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Arabian Medicinal Plants With Hepatoprotective Activity.

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ABSTRACT

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Drug-induced hepatic injury is the most common reason cited for withdrawal of an approved drug. Many medicinal plants showed hepatoprotective activity. The current review will discuss the medicinal plants possessed hepatoprotective effects.

Keywords: Medicinal plants, Hepatoprotective, Therapeutic, Pharmaceutical

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INTRODUCTION

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. Liver cell injury caused by various toxic chemicals like certain antibiotics, chemotherapeutic agents, carbon tetrachloride, thioacetamide, excessive alcohol consumption and microbes. Different medicinal plants extracts possessed hepatoprotective activity due to their contents of flavonoids, terpenoids, phenolic acids, stilbenes, alkaloids, antraquinones, curcuminoids, capsaicinoids and chromenes[1]. These constituents possessed their hepatoprotective activities via many mechanisms. Because of involvement of oxidative stress in the mechanisms of hepatic injury, the antioxidant properties of medicinal plants were involved in the mechanism of their hepatoprotective activity. They inhibited hepatic oxidative stress by many mechanisms[2]. They also enhanced antioxidant defense (superoxid dismutase, catalase and glutathione peroxidase activity) in addition, they reduced peroxidation[3-4]. Some plant constituents reversed hepatic fibrosis via enhancement of the expression of matrix metalloproteinase and removal of collagen deposits, with attenuation of hepatic stellate cells activation[5]. Many of medicinal plants produced hepatoprotective effects via their antiinflammatory activity and attenuation of many inflammatory processes. Furthermore, antifibrotic properties of plants and stimulation of extracellular matrix degradation were also participated in hepatoprotection of medicinal plants[1]. The current review discuss the medicinal plants showed hepatoprotective activities and explained their mechanism of action in liver injury.

Table 1: Medicinal plants with hepatoprotective activity

Plant	Extract or compound	Model	Results	Ref
Agrimonia eupatoria	water extract	chronic ethanol-induced liver injury in rats	Aanine aminotransferase (ALT) and aspartate aminotransferase AST) activities and pro-inflammatory cytokines markedly increased by alcohol, these changes were attenuated by water extract.	[6-7]
Alhagi maurorum	ethanolic extract	carbon tetrachloride – or or acetaminophen induced liver injury in rats	The level of transaminases was decreased in animals treated with a combination of ethanolic *Alhagi maurorum* extract plus CCl_4 or acetaminophen as compared to animals receiving CCl_4 or acetaminophen alone.	[8-12]
Allium sativum	aqueous extract, 60 and 120 mg /kg bw.	$CrCl_3$ induced hepatic injury in rats	Garlic inhibited the hepatotoxicity of $CrCl_3$, the concomitant use of garlic and $CrCl_3$ decreased the levels of AST and ALT.	[13-14]
Anchus strigosa	aqueous and ethanolic extracts	aryl hydrocarbon hydroxylase activity (AHH) and 3H-benzo (a) pyrene (3H-BP) binding to rat liver microsomal protein	Aqueous extracts showed no inhibitory effect while the ethanolic extracts exhibited strong inhibitory effect on both AHH and 3H-BP binding to the microsomal protein	[15-16]
Arctium lappa	aqueous extract of the root, 300 mg/kg bw.	CCl_4 or acetaminophen-intoxicated mice as well as the ethanol plus CCl_4-induced rat liver damage	*Arctium lappa* was shown to suppress the CCl_4 or acetaminophen-intoxicated mice as well as the ethanol plus CCl_4-induced rat liver damage. The hepatoprotective ability could be attributed to the decrease of oxidative stress on hepatocytes	[17-19]

			by increasing glutathione (GSH), cytochrome P-450 content and NADPH-cytochrome C reductase activity and by decreasing malondialdehyde (MDA) content	
Astragalus hamosus	flavonoid rhamnocitrin 4'-β-D-galactopyranoside (RGP) obtained from leaves	N-diethylnitrosamine (DENA)-induced hepatic cancer in rats	It showed anticancer activity against N-diethylnitrosamine (DENA)-induced hepatic cancer in rats	[20]
Bauhinia variegata	ethanolic extract of the stem of *B. variegate,* 100 and 200 mg/kg bw	hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in rats	It decreased the level of AST, ALT, ALP and GGT.	[21-22]
Brassica nigra	methanol extract of *Brassica nigra* leaves ,200 and 400 mg/kg bw	D-galactosamine (D-GalN)-induced hepatic and nephrotoxicity in rats	*Brassica nigra* reduced DGalN-induced hepatotoxicity as confirmed from biochemical parameters.	[23-24]
Brassica rapa	*Brassica rapa* juice, 16 ml/ kg bw	CCl_4-induced hepatotoxicity	significantly reduced the serum GOT, GPT, alkaline phosphatase (ALP) and bilirubin level. It also replenished the lowered nonprotein sulfhydryl (NP-SH) concentration in the liver tissue after $CC1_4$ treatment	[25]
	root ethanolic extract, 200 mg/kg bw	alloxan-induced diabetic rats	significantly decreased the levels of serum biomarkers of hepatic injury which further confirmed by liver histology.	[26]
	aqueous, 250 and 500 mg/kg bw	oxidative stress induced by Tertbutyl hydroperoxide (t-BHP) in rats	significantly combats the oxidative stress imposed by t-BHP in the hepatic tissues as evidenced by marked improvement in the antioxidant status and suppressing lipid peroxide levels.	[27]
	aqueous extract, 20 mg/ml	thioacetamide (TAA)-induced liver fibrosis	Anti-fibrogenic effect was demonstrated histopathologically and serologically. The animals fed with 20 mg/ml of turnip extracts showed the highest anti-fibrogenic effect	[28-29]
	Isorhamnetin 3-O-glucoside from the leaves	liver injury induced by the injection of CCl_4	suppressed increases in the plasma ALT and AST activities of mice.	[30]
Bryonia dioica	Bry The plant leaves Single oral dose dose of 250mg/kg for 7 days extract	Serum activities of transam as the biochemical marker of hepatotoxicity inases (ALT and AST)	The results indicated that pretreatment of rats with Bryonia extract prior to induction of hepatotoxicity offered a hepatoprotective action. ***Bryo***	[31-32]
Bryophyllum calycinum	The juice of the leaves and the ethanolic extract	CCl_4-induced hepatotoxicity	hepatoprotective as evidenced by *in vitro*, *in vivo* and histopathological studies	[33-34]

Casealpinia crista	methmnol extract, 50, 100 and 200 mg/kg bw.	CCl_4-induced hepatotoxicity in rats.	It produced significant ($p < 0.05$) hepatoprotective effect by decreasing the activity of serum enzymes, bilirubin, uric acid, and lipid peroxidation and significantly ($p < 0.05$) increased the levels of SOD, CAT, GSH, vitamin C, vitamin E and protein in a dose dependent manner.	[35]
	methmnol extract	iron-overload-induced liver injury	It showed a dose-dependent inhibition of lipid peroxidation, protein oxidation, and liver fibrosis. The serum enzyme markers were found to be less, whereas enhanced levels of liver antioxidant enzymes.	[36-37]
Calendula officinalis	flowers extracts	aflatoxins (AFs)-induced oxidative stress	It showed a significant decrease in oxidative damage markers, micronucleated cells, DNA fragmentation and modulation of the expression of pro-apoptotic genes	[38]
	hydroalcohol extract of the flowers	CCl_4-induced hepatotoxicity in rats	It reduced hepatocytolysis by 28.5 % due to reduction in GOT and GPT.	[39]
	hot water extract of flowers	In vitro anticancer test	exhibited antihepatoma activity against five human liver cancer cells - HepG2/C3A, SK-HEP-1, HA22T/VGH, Hep3B and PLC/PRF/5 – with an inhibitory effect of 25- 26% at a dose of 2000 µg/ml.	[40]
Calotropis procera	aqueous ethanolic extract of flowers with, 200 and 400 mg/kg bw.	paracetamol-induced hepatitis in rats	showed remarkable hepatoprotective activity as judged from biochemical parameters such as AST, ALT, ALP, total bilirubin, total protein, GGTP and levels of lipid peroxides in liver	[41]
	ethanolic extract of root, 150 and 300 mg/kg bw	CCl_4- induced hepatotoicity in rats	It did not protect the liver and kidney from CCl_4-induced toxicity	[42]
	chloroform extract, 100 and 200 mg/kg bw.	paracetamol-induced hepatotoxicity	showed remarkable hepatoprotective activity as judged from biochemical parameters such as AST, ALT, ALP, total bilirubin, total protein, GGTP and levels of lipid peroxides in liver.	[43-44]
Canna indica	methanol extract, 100 and 200mg/kg bw.	CCl_4- induced hepatotoicity in rats	The reduced GSH and catalase levels were in CCl_4- treated rats, became normal in extract treated rats.	[45-46]
Caparice spinosa	Ethanolic root bark extract, 100, 200 and	CCl_4 induced hepatocellular injury in	showed significant decrease in the levels of serum markers,	[47]

	400 mg/kg bw.	rats	indicating the protection of hepatic cells.	
	aqueous extract, 25, 50, 100, 200 mg/kg bw.	paracetamol-induced liver damage in rats	It decreased alanine amino transferase, aspartate amino transferase activity, total bilirubin and creatinine levels in comparison with non treated group, as well as improving the damaged liver tissues.	[48-49]
Capsella bursa-pastoris	aerial parts crude extractat, 500 mg/kg bw.	CCl_4 induced hepatocellular injury in rats	It showed significant decreases by (26.9 and 31.7 %) respectively, at the dose of 500 mg/kg bw, ($p<0.05$)	[50-51]
Carthmus tinctoriust	methanolic extract, 200 and 300 mg/kg bw.	isoniazid and rifampicin- induced hepatotoxicity	decrease in AST, ALT, ALP, and total bilirubin levels and elevated the level of GSH.	[52]
	hydroxysafflor yellow A, 5 mg/kg	liver fibrosis induced by CCl_4 in rats	It significantly reduced liver fibrosis. It down regulates α-smooth muscle actin (SMA), collagen α type I, matrix metalloproteinases (MMP)-9, and tissue inhibitors of metalloproteinases (TIMP)-1 gene expression, accompanied by a decreased expression of transforming growth factor (TGF)-β1 and phosphorylation.	[53]
	safflower injection	The effect on the lipid peroxidation level and expression of heme oxygenase-1 of the rat liver with chronic hypoxia and hypercapnia in rats.	The activity of SOD of the liver in Safflower injection group was significantly higher than those in chronic hypoxia and hypercapnia for four weeks group, and the content of MDA was significantly lower.	[54-55]
Carum carvi	essential oils of fruits	CCl_4- induced hepatotoicity	It exerted hepatoprotective effect and decreasing oxidative damage.	[56-59]
Cassia occidentalis	aqueous and aqueous ethanolic extract (50% v/v) of leaves	rat liver damage induced by paracetamol and ethyl alcohol	The extract of leaves of the plant produced significant hepatoprotection by restoring the liver functions	[60-63]
	chrysophanol isolated from *Cassia occidentalis,* 50 mg/kg bw and methanol fraction, (200 mg/kg bw.	paracetamol induced hepatotoxicity in rats	The elevated serum enzymatic levels of AST, ALT, ACP and ALP were significantly restored by pre-treatment with chrysophanol and methanol fraction methanol fraction. The histopathological studies also confirmed the hepatoprotective nature of the extracts.	[64]
	aqueous extract of *Cassia occidentalis*, 50, 250, and 500 mg/kg	antimutagenic potential against the chromosomal aberrations (CA) produced *in vivo* by	The chromosomal aberrations produced by B(a)P and CP were significantly reduced ($p<0.001$) by *C. occidentalis* pre-treatment. Animals treated with plant	[65-66]

		benzo(a)pyrene (B(a)P) and cyclophosphamide (CP) in mice.	extract showed a reduced level of cytochrome P450 and elevated levels of glutathione S-transferase activity and glutathione content in the liver.	
Casuarina equisetifolia	methanol extracts of *Casuarina equisetifolia*, 500 mg/kg bw.	liver damage induced in rats by CCl_4	It exhibited moderate protective effect by lowering the serum levels of ALT, AST and cholesterol to a significant extent. The hepatoprotective activity was also confirmed by attenuatation of the histopathological changes associated with CCl_4 induced hepatotoxicity	[67-69]
Celosia cristata	triterpenoid saponin, semenoside A, isolated from Semen *Celosia cristatae*, 1, 2, and 4 mg/kg bw.	CCl_4-induced hepatotoxicity in mice	It exerted significant hepatoprotective effects ($p < 0.01$)	[70]
	cristatain saponin	CCl_4 - and N, N-dimethylformamide (DMF)-induced hepatotoxicity in mice	It showed significant decreases in the values of AST, ALT and ALP of serum and histopathological pathological changes.	[71-72]
Chenopodium album	Extract, 300 and 450 mg/kg bw.	CCl_4- induced hepatotoxicity in rats	It exerted antioxidant effects, inhibited the elevated biochemical parameters and attenuated histopathologic effects associated with induction of hepatotoxicity by CCl_4.	[73]
	alcoholic and aqueous extracts of the aerial parts, 200 and 400 mg/kg bw.	paracetamol induced hepatotoxicity	The aqueous extract at a dose of 400 mg/kg was found to be more potent when compared to Silymarin. The alcoholic and aqueous extracts of *Chenopodium album* significantly restore physiological integrity of hepatocytes.	[74]
	dried whole plant acetone and methanol extracts in ratio of (50:50)	paracetamol induced hepatic injury.	Acetone and methanol extract at adose of 400mg/kg orally, showed significant ($p<0.001$) hepatoprotective activity, their effect was similar to the standard drug, silymarin.	[75-76]
Cicer arietinum	Many extracts of aerial parts, 200 and 400 mg/kg bw.	CCl_4 induced hepatotoxicity in rats.	Pre-treatment of the rats with petroleum ether, methanol and aqueous extract prior to CCl_4 administration caused a significant reduction in the values of SGOT, SGPT, SALP, LPO, total bilirubin and significant increase in SOD, CAT, GSH ($P<0.01$), almost comparable to the Silymarin. The hepatoprotective activity was confirmed by histopathological examination of the liver tissue of control and	[77-78]

			treated animals.	
Cichorium intybus	aqueous-methanolic extract, 500 mg/kg bw.	acetaminophen and CCl_4-induced hepatic damage	Pretreatment of rats with plant extract significantly lowered the respective serum ALP, GOT and GPT levels.	[79].
	root and root callus extracts	CCl_4 induced hepatotoxicity in rats.	The increased levels of serum enzymes (aspartate transaminase, alanine transaminase) and bilirubin were very much reduced in the animals treated with natural root and root callus extracts and CCl_4.	[80]
	esculetin, a phenolic compound found in *Cichorium intybus*, 6 mg/kg bw.	paracetamol and CCl_4-induced hepatic damage in mice and rats.	Pretreatment of rats with esculetin (6 mg/ kg) prevented the paracetamol-induced rise in serum enzymes.	[81]
	methanol extract of chicory (250 and 500 mg/kg) alone or mixed with ginger (250 and 500 mg/kg) (1:1 wt/wt).	CCl_4 induced hepatotoxicity in rats.	Methanol extract of chicory (250 and 500 mg/kg) alone or mixed with ginger (250 and 500 mg/kg) (1:1 wt/wt) significantly restored the carbon tetrachloride-induced alterations in the biochemical and cellular constituents of blood.	[82]
	water extract,70 mg/kg bw.	oxytetracyclin-induced fatty liver	The treatment with chicory ameliorated most of the evaluated biochemical parameters and improved the induced degenerative histopathological changes. The pretreatment with chicory before the induction of fatty liver, gave some protection against experimentally induced fatty liver.	[83]
	aqueous -ethanolic (30:70 %) extract of fresh dried leaves, 100, 200 and 300 mg/kg bw.	Nimesulide intoxicated rats	The significant changes in biochemical parameters (increases in serum SGPT, SGOT, ALP and total bilirubin in Nimesulide intoxicated rats, were restored towards normal values in *Cichorium intybus* leaves extract.	[84]
	Cichotyboside isolated from the seeds of *Cichorium intybus*	CCl_4 induced hepatotoxicity in rats.	It reduced the elevated levels of liver enzymes, SGOT by 52 units/ml; SGPT 38 units/ml; ALKP 24.97 units/ml, with 7.54 g/dl and 5.48 g/dl increase in total protein and albumin.	[85]
	root extract	CCl_4-induced hepatitis in rats.	It normalized some morphofunctional liver features (decreases glycogen content and necrosis and increases the number of cells with pronounced protein synthesis activity. The	[86-88]

			elevated serum markers and liver tissue microvesicular steatosis were significantly reduced.	
	seed extract	hepatic steatosis caused by early and late stage diabetes in rats, and induced in HepG2 cells (*in vitro*) by BSA-oleic acid complex (OA).	The expression levels of sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor alpha (PPARα) were determined. Significant histological damage (steatosis-inflammation-fibrosis) to the cells and tissues and down-regulation of SREBP-1c and PPARα genes that followed steatosis induction were prevented by *Cichorium intybus* seed extract in simultaneous treatment.	[89-90]
Cistanche tubulosa	aqueous ethanol extract of roots, 400 mg/kg bw.	D-galactosamine (D-GalN) /lipopolysaccharide (LPS) -induced liver injury in mice and in primary cultured mouse hepatocytes.	Among the isolated compounds, echinacoside, acteoside, isoacteoside, acetylacteoside, and tubuloside A, inhibited D-GalN-induced death of hepatocytes. These five compounds, and cistantubuloside B also reduced TNF-alpha-induced cytotoxicity in L929 cells.	[90-93].
Citrullus colocynthis	methanolic extract, 200 and400 mg/kg bw.	nitrosodiethylamine induced hepatic damage in male rats.	significantly reduced the biochemical alterations induced by DEN/PB	[94-95].
Citrus species	methanolic extract and aqueous extract of *Citrus aurantifolia*, 500 mg/kg bw.	Aflatoxin B1 (AFB1)-induced liver injury in rat model.	The treatment was significantly inhibited DNA fragmentation. Nucleus structures were well maintained. The results demonstrate that *Citrus aurantifolia* has a cytoprotective effect against AFB1-induced liver injury	[96]
	ethanol extract of *Citrus limon* fruits, 150, 300 and 500 mg/kg bw.	Hepatoprotective effect was evaluated in CCl_4-induced hepatitis in rats and HepG2 cell line.	Ethanol extract normalized the levels of SGOT, SGPT, alkaline phosphatase, and total and direct bilirubin. The treatment also significantly raised the levels of antioxidant enzymes superoxide dismutase and catalasein the liver tissue. It improved the reduced glutathione levels in treated rats. The treated rats also exhibited restoration of the liver architecture toward normal. Significant reduction in cell viability was observed in cells exposed to CCl_4. A dose-dependent increase in the cell viability was observed when CCl_4-exposed HepG2 cells were	[97-98]

			treated with different concentrations of ethyl acetate soluble fraction of the ethanol extract.	
	orange essential oils	CCl_4 induced hepato-toxicity in rats.	Orange essential oils significantly reduced the serum ALT level when compared to CCl_4 group	[99]
Clerodendron inerme	ethanolic extract, 200 mg/kg bw.	paracetamol induced liver damage in rats.	It possessed significant protective effect by lowering serum levels of glutamicoxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase and total bilirubin.	[100-101]
Clitoriaternatae	petroleum ether, chloroform, and methanol extracts of roots of blue and white flowered varieties.	CCl_4 - induced hepatotoxicity in rats.	The substantially elevated serum enzymatic levels of serum transaminases, alkaline phosphatase and total bilirubin were significantly restored towards normalization with the plant extracts.	[102-103].
Convolvulus arvensis	ethanolic extract, 200 and 500 mg/kg bw.	paracetamol-induced hepatotoxicity in mice	It produced significant ($p<0.05$) decrease in paracetamol induced increased levels of liver enzymes and total bilirubin.	[104-105].
Cordia myxa	several extracts of *Cordia myxa*	CCl_4 and thioacetamide (TA)- induced oxidative damage in rats	A significant (P=0.05) liver recovery was noticed when animals treated with CCl_4/TA were fed with CM extracts.	[106-107]
	extracts by different solvents, 50-500mg/kg)	liver fibrosis induced by carbon tetrachloride or thioacetamide (TA) in rats.	The AST, ALT and ALP were significantly improved in rats after administration of (CCl_4) + CM, or (TA) + CM	[108]
Coriandrum sativum	aqueous extract	paracetamol-induced hepatotoxicity	It showed significant improvement in all biochemical parameters, which become near to control, the results were confirmed by histopathological examination of the liver tissue.	[109-110]
	aqueous extract of, 100 and 200mg/kg bw.	CCl_4 treated oxidative stress in rats.	It significantly lowered SGOT, SGPT and TBARS levels against CCl_4 treated rats. Hepatic enzymes like SOD, CAT, GPx were significantly increased by treatment with plant extract against CCl_4 treated rats.	[111]
	ethanol extract of leaves, 300 mg/kg	CCl_4 induced hepatotoxicity	It possessed hepatoprotection by reducing the liver weight, activities of SGOT, SGPT, and ALP, and direct bilirubin of CCl_4 intoxicated animals	[112]
	Essential oils of *Coriandrum sativum*	assayed for their *in vitro* and *in vivo* antioxidant activity and	The essential oils reduced the stable DPPH in a dose-dependent manner and neutralize H_2O_2, with	[113]

		hepato-protective effect against CCl_4 damage	IC_{50} values of 4.05 microl/ml.	
Crocus sativus	saffron extract, 30 mg/kg, or crocin, 30 mg/kg bw. ,	chronic - stress induced oxidative stress damage of the brain, liver and kidneys in rats.	Both saffron extract and crocin were able to reverse these changes in the stressed animals as compared with the control groups ($P<0.05$). These observations indicate that saffron and its active constituent crocin can prevent chronic stress-induced oxidative stress damage.	[114-115]
	hydroalcoholic extract of *Crocus sativus* petals, 10 and 20 mg/kg bw.	Acetaminophen (APAP) -induced hepatotoxicity	The administration of 20 mg/kg resulted in lower levels of AST, ALT and bilirubin, with a significant higher concentration of total protein and albumin and normalized the histological changes.	[116]
	saffron ethanol extract (SEE)	hepatic ischemia-reperfusion injury in rats.	Pretreatment with SEE significantly restored the content of antioxidant enzymes (SOD and catalase) and remarkably inhibited the intracellular ROS concentration in terms of reducing p47phox translocation. SEE administration also attenuate the carbonylation level of several chaperone proteins.	[117]
	ethanolic extract of *Crocus sativus* stigma (EECSL.S), 40 and 80 mg/kg bw.	rifampin-induced hepatotoxicity in rats.	EECSL.S (40 and 80 mg/kg) significantly decreased the levels of serum biomarker of hepathic injury and total bilirubin and elevated the levels of albumin and total proteins. Histopathologically, EECSL.S ameliorated rifampin induced hepatic injury.	[118]
	crocin dyes, 50 mg/kg bw.	aflatoxin B1 hapatotoxicity in rats	It reduced hepatic (AST, ALT, ALP and γ-GGT) via its antioxidant activity.	[119]
Crotalaria juncea	petroleum ether extract, 100 and 500mg/kg bw.	thioacetamide induced acute hepatic damage in rats	*Crotalaria juncea*seed extract possessed hepatoprotective potency in a dose dependent manner by reducing the elevated levels of marker enzymes and by increasing the decreased antioxidant enzyme activity.	[120-121].
Cuminum cyminum	Aqueous seed extract, 100 mg/kg bw.	profenofos induced nephrotoxicity in mice	Cumin was effective in normalizing the uric acid and creatinine level.	[122-123]
	6% *Cuminum cyminum* fruit diet	Depression in growth, hepatotoxicity and nephrotoxicity were observed in rats that	The recovery of paracetamol hepatotoxicity was evidenced by increase in body weight, absence of hepatocellular fatty	[124]

		had been given paracetamol at 500 mg/kg orally for 4 weeks	vacuolation and significant improvement of serbiochemical and hematological parameters.	
Cupressus sempervirens	methanol leaves extract, 300 mg/kg bw.	CCl_4 hepatotoxicity in rat	Treatment with extract ameliorated the levels of the disturbed biochemical parameters **(**serum total proteins, albumin**,** urea, creatinine, LDH**).** Histopathological liver & kidney profiles f the treated animals were close to those of the control group.	[12((125-126)
	hydroethanolic extract, 250 mg/kg bw.	Paracetamol- induced hepatotoxicity	It caused marked decline in the DNA fragmentations and inhibition in the percentage of chromosomal aberrations in bone marrow cells.	[127]
Cuscuta planiflora	methanolic extract of whole plant	CCl_4 - induced hepatotoxicity in rats.	It possessed significant hepatoprotective activity against CCl_4 induced hepatotoxicity by suppressing CCl_4 induced cellular oxidative stress.	[128]
Cynodon dactylon	methanolic extract of roots, 50 mg/kg bw.	diethyl nitrosamine (DEN) induced liver cancer in mice	A highly significant (p<0.01) elevation in GPx activity was observed in DEN treated mice, whereas DEN + *Cynodon dactylon* showed low significant alteration, while saline and DEN + tamoxifen treated animals did not show any significant alteration. DEN, DEN + *Cynodon dactylon* showed low significant depletion (p<0.05) in liver CAT activity with respect to control.	[129]
	Alcoholic extracts of roots, 100mg/kg bw.	CCl_4 induced hepatotoxicity in rabbits.	*Cynodon dactylon* extract was able to bring down the level of serum transaminase, serum alkaline phosphatase, serum bilirubin and increased in serum albumin significantly (p<0.001).	[130]
Cyperus rotuntdus	hexane fraction of *Cyperus rotundus* rhizome extract	cellular lipogenesis and non-alcoholic/diet-induced fatty liver disease,.	It reduced the elevated transcription levels of sterol regulatory element binding protein-1c (SREBP-1c) in primary hepatocytes following exposure to the liver X receptor α (LXRα) agonist.	[131-132]
Datura **species**	Datura seed extract (DSE) , 7.5 mg/kg bw.	in organophosphate (OP) poisoning in rats.	Median survival time was 22 minutes 30 seconds for the control group and greater than 24 hours for the DSE-pretreated group.	[132]
	leaves ethanolic extract	acute carbaryl toxicity in rats	Tropane alkaloids contents of *Datura stramonium* abolished	[133-134]

			carbaryl cholinergic toxic effect by blocking the muscarinic receptors of parasympathetic nerve ending and increased survival rate.	
Dacus carota	Seeds extract	thioacetamide induced oxidative stress in rats.	A significant decrease in SGPT, SGOT and ALP levels was observed in extract treated groups as compared to thioacetamide group ($P < 0.001$), furthermore, significant ($P < 0.001$) increase in SOD, CAT, GRD, GPX and GST was observed in extract treated groups as compared with thioacetamide group.	[135-139]
	carrot extract	CCl_4-induced acute liver damage in mice	The extracts significantly lowered the serum levels of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, sorbitol, glutamate dehydrogenase, bilirubin and urea, elevated by CCl_4-induction. The increased activities of hepatic 5'-nucleotidase, acid phosphatase, acid ribonuclease and decreased levels of succinic dehydrogenase, glucose-6-phosphatase and cytochrome P-450 produced by CCl_4 were reversed by the extract in a dose-responsive way.	[140]
	kaempferol isolated from *Daucus carota* leaves, 100 and 200 mg/kg bw.	paracetamol induced liver damage of rats.	Paracetamol induced significant ($P<0.05$) increase in liver enzymes along with hepatic necrosis and other visible disarrangements in hepatic tissues. Oral treatment with kaempferol reversed to all the serum and liver parameters, dose-dependently.	[141]
Desmostachia bipinnata	polyphenolic fraction of root (PFDB).	tamoxifen-induced hepatotoxicity in female rats.	Pretreatment with PFDB exhibited a significant ($P \leq 0.05$) protective effect by lowering liver enzymes, triglycerides, cholesterol, urea, uric acid, bilirubin and creatinin levels and improving protein level in serum in dose-dependent manner. In addition, PFDB prevented elevation of reduced glutathione, glutathione peroxidase, superoxide dismutase and catalase in the tamoxifen-intoxicated rats in concentration-	[142].

			dependent manner and significantly ($P < 0.05$) reduced the lipid peroxidation in the liver tissue.	
	roots extract, 100 and 200mg/kg bw.	paracetamol- induced liver damage in rats	It showed significant reduction in the elevated level of serum marker enzymes, MDA, LH, bilirubin and significant improvement in the antioxidant enzymes when compared to paracetamol damaged rats.	[143]
***Digitalis* species**	Four different glycosides (acteoside, purpureaside A, calceolarioside B and plantainoside D)	to induce glutathione S-transferase (GST) and their protective efficiencies against aflatoxin B1-induced cytotoxicity	Acteoside significantly inhibited the cytotoxicity induced by aflatoxin B1 (AFB1) and also selectively increased GSTalpha protein levels. Reporter gene analysis using an antioxidant response element (ARE) containing construct and subcellular fractionation assays, revealed that GST alpha induction by acteoside might be associated with Nrf2/ARE activation	[144-147]
Dodonaea viscosa	crude leaves of *D.viscosa*, 100 mg/100 g bw.	lead acetate induced synthesis of glycoproteins and sialic acid in liver and plasma.	It effectively suppressed the synthesis of glycoproteins and sialic acid in liver and thereby controlling the concentration in plasma.	[148-149].
Dolichos lablab	Dolichos lablab water extract (DLL-Ex)	in vitro cellular model in which nonalcoholic fatty liver disease (NAFLD) was simulated by inducing excessive FFA influx into hepatocytes.	DLL-Ex significantly attenuated FFA-mediated cellular energy depletion and mitochondrial membrane depolarization. In addition,, It enhanced phosphorylation of AMPK, indicating that AMPK is a critical regulator of DLL-Ex-mediated inhibition of hepatic lipid accumulation	[150-151].
***Ephedra* species**	crude extract, 250 and 500 mg/kg bw.	CCl_4 induced hepatotoxicity in rats	At the lower doses (250 mg/kg) the extract treatment resulted in a significant reduction in SGOT, ALP and bilirubin.	[152-153].
Equisetum arvense	Methanol extract	tacrine-induced cytotoxicity in human liver-derived Hep G2 cells	It appeared that onitin and luteolinisolated from the methanolic extract of *Equisetum arvense* possessed hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells.	[154-155].
Eupatorium cannabinum	aqueous extract (125, 250, 500 and 1000 mg/kg bw.	$CC1_4$-induced hepatotoxicity .	It showed a significant decrease of GPT levels at 250, 500, and 1000 mg/kg.	[156-157]
	aqueous extract	$CC1_4$-induced hepatotoxicity .	It exhibited anti-necrotic activity against carbon tetrachloride-induced hepatotoxicity in rats.	[158]

			The effect is attributed to the presence of flavonoids, rutoside, hyperoside and quercetin; phenolic acids, caffeic and chlorogenic.	
Euphorbia hirta	hydroalcoholic extract of whole *Euphorbia hirta* extracts, 125 and 250 mg/kg bw.	CCl_4 or paracetamol induced liver injury in rats.	Serum levels of alanine aminotransferase and aspartate aminotransferase in rats given the 125 mg/kg bw of the extracts were significantly lower ($p<0.05$ and 0.01 respectively)	[159-160]
Foeniculum vulgare	essential oils, 200 and 400 mgkg bw.	CCl_4- induced fibrosis in rats.	It showed a significant protection against induced increase in serum liver enzyme (AST,ALT, ALP), restored total protein level and ameliorate the increased triglycerides, total, cholesterol, LDL and decreased the HDL.	[161-162]
	whey protein concentrate (WPC) (0.5g/kg/ bw day) or fennel seed extract (FSE) (200mg/ kg/ bw day).	paraoxonase-1 activity (PON1) and oxidative stress in liver of tienilic acid (TA) treated rats.	WPC or FSE significantly protected the liver against the injurious effects of tienilic acid. This appeared from the improvement of hepatic functions, atherogenic markers, Na^+/K^+-ATPase activity, endogenous antioxidants and hepatic lipid peroxidation level.	[163-166]
Fumaria officinalis	ethanolic extract, 200 and 500 mg/ kg bw.	CCl_4- induced liver injury in rats.	It induced significant ($p<0.001$) hepatoprotective effect by reducing the serum marker enzymes like SGPT, SGOT, ALP. Extract also reduced the elevated levels of serum total and direct bilirubin, cholesterol and triglycerides.	[167]
Fumaria parviflora	ethanol extract of the aerial part , 250 mg/kg bw.	CCl_4 - induced liver injury in rats.	The extract possessed hepatoprotective effects based on serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase and total bilirubin. The normal histological appearance of hepatocytes indicated a good protection of the extract against CCl_4 hepatotoxicity.	[168]
	Fumaria parviflora extracts, 200 mg/kg bw.	on nimesulide induced cell in primary rat hepatocyte cultures and in rats fed with nimesulide.	*Fumaria parviflora* extract treated cells showed increased viability as compared to nimesulide stressed cells as assessed by MTT assay. The data suggested that apoptosis was the predominant mechanism responsible for cell death. In in vivo study, it significantly reduced the impact of nimesulide induced	[169-170]

			toxicity as evident from the serum biomarkers of liver damage and histopathology. It also modulated antioxidant enzymes mRNA expression as well as activity (SOD, glutathione peroxidase, glutathione reductase) and reduced lipid peroxidation during nimesulide toxicity.	
	aqueous-methanolic extract, 500 mg/kg bw.	paracetamol- and CCl_4-induced hepatic damage in rats.	Pretreatment of rats with plant extract (500 mg/kg, orally twice daily for 2 days) prevented ($P < 0.001$) the paracetamol (640 mg/kg)- induced rise in serum enzymes alkaline phosphatase and transaminases (GOT and GPT), whereas the same dose of the extract was unable to prevent ($P > 0.05$) the CCl_4-induced rise in serum enzyme levels. Posttreatment with 3 successive doses of the extract (500 mg/kg, 6 hourly) also restricted the paracetamol-induced hepatic damage.	[171-172]
Galium aparine	mixture of *Berberis lycium, Galium aparine* and *Pistacia integerrima*	CCl_4-induced hepatic toxicity in rats.	The results indicated that a mixture of *Berberis lycium*, *Galium aparine* and *Pistacia integerrima* possessed hepatoprotective effects through correction of biochemical parameters.	[173]
Galium verum	*Galium verum* (I and II dry extracts, 25 mg/kg bw).	CCl_4-induced acute hepatitis in rats	I and II extracts at the dose of 25 mg/kg decreased activities of serum ALT, AST, and ALP.	[174-175]
Geum urbanum	A-Hepatica is an herbal combination (contained ten herbs included *Geumurbanum* (Clove root- 6.5 ml)	detoxification of the liver	A-Hepatica regulates secretion and absorption in the digestive system, has anti-inflammatory and antispasmolytic function in the portal vein, stimulates bile flow and increases detoxification of the liver.	[176]
Glycyrrhiza glabra	aqueous and ethanol extract, 250, 500 mg/kg bw.	CCl_4- induced hepatotoxicity in rats	Both extracts inhibited the activities of AST and ALT which elevated by CCl_4 and increased the activity of superoxide dismutase which decreased by CCl_4.	[177]
	aqueous extract, 2gm/kg bw.	CCl_4- induced liver injury in rabbits.	It possessed significant effect in amiolerating liver functions as well as restoring hepatic tissue in acute liver diseases.	[178]
	hydromethanolic extract, 300 and 600mg/kg bw.	CCl_4-induced oxidative-stress mediated hepatotoxicity in liver	It possessed significant hepatoprotective potential against CCl_4 induced oxidative	[179-180]

		tissue of mice	stress mediated hepatotoxicity ($p<0.05$).	
	of intravenous glycyrrhizin, 100 ml/day	in the early stage of acute onset autoimmune hepatitis was studied clinically	administration of sufficient doses of intravenous glycyrrhizin prevented disease progression in patients with acute onset autoimmune hepatitis	[181]
	methanol extract, 1 g/kg bw.	on the metabolism of acetaminophen in male rats	significantly increased the cumulative biliary (156%) and urinary (132%) excretions of acetaminophen, glucuronide conjugate within 120 min after the administration of acetaminophen (150 mg/kg, iv) without affecting thioether and sulfate conjugates. Glycyrrhiza glabra and glycyrrhizin caused increases in specific activities of UGT1A by 111% and 96%, respectively. Concentration of UDP-glucuronic acid was increased 257% by Glycyrrhiza glabra and 484% by glycyrrhizin.	[182]
***Gossypium* species**	*Gossipium hirsutum* extracts	studied in acute experimental hepatic injury in rats	*Gossipium hirsutum* extracts significantly decrease the serum transaminase activities ($P < 0.01$), increased the SOD activities ($P < 0.01$) and decreased MDA content.	[183-184]
Hedera helix	α-, β-, and δ-Hederin	the clastogenicity of doxorubicin and *in vitro* antimutogenicity test.	α-Hederin exerted an antimutagenic effect against the clastogenicity of doxorubicin. α-, β-, and δ-Hederin from *H. helix* were found non-mutagenic; it even showed antimutagenic activity in a dose dependent manner against known promutagens: benzo(α)pyrene (1 µg) and mutagenic urine concentrate from a smoker.	[185-187]
Helianthus annuus	ethanolic and flowers aqueous extracts, 200mg/kg bw.	CCl_4 induced hepatotoxicity in rats.	They significantly ($p<0.001$) reduced elevated serum enzymatic level, AST and ALT, ALP and total bilirubin . The biochemical effects were further confirmed by histopathology.	[188-192]
Heliotrpium undulatum	n- butanol extract, 200 mg/kg bw.	acetylhydrazide (ACHD) induced hepatotoxicity in rats.	It decreased LPO levels, the transaminase and ALP levels and restored the GSH and its related enzymes (GPx, GST, GR) (50-62 %).	[193]
Hibiscus cannabinus	aqueous leaf extract, 1.6 g/ kg bw.	CCl_4 and paracetamol induced hepatotoxicity in rats.	possessed significant ($p<0.05$) hepatoprotective activity against hepatic damage represented by lowering the plasma transaminases and bilirubin	[194-195].

			concentration significantly ($p<0.05$), absents of necrosis in liver cells of rats pretreated with extrac and inhibition of lipid peroxidation.	
Hibiscus rosa-sinensis	*Hibiscus rosa sinensis* sinensis petal partially purified anthocyanin extract	carbon tetrachloride-induced lipoperoxidation	possessed a hepato protective effects biochemically and histologically	[196-198]
	flower extracts (HRS) (acute :80mg, 160 and 240 mg / kg bw.	diet induced hypercholesterolaemic rat hepatocytes.	The body weight was increased in cholesterol fed experimental animals which was reversed with HRS fed groups. There was a dose dependent increase in serum hepatic marker enzymes and total protein levels significantly ($p>0.001$) in the cholesterol fed groups and reversed with HRS flower extract fed acute ($p>0.005$) and chronic ($p>0.001$) groups.	[199]
	alcoholic leaf extract, 30 mg/kg bw.	piroxicam-induced toxicity in mice	AEH used in a combination with piroxicam treatment retrieved or partially antagonized the effects induced by piroxicam toward the normal values. Histopathological observations also corroborate with the protective effects of AEH.	[200-201]
Hibiscus sabdariffa	water extract of the dried flowers, 50, 100 and 200 mg/kg bw.	paracetamol-induced hepatotoxicity in rats.	At a dose of 200 mg/kg, the hepatic histology and the biochemical indices of liver damage were restored to normal.	[202]
	Dried flower *Hibiscus sabdariffa* (HSE) extracts ,1-5%	liver fibrosis induced by CCl_4 in rats.	It significantly reduced the liver damage including steatosis and fibrosis in a dose dependent manner. HSE also significantly decreased the elevation in plasma AST and ALT and restored the decrease in glutathione content and inhibited the formation of lipid peroxidative products.	[203]
	aqueous extract	Cd induced hepatotoxicity in rats.	Aqueous extract of *H. sabdariffa* resulted in significantly less hepatotoxicity than with Cd alone as measured by plasma ALT and liver ALT and AST activities.	[204]
	anthocyanin-rich extract of *H. sabdariffa* calyces (HSARE), 100 mg/kg bw.	thioacetamide (TAA)-induced hepatotoxicity in rats.	HSARE significantly reduced the serum levels of AST, ALT and hepatic malondialdehyde by 37.96, 42.74 and 45.31%, respectively. It also decreased hepatic inflammatory markers: tumour necrosis factor alpha,	[205]

			interleukin-6 and interferon gamma (INF-γ), by 85.39, 14.96 and 70.87%, respectively.	
	Hibiscus sabdariffa extract 200, 400 and 600 mg/kg bw.	acetaminophen - induced liver injury in mice.	decreased lipid peroxidation and increased catalase activity, glutathione level and decreased pathological changes in liver.	[206]
	polyphenol extract (HPE), 100, 200 and 300 mg/kg bw.	acetaminophen - caused liver damage in mice.	The pretreating with HPE increased the level of glutathione (GSH), decreased the level of lipid peroxidation, and increased catalase activity in the liver. Histopathological evaluation showed that HPE decreased AAP-induced liver sterosis accompanied by a decreased expression of AIF, Bax, Bid, and p-JNK in the liver.	[207]
	H. sabdariffa extract	Chemical induced toxicities including hepatotoicity.	Administering of *H. sabdariffa* extract at the doses of 300 and 600 mg/kg caused the reversal of the pathological effects induced by chemical intoxication.	[208-212]
***Hyoscyamus* Species**	methanolic extracts of leaves.	hepatotoxicity induced by CCl_4.	It reduced the biochemical markers TGO, TGP, ALP and BT elevated by CCl_4. Histological lesions induced by CCl_4 (necrosis , inflammatory cells infiltration and the congestion of the centrolobular vein) were absent in the group treated with *Hyoscyamus albus* extract.	(213)
Hypericum triquetrifolium	*Hypericum triquetrifolium* extract 25, 50 and 100 mg/kg bw.	cyclophosphamide - induced hepatotoxicity.	It decreased the levels of AST, ALT, ALP, LDH, TOS and OSI. Liver histological gave further evidence for the protective effect of *Hypericum triquetrifolium*.	[214-215].
Juglans regia	polyphenol-rich fraction (WP, 45% polyphenol), 200 mg/kg bw.	liver injury induced by carbon tetrachloride	It significantly suppressed serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) elevation in liver injury induced by carbon tetrachloride	[216]
Juniperus communis	ethyl acetate fraction (EAF) of *Juniperus communis* leaves.	paracetamol-induced hepatic damage in rats.	Extract treated group shows remarkable decrease in serum Aspartate aminotransferase, serum Alanine aminotransferase, total bilirubin, direct bilirubin, and alkaline phosphatase level.	[217-218]
	ethanolic fruits extract of *Solanum xanthocarpum* (SX) and *Juniperus communis* (JC)	paracetamol (PCM) and azithromycin (AZM) induced liver toxicity in rats.	Chronic treatment of SX and JC extract significantly and dose-dependently attenuated the liver toxicity by normalizing the biochemical factors and	[219]

			histopathological changes.	
Jussiaea repens	*Jussiaearepens* etract, 200 mg/kg bw.	*Schistosoma mansoni* infection.	The elevation of malondialdehyde (MDA) and glutathione (GSH) levels in liver homogenate (6- and 2-folds, respectively) of animals infection with *Schistosoma mansoni*, was significantly reduced by 50% and 41% on treatment with the low dose of extract (100mg/kg bw). The percentage of this reduction was increased at the high dose (200mg/kg bw) in comparison with silymarin.	(220)

CONCLUSION

Hepatotoxicity, or liver damage, is caused by hepatotoxins, which may source from chemicals, dietary supplements and pharmaceutical drugs. Many medicinal plants showed hepatoprotective activity by different mechanisms. The current review will discuss the medicinal plants possessed hepatoprotective effects.

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