was found to contain mainly citro-

nellol, 1,8-cineole, camphor, linalool, pinene, thymol and myrcene [20].

Ethyl methyl ketone (1000 µg/ml) and methanol (500 and 1000 µg/ml) sub-fractions of total methanolic extract of *Baliospermum montanum* (*Euphorbiaceae*) restored significantly the altered hepatocyte viability and the biochemical parameters such as release of transaminases, total protein due to carbon tetrachloride in primary cultures of rat hepatocytes *in vitro*. The ethyl methyl ketone fraction (50, 100 and 150 mg/kg bw), methanol sub-fraction (150 mg/kg) of the bio-active total methanolic extract and silymarin (100 mg/kg) enhanced liver cell recovery by restoring all the altered biochemical parameters such as serum transaminases, alkaline phosphatase, total bilirubin, total cholesterol, albumin together with total protein and histopathology altered due to carbon tetrachloride back to normal showing that *B. montanum* produced hepatoprotective activity against carbon tetrachloride [21].

The alcoholic extract of kachnar (*Bauhinia variegate*) stem bark belonging to family Fabaceae at 200 and 400 mg/kg, p.o. for 15 days showed significant hepatoprotective activity compared with standard drug silymarin at 50 mg/kg bw in isoniazid (50 mg/kg p.o.) plus rifampicin (100 mg/kg, p.o.)-induced hepatic damage in Wistar albino rats by lowering the levels of serum marker enzymes and lipid peroxidation [22].

Pretreatment of methanolic extract of Silk-cotton tree (*Bombax ceiba*) flower belonging to family Malvaceae at the doses of 150, 300 and 450 mg/kg, i.p. produced significant hepatoprotective effect against isoniazid plus rifampicin-induced hepatotoxicity in rats showing significant decreases in AST, ALT, ALP, and total bilirubin levels but increased the levels of total protein as compared with control group and also improved the hepatotoxicity [23].

The methanolic extract of spider flower (*C. chelidonii*) belonging to family Cleomaceae at 400 mg/kg, bw showed hepatoprotection comparable with that of silymarin against paracetamol (2 g/kg) plus ethanol (2 ml/100 g, b.w.)-induced hepatotoxicity in rats by significantly declining in the levels of hepatic enzymes and increased free radical scavenging activity supported by the favorable histopathological result [24].

The methanolic and chloroform extracts of crown flower (*Calotropis gigantea*) leaves belonging to family Asclepiadaceae showed significant hepatoprotective activity against hepatic damage induced by acetaminophen in experimental animals comparable to Silymarin. While acetone and petroleum ether extracts showed nominal response [25].

The aqueous and methanolic extracts of Kair (*Capparis deciduas*) stem belonging to family *Capparidaceae* at doses of 200 and 400 mg/kg p.o. produced a significant protective effect on liver against carbon tetrachloride (0.2 ml/kg bw for 10 days)-induced liver damage in rats and recovered the liver fatty changes induced by the hepatotoxic compound observed in the intoxicated control rats where the results were comparable with standard drug silymarin. Slight to mild changes in hepatocytes were observed in rats administered with aqueous extract and a higher dose of methanolic extract, whereas the lower dose of methanolic extract revealed more severe lesions than the higher dose [26].

The alcoholic and aqueous extracts of the Chicory (*Cichorium intybus*) roots belonging to family Asteraceae were found to have significant hepatoprotective activity, reduced the elevated levels of SGOT, SGPT, ALP and total bilirubin as compared to a toxic group where carbon tetrachloride induced hepatotoxicity in Wistar albino rats. The aqueous extract (400 mg/kg, bw) was found to have hepatoprotective activity almost comparable to standard drug silymarin showing regeneration of hepatocytes to normal [27].

The pretreatment of mice and rats with the chloroform extract of spotted gum (*Eucalyptus maculata*) belonging to family Myrtaceae at the doses of 125 and 250 mg/kg bw protected them against the acetaminophen (1 g/kg body weight)-induced mortalities by 66%. The chloroform extract (250 mg/kg) or pure phenolic isolate (20 mg/kg) significantly reduced the increase in serum level of different enzymes which may be due to antioxidant activity [28].

The hydroalcholic and aqueous extracts of Patharchatta (*Elytraria acaulis*) belonging to the family Acanthaceae showed protective effect at 200 mg/kg dose in CCl_4 induced liver damage in Swiss albino rats and brought back the altered

level of Alanine Aminotransferase (ALT), aspartate aminotransferase (AST) and total cholesterol, HDL, LDL, triglycerides, liver glycogen and liver protein to normal which was well supported by histopathology [29].

Ethanolic extract of Bhringaraja *(Eclipta alba)* belonging to family Compositae had shown protective effect against paracetamol and carbon tetrachloride-induced hepatotoxicity in mice, and significantly decreased the elevated serum transaminase levels [30, 31].

Essential oil of fennel seeds (*Foeniculum vulgare*) belonging to family Umbelliferae containing trans-anethole, fenchone, methylchavicol, limonene, α-pinene, camphene, β-pinene, β-myrcene, α-phellandrene, 3-carene, camphor, and cis-anethole produced significant hepatoprotective activity against carbon tetrachloride induced liver fibrosis in rats and significantly decreased the levels of SGPT, SGOT, ALP and total bilirubin [32].

Supplementation with grape (*Vitis vinifera*) belonging to family Vitaceae seed proanthocyanidins (100 mg/kg b.w.) alleviated all the Cadmium (5 mg/kg bw) induced molecular changes such as hepatic inflammation, apoptosis and hepatic mitochondrial toxicity, hepatocyte DNA damage in male Wistar rats supporting hepatoprotective activity of grape seed proanthocyanidins. It also indicated that the free radical scavenging, metal chelating and antioxidant potentials of grape seed proanthocyanidins might be the possible reason, responsible for the rescue action against Cadmium induced mitochondrial damage in the liver of rats [33].

The methanolic extract of Diamond flower (*Hedyotis corymbosa*) belonging to family Rubiaceae at the doses of 100 and 200 mg/kg bw significantly and dose dependently normalized the elevated level of various hepatic enzymes in D-galactosamine (200 mg/kg, i.p.) induced hepatotoxicity in Wistar rats supported by histopathology of liver tissues [34].

The alcoholic extract of stem of Black henna (*Indigofera aspalathoide*) belonging to family Fabaceae showed significant hepatoprotective effect against CCl_4-induced hepatic damage in rats when the biochemical parameters such as Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate Oxaloacetate Transaminase (SGOT), Alkaline Phosphatase (ALP), total bilirubin and gamma glutamate transpeptidase (GGTP) were evaluated and histopathological changes of liver sample were observed [35].

The methanolic extract of leaves of Nettlespurge (*Jatropha tanjorensis*) belonging to family Euphorbiaceae at the doses of 200 and 400 mg/kg for 14 days significantly ($p < 0.05$) lowered the serum levels of ALP, AST, ALT as compared to CCl_4 (4 ml/kg i.p. of 25% carbon tetrachloride in liquid paraffin)-induced hepatic damage in rats. The dose of 400 mg/kg of the extract significantly ($p < 0.05$) reduced the level of Total Cholesterol (TC), Triglyceride (TG), and Low-density Lipoprotein Cholesterol (LDL-C), and significantly ($p < 0.05$) increased the level of high-density lipoprotein cholesterol (HDL-C) in the treated rats when compared to the negative control rats. The dose of 200 mg/kg significantly ($p < 0.05$) lowered the level of TG and LDL-C but could not cause any significant ($p < 0.05$) change in the levels of TC, HDL-C and VLDL-C in the treated groups when compared with the negative control [36].

Methanolic extract of wild sage (*Lantana camera*) belonging to family Verbenaceae at the dose of 200 mg/kg bw exhibited hepatoprotective effect compared with silymarin 100 mg/kg bw in CCl_4-induced hepatotoxicity in rats when assessed for the serum marker enzymes, *viz*., AST, ALT, ALP and GGT and liver protein and lipids [37].

The ethyl acetate extract (200 mg/kg bw) of aerial parts of Wild lettuce (*Launaea intybacea*) belonging to family Asteraceae showed antioxidant and protective effect against paracetamol induced hepatotoxicity in albino rats compared with standard drug silymarin The extract significantly decreased serum levels of SGPT, SGOT, ALP, LDH, total bilirubin and liver homogenates LPO, SOD, CAT, GPX, GST and GSH [38].

Pre and post treatment with n-hexane extract (100 and 200 mg/kg bw) of Maidenhair creeper (*Lygodium flexuosum*) belonging to the family Lygodiaceae prevented the elevation of levels of SGPT, SGOT, ALP, LDH and liver lipid peroxides against carbon tetrachloride induced hepatotoxicity in Wistar rats [39].

Pretrement by the aqueous and alcoholic extracts (500 mg/kg bw) of stem of Banana (*Musa paradisiaca*) belonging to family Musaceae more significantly reduced the elevated levels of the se-

rum enzymes like SGPT, SGOT, ALP, and total bilirubin in CCl_4 and paracetamol induced hepatotoxicity in rats supported by reversed hepatic damage towards the normal which gives the evidence of hepatoprotective activity of stem of *Musa paradisiacal* [40].

The hydro-alcoholic extract (500 mg/kg bw) of leaves of Drumstick tree (*Moringa oleifera*) belonging to family Moringaceae significantly ($p<0.01$) decreased the elevated ALP, AST, ALT, lipid peroxidation levels, increased the decreased SOD levels and prevented increase in cadmium accumulation in liver in cadmium chloride (200 ppm/kg bw for 28 days) induced hepatotoxicity in rats [41].

The 600 and 900 mg/kg p.o. doses of ethanolic extract of leaves of Indian borage (*Plectranthus amboinicus*) elicited significant ($p<0.05$) changes in serum hepatic marker enzymes and hepatic tissues showing a protective effect against isoniazid plus rifampicin-induced hepatotoxicity in rats [42].

The methanolic and aqueous extracts (25 mg/kg/day p.o. dose for 10 days) of stem bark of Malabar kino (*Pterocarpus marsupium*) belonging to family Fabaceae showed hepatoprotective activity in CCl_4-induced hepatic damage in rats. It reduced the level of various hepatic marker enzymes and increased the level of total protein and albumin compared to toxic control group supported by normal hepatic cords, absence of necrosis and fatty infiltration in the liver histopathology of extract treated rats [43].

The suspension of chloroform extract of the leaves of Field Milkwort (*Polygala arvensis*) belonging to family Polygalaceae in 0.3% carboxy-methyl cellulose (200 and 400 mg/kg bw) significantly decreased the levels of ALT, AST, LDH, ALP, total bilirubin, triglycerides, total cholesterol, and increased the levels of total protein and albumin as compared to D-galactosamine (400 mg/kg i.p.)-induced hepatic necrosis in Wistar albino rats [44].

The milk extract of Long pepper (*Piper longum*) belonging to family Piperaceae at the dose of 200 mg/kg bw showed a hepatoprotective effect against carbon tetrachloride (0.5 ml/kg p.o.) with olive oil (1:1) thrice a week for 21 days which was comparable to the standard drug silymarin. It significantly reduced the levels of serum enzymes, total bilirubin and direct bilirubin [45].

The 250 and 500 mg/kg p.o. dose of methanolic extract of the leaves of Devil's claws (*Pisonia aculeata*) belonging to family Nyctaginaceae showed potent hepatoprotective and antioxidant activities against rifampicin plus isoniazid induced hepatotoxicity in rats. It produced dose dependent protective effect and normalized the elevated levels of hepatic enzymes, superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, vitamin C and E supported well by liver histopathology [46].

The aqueous and ethanol extracts of stem bark of Red sandalwood (*Pterocarpus santalinus*) belonging to family Fabaceae in 1 % gum tragacanth were evaluated for hepatoprotective activity in CCl_4-induced hepatic damage in rats for 14 days. There was a significant increase in the serum levels of bilirubin, ALT, aspartate transaminase and alkaline phosphatase with a decrease in total protein level in the CCl_4-treated animals, reflecting liver injury. Histological study of treated group showed normal hepatic lobules [47].

Paracetamol (500 mg/kg) and ranitidine (150 mg/kg) induced hepatotoxicity in 7 and 21 days respectively and enhanced the SGPT, SGOT, ALP, liver weight and reduced the total proteins in Wistar rats. Treatment with methanolic extract (150 mg/kg and 300 mg/kg) of leaves of Adavivuluva (*Rhynchosia beddomei*) belonging to family Fabaceae significantly normalized the altered levels of biochemical markers in a dose-dependent manner in paracetamol (500 mg/kg) and ranitidine (150 mg/kg) induced Wistar rats which was supported by histopathological studies of liver tissue and reported to be due to the presence of flavonoids [48].

Silymarin from Milk thistle (*Silybum marianum*) belonging to family Asteraceae showed significant hepatoprotective effect against carbon tetrachloride, ethanol, acetaminophen, D-galactosamine, and *Amanita phalloides* toxin induced hepatotoxicity. Nowaday, silymarin is used as a standard drug in several hepatoprotective experimental models [49-54].

The 100 µg/ml aqueous extract of poisonberry (*Solanum nigrum*) belonging to family Solanaceae prevented hepatocytic damage in the cells treated with ethanol as compared with standard group, and glutathione S-transferase ($p<0.01$) was more sensitive than ALT. The 150 mg/kg bw of aqueous ex-

tract of poisonberry in the treated mice declined serum transaminases ($p<0.01$), hepatic oxidative indices ($p<0.05$) and glutathione S-transferase ($p<0.05$) as compared with standard group and high dose of *S. nigrum* extract (200 mg/kg) showing that *S. nigrum* has hepatoprotective effect against ethanol-induced injury in both *in vitro* and *in vivo* models [55].

Petroleum ether extract along with ethanolic extract of Fenugreek (*Trigonella foenum graecum*) seeds belonging to family Leguminosae containing polyphenols significantly increased the hepatic cell viability in a dose-dependent manner, caused a reduction in lactate dehydrogenase leakage and normalized the ratio of reduced glutathione to oxidized glutathione. It also produced protective effect on liver against ethanol induced hepatotoxicity in rats, and also suppressed the growth of changed liver cells and induced cytotoxicity, oxygen radical formation and mitochondrial dysfunction [56].

The methanolic extract of leaves of Indian Ipecacuanha (*Tylophora indica*) belonging to family Asclepiadaceae at doses of 200 and 300 mg/kg bw, i.p. revealed hepatoprotective activity against carbon tetrachloride induced liver failure in albino rats comparable to silymarin 25 mg/kg, i.p. It exhibited a significant reduction in serum hepatic enzymes when compared to toxic control group rats supported by histopathology of liver tissues [57].

The root extract of Marigold (*Tagetes erecta*) belonging to family Asteraceae at the doses of 200 and 400 mg/kg significantly ($p<0.05$) decreased all the hepatic enzymes and increased total protein towards normal level as compared with silymarin 200 mg/kg supported by improvement in the structural design of liver histopathology showing its hepatoprotective activity in ethanol induced hepatotoxicity in rats [58].

The aqueous extract (50-100 mg/kg) of the leaves of Bitter leaf (*Veronica amygdalina*) belonging to family Compositae showed positive hepatoprotective and antioxidant effects against acetaminophen (300 mg/kg, i.p. for 7 days) induced hepatotoxicity and oxidative stress in mice. Its pretreatment resulted in a dose dependent reversal of acetaminophen induced alterations of liver marker enzymes in serum (ALT, AST, LDH, and ALP) and bilirubin by 51.9-84.9% and suppression of acetaminophen-induced lipid peroxidation and oxidative stress [59]. The pharmacologically reported hepatoprotective drugs with the part(s) used are described in Table **2**.

3. PROMISING POLYHERBAL FORMULATIONS

Pretreatment or post-treatment by the oral dose of 2 ml/kg bw of polyherbal formulation Mentat to the Sprague-Dawley rats significantly ($p < 0.05$) decreased the serum SGOT, SGPT, ALP and TB activities as compared to toxic group where CCl_4 (50% CCl_4 in olive oil i.p. every 72 hr for 10 days) induced hepatotoxicity demonstrating that Mentat possesses hepatoprotective effect against CCl_4 induced hepatotoxicity and that the effects are both preventive and curative [60].

Pretreatment by 50 ml/kg dose of Kabideen syrup significantly reduced the serum ALT, AST, ALP and cholesterol levels, and increased the total protein level in rats treated with carbon tetrachloride when compared to the toxic group supported by histopathological findings revealing hepatoprotective potential of Kabideen syrup [61].

Pre-treatment with the polyherbal formulation livopick at the doses of 150 mg/kg and 100 mg/kg showed more potent hepatoprotective effect in acute experimental liver injury induced by paracetamol in rats as evident by the significant reduction in the elevated serum marker enzyme levels and supported by antioxidant and histopathological studies [62].

Pretreatment with the polyherbal formulation Livomyn at a dose of 120, 240, 480 mg/kg/day po for 7 days showed significant hepatoprotective activity in experimental liver injury induced by carbon tetrachloride in rats as indicated by a decrease in elevated serum marker enzymes, SGPT, SGOT, ALP, TB in a dose dependent manner and supported by its histopathological antioxidant and free radical scavenging activities [63].

Supplementation of the polyherbal formulation Livina at the doses of 0.5 and 1 ml/day showed significant hepatoprotective effect in experimental liver injury induced by paracetamol (200 mg/kg i.p.) in Swiss albino mice as evidenced by significant

Table 2. Pharmacologically reported hepatoprotective drugs with the part(s) used.

Plant Name	Common Name	Family	Part(s) Used
Adenanthera pavonina	Bead Tree	*Leguminosae*	leaves, seed and bark
Aegle marmelos	Golden apple	*Rutaceae*	leaves
Aerva lanata	Mountain knotgrass	*Amaranthanthaceae*	whole plant
Alocasia indica	Giant Taro	*Araceae*	leaves
Amorphophallus campanulatus	Corpse flower	*Araceae*	tubers
Amorphophallus paeoniifolius	Elephant foot yam	*Araceae*	tubers
Annona squamosa	Sugar apple	*Annonaceae*	leaves
Aquilaria agallocha	Agarwood	*Thymelaeaceae*	leaves
Argemone mexicana	Mexican prickly poppy	*Papaveraceae*	whole plant
Artemisia capillaris	Sweet sagewort	*Asteraceae*	essential oil from the plant
Averrhoa bilimbi	Cucumber tree	*Oxalidaceae*	fruit
Baliospermum montanum	Red physic nut	*Euphorbiaceae*	roots
Bauhinia variegate	Kachnar	*Fabaceae*	stem bark
Bombax ceiba	Silk-cotton tree	*Malvaceae*	flower
C. chelidonii	Spider flower	*Cleomaceae*	whole plant
Calotropis gigantea	Crown flower	*Asclepiadaceae*	leaves
Capparis deciduas	Kair	*Capparidaceae*	stem
Cichorium intybus	Chicory	*Asteraceae*	roots
Eclipta alba	Bhringaraja	*Compositae*	whole plant
Elytraria acaulis	Patharchatta	*Acanthaceae*	whole plant
Eucalyptus maculata	Spotted gum	*Myrtaceae*	stem
Foeniculum vulgare	fennel	*Umbelliferae*	seed
Hedyotis corymbosa	Diamond flower	*Rubiaceae*	whole plant
Indigofera aspalathoide	Black henna	*Fabaceae*	stem
Jatropha tanjorensis	Nettlespurge	*Euphorbiaceae*	leaves
Lantana camera	Wild sage	*Verbenaceae*	rind
Launaea intybacea	Wild lettuce	*Asteraceae*	aerial parts
Lygodium flexuosum	Maidenhair creeper	*Lygodiaceae*	whole plant
Moringa oleifera	Drumstick tree	*Moringaceae*	leaves
Musa paradisiaca	Banana	*Musaceae*	stem
Piper longum	Long pepper	*Piperaceae*	fruits and roots
Pisonia aculeata	Devil's claws	*Nyctaginaceae*	leaves
Plectranthus amboinicus	Indian borage	*Lamiaceae*	leaves

(Table 2) Contd….

Plant Name	Common Name	Family	Part(s) Used
Pterocarpus marsupium	Malabar kino	*Fabaceae*	stem bark
Pterocarpus santalinus	Red sandalwood	*Fabaceae*	stem bark
Rhynchosia beddomei	Adavivuluva	*Fabaceae*	leaves
Silybum marianum	Milk thistle	*Asteraceae*	seeds
Solanum nigrum	Poison berry	*Solanaceae*	whole plant
Tagetes erecta	Marigold	*Asteraceae*	root
Trigonella foenum graecum	Fenugreek	*Leguminosae*	seeds
Tylophora indica	Indian Ipecacuanha	*Asclepiadaceae*	leaves
Veronica amygdalina	Bitter leaf	*Compositae*	leaves
Vitis vinifera	Grape	*Vitaceae*	seed

($p<0.05$, $p<0.001$) reduction in the damaging effects of paracetamol on liver and supported by histopathological changes towards normal. The effectiveness of Livina was found to be almost parallel with silymarin, indicating the herbal formulation to be almost as effective as the standard drug [64].

Polyherbal formulation Livergen at the dose of 2.60 ml/kg, bw, p.o. showed significant reduction in SGOT, SGPT, ALP, cholesterol, bilirubin levels, and normalized the elevated total protein level in carbon tetrachloride (0.7ml/kg, i.p.) induced hepatotoxicity in rats suggesting significant hepatoprotective activity [65].

Pretreatment with polyherbal (*Allium sativum, Ocimum sanctum, Curcuma longa, Aloe barbadensis*) syrup at the doses of 100 mg/kg, 300 mg/kg and 500 mg/kg showed hepatoprotective effect in paracetamol induced hepatotoxicity in adult male Wistar rats and showed decrease in elevated AST, ALT, LDH, and total bilirubin levels due to paracetamol treatment which was comparable to standard group (Liv 52, 5.2 ml/kg). In the near future, polyherbal syrup could lead to the discovery of novel herbal combination drug for the treatment of hepatotoxicity [66].

Pretreatment with polyherbal (*Cassia fistula, Coccina indica* and *Vigna mungo*) formulations F1 (Crude drugs formulation), F2 (Lab extracts formulation) and F3 (commercial extracts formulation) showed hepatoprotective activity in acute liver toxicity models of CCl_4 induced liver damage in rats. The formulations F2 and F3 showed significant hepatoprotective activity at dose of 500 mg/kg, p.o., when compared to the CCl_4 toxic control group. Formulations F2 and F3 were effective in experimental liver damage. Biochemical parameters AST, ALT, ALP and total proteins showed better results in lab extracts formulations [67].

The polyherbal (Emblica officinalis fruits, Terminalia chebula fruits, Terminalia bellirica fruits, Picrorhiza kurroa rhizomes, Tinospora cordifolia stem, Swertia chirata entire herb, Azadirachta indica bark, Adhatoda vasica stem bark) formulation showed hepatoprotective activity in paracetamol (300 mg/kg, bw) induced hepatic damage in Mus muscullus female mice using Liv 52 as standard drug. The formulation showed significant liver protection at 300, 400 and 500 mg/kg bw by lowering the levels of AST, ALT, ALP, total bilirubin parameters ($p<0.05$), lipid profiles- cholesterol, triglycerides, LDL and histopathological studies showed that 300 and 400 mg/kg formulation have significant ($p<0.05$) hepatoprotective effect [68].

The polyherbal (*Phyllanthus amarus, Terminalia chebula, Ricinus communis, Cichorium intybus, Vitex negundo, Aloe vera*) extract formulation showed dose-dependent effect at the doses of 300 and 600 mg/kg bw as compared to 100 mg/kg dose of silymarin in preventing the rise in the levels of ALP, SGOT, SGPT and total bilirubin compared to ethanol induced hepatotoxicity in rats. The presence of flavonoids, terpenoids, tannins, saponins and polyphenolic compounds present in the herbal extracts might be responsible for the anti-

oxidant and hepatoprotective activities of herbal formulation [69].

The polyherbal hepatoprotective formulations Liv 52 and Livergen (2.60 ml/kg/day for 7 days) were most effective at normal doses used in the study in acute liver toxicity in Swiss albino mice of either sex model induced by paracetamol (500 mg/kg, bw on day 8) justifying its use as a hepatoprotective agent. However, Livokin, Octogen, Stimuliv and Tefroliv showed similar effects only at higher doses which were twice that of the recommended dose. There was no observed toxicity in any of the polyherbal drug pretreated groups even though no separate toxicity study was conducted [70].

Girish et al. (2009) also evaluated hepatoprotective effect of six polyherbal formulation (PHFs) in CCl_4 induced hepatic damage in mice. The pretreatment with six PHFs at 2.6 ml/kg were found to be ineffective as hepatoprotection. It showed protective effect at high dose (5.2 ml/kg, bw) of pretreatment, PHFs at this dose reduced hepatic markers enzymes in CCl_4 treated animals, but the difference was found to be statistically significant only with Liv 52 and Livergen [71].

4. DISCUSSION

Very recently, hydroalcoholic extract of *Anacyclus pyrethrum* Linn root at the doses of 200 and 400 mg/kg/day po, respectively, for 28 days had also shown hepatoprotective activity against isoniazid plus rifampicin (each 50 mg/kg/day po)-induced hepatotoxicity in SD rats, well supported by the histopathological results. Rats treated with the extract of *Anacyclus pyrethrum* Linn 400 mg/kg/day showed significant ($p < 0.01$) decrease in SGPT, SGOT, ALP, LDH, cholesterol, serum bilirubin, liver weight and relative liver weight Levels, while significant ($p < 0.01$) increase in final body weight (b. wt.), total protein and albumin levels as compared to toxic group rats and comparable to that of silymarin 100 mg/kg/day [72]. For the decades, natural herbal medicines have been a source of remedy and drugs lead [73]. Natural herbal medicines and the products condition the inspiration for sorts of strategies used in the diversity-oriented synthesis of the novel small moiety libraries. An enhancing body of the evidence supports the effectiveness of these planning of the operation for recognizing new biologically active moiety [74]. At least one quarter of the patients with liver diseases, nowadays, are using ethno-medicines because of increasing global popularity of the herbal remedy. Several herbal medicines are on the market to relieve symptoms, cure diseases and support health. However, most of them lack pharmacological and scientific validations. In the experimental models of hepatotoxicity on laboratory animals, several herbal medicines exerted curative/hepatoprotective effects that warrant their clinical testing. The methodological scientific evaluation approach will help exploring the real therapeutic value of these natural herbal medicines and standardized the dosage regimen on evidence-based findings to become more than a fashionable trend.

CONCLUSION

In the present review article, an effort has been taken to collect and compile the details regarding a few hepatoprotective herbal medicines and their polyherbal formulations available in India and abroad as a hepatoprotectant, which will be useful to the global society to venture into a field of alternative and integrative systems of medicine.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Singh K, Verma B. Hepatoprotection through Ayurvedic herbs. Int J Ayu Herb Med 2012; 2(5): 885-96.

[2] Ravishah S, Manjula SN, Mruthunjaya K, *et al*. Hepatoprotective activity of roots of *Lawsonia inermis* against paracetamol and anti-tubercular drugs induced hepatotoxicity in rats. Int J Pharm 2012; 2(2): 306-16.

[3] Ostapowicz G, Fontana RJ, Schiodt FV, *et al*. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Annals Intern Med 2002; 137(12): 947-54.

[4] Menghini L, Genovese S, Epifano F, Tirillini B, Ferrante C, Leporini L. Antiproliferative, protective and antioxidant effects of artichoke, dandelion, turmeric and rosemary extracts and their formulation. Int J Immunopathol Pharmacol 2010; 23(2): 601-10.

[5] Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products. J Diabetes Metab Disord 2015; 14: 57.

[6] Jain A, Jain IP, Singh IP, Agarwal A. To evaluate hepatoprotective activity of roots of *Cynodon Dactylon* an experimental study. Asian J Pharm Clin Res 2013; 6(2): 109-12.

[7] Ozougwu, JC. Herbal options for the management of drug induced liver damage: A Review. Pharmacologyonline 2011; 3: 1481-90.

[8] Fraschini F, Demartini G, Esposti D. Pharmacology of silymarin. Clin Drug Invest 2002; 22(1): 51-65.

[9] Alam J, Mujahid MD, Badrudden, Jahan Y, Bagga P, Rahman MA. Hepatoprotective potential of ethanolic extract of *Aquilaria agallocha* leaves against paracetamol induced hepatotoxicity in SD rats. J Trad Complement Med 2017; 7: 9-13.

[10] Rahman H, Vakati K, Eswaraiah MC, Dutt AM. Evaluation of hepatoprotective activity of ethanolic extract of *Aquilaria agallocha* leaves (EEAA) against CCl_4 induced hepatic damage in rat. Scholars J Appl Med Sci 2013; 1(1): 9-12.

[11] Selvam TN, Santhi PS, Sanjayakumar YR, *et al*. Hepatoprotective activity of *Averrhoa bilimbi* fruit in acetaminophen induced hepatotoxicity in wistar albino rats. J Chem Pharm Res 2015; 7(1): 535-40.

[12] Mujahid M, Siddiqui HH, Hussain A, Hussain MS. Hepatoprotective effects of *Adenanthera pavonina* (Linn.) against anti-tubercular drugs-induced hepatotoxicity in rats. Pharmacog J 2013; 5: 286-90.

[13] Das PK, Prasanna P, Somya RP, Ranjan S. Hepatoprotective activity of plant *Argemon mexicana* against $CC1_4$ induced hepatotoxicityin rats. Int J Pharm Res Develop 2009; 8: 2-3.

[14] Manoharan S, Jaswanth A, Sengottuvelu S, *et al*. Hepatoprotective activity of *Aerva lanata* against paracetamol induced hepatotoxicity in rats. Res J Pharm Technol 2008; 1(4): 398-400.

[15] Wahid AM, Vijay R Salunkhe, Satish B Bhise. Hepatoprotective activity of hydroalcohalic extract o leaves of *Alocasia indica* (Linn). Indian J Exp Biol 2008; 47: 816-21.

[16] Jayachandra K, Sivaraman T. Hepatoprotective Effect of *Aegle Marmelos (L.)* leaf powder (crude) against carbon tetrachloride-induced hepatic damage in albino rats. J Pharm Sci Res 2011; 3(7): 1360-63.

[17] Sanjay J, Dixit VK, Malviya N, Ambawatia V. Antioxident and hepatoprotective activity of ethanolic and aqueous extract of *Amorphophallus campanulatus* Roxb. Acta Pol Pharm 2009; 66(4): 423-28.

[18] Hurkadale PJ, Shelar PA, Palled SG, Mandavkar YD, Ajay S, Khedkar AK. Hepatoprotective activity of *Amorphophallus paeoniifolius* tubers against paracetamol-induced liver damage in rats. Asian Pac J Trop Biomed 2012; S238-42.

[19] Raj DS, Vennila JJ, Aiyavu C, Panneerselvam K. The hepatoprotective effect of alcoholic extract of *Annona squamosa* leaves on experimentally induced liver injury in Swiss albino mice. Int J Integr Biol 2009; 5(3): 182-6.

[20] Gao Q, Xin-Zhao X, Yin L, *et al*. The essential oil of *Artemisia capillaris* protects against CCl_4-induced liver injury *in vivo*. Revista Brasileira de Farmacog 2016; 26(3): 369-74.

[21] Kumar SSV, Mishra SH. Hepatoprotective activity of *Baliospermum montanum* (wild) in rats treated with carbon tetrachloride: *In vivo* and *in vitro* studies. Phcog Mag 2009; 5(19): 196-202.

[22] Marasani A. Hepatoprotective activity of *Bauhinia variegata* against isoniazid and rifampicin induced toxicity in experimental rats. Int J Pharm Pharm Sci 2014; 6(4): 177-81.

[23] Ravi V, Patel SS, Verma NK, *et al*. Hepatoprotective activity of *Bombax ceiba* linn against isoniazid and rifampicin-induced toxicity in experimental rats. Int J Appl Res Nat Prod 2010; 3(3): 19-26.

[24] Begum MM, Kiran KR. Evaluation of methanolic extract of *Cleome chelidonii* for hepatoprotective activity against paracetamol and ethanol induced hepatotoxicity in rats. Int J Pharm Res Rev 2016; 5(1): 28-36.

[25] Usmani S, Kushwaha P. Hepatoprotective activity of extracts of leaves of *Calotropis gigantea*. Asian J Pharm Clin Res 2010; 3(3): 1-8.

[26] Ali AS, Gameel AA, Mohamed AH, Hassan T. Hepatoprotective activity of *Capparis deciduas* aqueous and methanolic stems extracts against carbon tetrachloride induced liver histological damage in rats. J Pharmacol Toxicol 2010; 6(1): 62-8.

[27] Nallamilli BR, Kumar CP, Reddy KV, Prasanna MK, Maruthi V, Sucharita P. Hepatoprotective activity of *Cichorium intybus* (Linn.) root extract against carbon tetrachloride induced hepatotoxicity in albino Wistar rats. Drug Invent Today 2013; 5: 311-14.

[28] Mohamed AF, Ali-Hasan AG, Hamamy MI, Abdel-Sattar E. Antioxidant and hepatoprotective effects of *Eucalyptus maculata.* Med Sci Monit 2005; 11(11): BR426-31.

[29] Reddy GVR, Kumar RV, Rama V, Reddy MK, Reddy YN. Preliminary hepatoprotective activity of medicinal plant extracts against carbon tetrachloride induced hepatotoxicity in albino rats. Int J Rec Sci Res 2015; 6(7): 4946-51.

[30] Mama K, Nyunt N, Maung. The protective effect of *Eclipta alba* on carbon tetrachloride-induced acute liver damage. Toxicol Appl Pharmacol 1978; 45(3): 723-8.

[31] Tabassum N, Agrawal SS. Hepatoprotective activity of *Eclipta alba* Hassk. against paracetamol induced hepatocellular damage in mice. Exp Med 2004; 11(4): 1-7.

[32] Ozbek H, Ugras S, Bayram I, *et al*. Z. Hepatoprotective effect of *Foeniculum vulgare* essential oil: A carbon tetrachloride induced liver fibrosis model in rats. J American Ass Lab Anim Sci 2004; 3(1): 1-8.

[33] Miltonprabu S, Nazimabashir, Manoharan V. Hepatoprotective effect of grape seed proanthocyanidins on cadmium-induced hepatic injury in rats: Possible involvement of mitochondrial dysfunction, inflammation and apoptosis. Toxicol Rep 2016; 3: 63-77.

[34] Gupta RK, Singh RK, Swain SR, Hussain T, Rao CV. Anti-hepatotoxic potential of *Hedyotis corymbosa* against D-galactosamine-induced hepatopathy in experimental rodents. Asian Pac J Trop Biomed 2012; 2(3): S1542-7.

[35] Rajkapoor B, Jayakar B, Kavimani S, Murugesh N. Protective effect of *Indigofera aspalathoides* against CCl_4-induced hepatic damage in rats. J Herb Pharmacother 2006; 6(1): 49-54.

[36] Gideon MK, Omeh YN, Matthew IA. Hepatoprotective activity of methanolic extract of *Jatropha tanjorensis* in carbon tetrachloride induced hepatotoxicity. Arch Appl Sci Res 2015; 7(5): 45-8.

[37] Asija R, Kumar V, Sharma AK. Hepatoprotective activity of *Lantana Camera* against carbon tetrachloride induced hepatotoxicity in wistar rat. Int J Pharm Erudit 2015; 4(4): 1-7.

[38] Takate SB, Pokharkar RD, Chopade VV, Gite VN. Hepatoprotective activity of ethyl acetate extract of *Launaea intybacea* in paracetamol inuced hepatotoxicity in Albino rat. Int J Pharm Sci Rev Res 2010; 1(2): 72-4.

[39] Wills PJ, Asha VV. Protective effect of *Lygodium flexuosum* (L.) Sw extract against carbon tetrachloride-induced acute liver injury in rats. J Ethnopharmacol 2006; 108(3): 320-6.

[40] Dikshit P, Mool KT, Kirtikar, Sonal, Jasvindar, Rimi S. Hepatoprotective effect of stem of *Musa sapientum* in rats intoxicated with carbon tetrachloride. Ann Hepatol 2011; 10(3): 333-9.

[41] Toppo R, Roy BK, Gora RH, Baxla SL, Kumar P. Hepatoprotective activity of *Moringa oleifera* against cadmium toxicity in rats. Vet World 2015; 8(4): 537-40.

[42] Sheney S, Kamathan P, Azhar M, *et al.* Hepatoprotective activity of ethanolic extract of *Plectranthus amboinicus* against antitubercular drugs induced hepatotoxicity in Wistar rat. Int J Pharm Pharm Sci 2014; 2(5): 1027-33.

[43] Mankani KL, Krishna V, Manjunatha BK, Vidya SM, Jagadeesh-Singh SD. Evaluation of hepatoprotective activity of stem bark of *Pterocarpus marsupium* Roxb. Indian J Pharmacol 2005; 37(3): 165-8.

[44] Dhanabal SP, Syamala G, Satish KMN, Suresh B. Hepatoprotective activity of the Indian medicinal plant *Polygala arvensis* on D-galactosamine-induced hepatic injury in rats. Fitoterapia 2006; 77(6): 472-4.

[45] Patel JA, Shah US. Hepatoprotective activity of *Piper longum* traditional milk extract on carbon tetrachloride induced liver toxicity in Wistar rats. Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas 2009; 8(2): 121-9.

[46] Anbarasu C, Kapoor Raj, Kalpana. Protective effect of *Pisonia aculata* on rifampicin and isoniazid induced hepatotoxicity in rats. Int J Phytomed 2011; 3(1): 188-90.

[47] Manjunatha BK. Hepatoprotective activity of *Pterocarpus santalinus* an endangered medicinal plant. Indian J Pharmacol 2006; 38(1): 25-8.

[48] Reddy SNV, Anjum M, Aveti S, Raju GM. Hepatoprotective activity of methanolic extract of whole plant of *Rhynchosia beddomei* in Wistar rats. J Pharm Chem Biol Sci 2015; 3(3): 378-87.

[49] Sharma A, Chakraborti KK, Handa SS. Anti-hepatotoxicactivity of some Indian herbal formulations as compared to silymarin. Fitoterapia 1991; 62: 229-35.

[50] Shukla B, Visen PKS, Patnaik GK, Dhawan BN. Choleretic effect of andrographolide and silymarin in rats and guinea pigs. Planta Med 1992; 58: 146-9.

[51] Wang M, Grange LL, Tao J, Reyes E. Hepatoprotective properties of *Silybum marianum* herbal preparation on ethanol-induced liver damage. Fitoterapia 1996; 67(2): 166-71.

[52] Saraswat B, Visen PKS, Patnaik GK, Dhawan BN. Effect of *Andrographolide* against galactosamine-induced hepatotoxicity. Fitoterapia 1995; 66: 415-20.

[53] Desplaces A, Choppin J, Vogel G. The effects of silymarin on experimental phalloidine poisoning. Arzneimittel forschung 1975; 25: 89-96.

[54] Vogel G, Tuchweber B, Trost W. Protection by silibinin against *Amanita phalloides* intoxication in beagles. Toxicol Appl Pharmacol 1984; 73: 355-62.

[55] Liu FP, Ma X, Li MM, *et al*. Hepatoprotective effects of *Solanun nigrum* against ethanol-induced injury in primary hepatocytes and mice with analysis of glutathione S-transferase A1. J Chinese Med Ass 2016; 79(2): 65-71.

[56] Kaviarasan S, Ramamurty N, Gunasekaran P, Varalakshmi E, Anuradha CV. Fenugreek (*Trigonella foenum graecum*) seed extract prevents ethanol-induced toxicity and apoptosis in chang liver cells. Alcohol Alcoholism 2006; 41(3): 267-73.

[57] Mujeeb M, Aeri V, Bagri P, Khan SA. Hepatoprotective activity of the methanolic extract of *Tylophora indica* (Burm. f.) Merill. leaves. Int J Green Pharm 2009; 3(2): 125-7.

[58] Karwani G, Sisodia SS. Hepatoprotective activity of *Tagetes erecta* Linn. in ethanol induced hepatotoxicity in rats. Scholars Acad J Pharm 2015; 4(3): 181-9.

[59] Iwalokun BA, Efedede BD, Alabi-Sofunde JA, Oduala, T, Magbagbeola OA. Hepatoprotective and antioxidant activities of *Vernonia amygdalina* on acetaminophen-induced hepatic damage in mice. J Med Food 2006; 9(4): 524-30.

[60] Rastogi C, Ahmed SA, Jawaid T, Awasthi R, Kalpana, Kamal M. Hepatoprotective effect of polyherbal formulation "Mentat" against carbon tetrachloride induced hepatotoxicity in rats. World J Pharm Res 2016; 5(1): 742-6.

[61] Zameer M, Rauf A, Qasmi IA. Hepatoprotective activity of a unani polyherbal formulation "Kabideen" in CCl_4 induced liver toxicity in rats. Int J Appl Biol Pharm Technol 2015; 6(1): 8-16.

[62] Ahmed R, Gupta K, Naik MK, Afsal M, Hamza S. Preclinical evaluation of hepatoprotective activity of

the polyherbal formulation "LIVOPICK". Int J Pharm Sci Res 2015; 6: 180-4.

[63] Harshitha D, Rodda R, Rao UM. Evaluation of polyherbal formulation, Livomyn for it's hepatoprotective and antioxidant activity. Scholars Res Library 2013; 5(6): 135-41.

[64] Darbar S, Bhattacharya A, Chattopadhyay S. Antihepatoprotective potential of Livina, a polyherbal preparation on paracetamol induced hepatotoxicity: a comparison with silymarin. Asian J Pharm Clin Res 2011; 4(1): 72-7.

[65] Arsul VA, Wagh SR, Mayee RV. Hepatoprotective activity of Livergen, a polyherbal formulation against carbon tetrachloride induced hepatotoxicity in rats. Int J Pharm Pharm Sci 2011; 3(3): 228-31.

[66] Patel DK, Shah KH, Tank MK. Evaluation of hepatoprotective activity of polyherbal formulation in paracetamol induced hepatotoxicity in rats. Int J Pharm Sci Rev Res 2013; 22(1): 134-9.

[67] Patidar P, Sharma M, Dubey D, Dashora K. Development of polyherbal formulations for hepatoprotective activity. Int J Res Pharm Biomed Sci 2012; 3(4): 1577-9.

[68] Saroj BK, Mani D, Mishra SK. Scientific validation of polyherbal hepatoprotective formulation against paracetamol induced toxicity. Asian Pacific J Trop Biomed 2012; S1742-6.

[69] Rao AS, Satyanarayana S. Hepatoprotective activity of herbal extract mixture (HEM) on ethanol induced hepatotoxicity in rats. Scholars Acad J Pharm 2015; 4(2): 93-101.

[70] Girish C, Koner BC, Jayanthi S, Rao KR, Rajesh B, Pradhan SC. Hepatoprotective activity of six polyherbal formulations in paracetamol induced liver toxicity in mice. Indian J Med Res 2009; 129: 569-78.

[71] Girish C, Koner BC, Jayanthi S, Rao KR, Rajesh B, Pradhan SC. Hepatoprotective activity of six polyherbal formulations in CCl_4 induced liver toxicity in mice. Indian J Exp Biol 2009; 47: 257-63.

[72] Usmani A, Mujahid M, Khushtar M, Siddiqui HH, Rahman MA. Hepatoprotective effect of *Anacyclus pyrethrum* Linn. against antitubercular drug-induced hepatotoxicity in SD rats. J Complement Integr Med 2016; 13(3): 295-300.

[73] Brahmachari UN. The role of science in recent progress of medicine. Curr Sci 2001; 81(1): 15-6.

[74] Khare CP. Indian medicinal plants. Springer 2007; 422-3.