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Medicinal plants possessed hepatoprotective activity

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ABSTRACT: In this study, online databases including Web Science, PubMed, Scopus and Science Direct, were searched for papers studied the hepatoprotective effects of medicinal plants against carbon tetrachloride, D-galactosamine (D-GalN), D-galactosamine (D-GalN)/ lipopolysaccharide (LPS), N, N-dimethylformamide (DMF), oxytetracyclin thioacetamide (TAA), nitrosodiethylamine, paracetamol, rifampin, INH, aflatoxins, iron-overload and oxidative stress induced hepatotoxicity and against hepatic cancer induced chemically.

Keywords: Medicinal plants, Hepatoprotective, Therapeutic, Pharmaceutical

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I. INTRODUCTION:

The preventive activities focus on maintaining the health of individuals with chronic conditions, delaying progression of their conditions, and preventing complications. 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. Medicinal plants possessed hepatoprotective activity through many mechanisms, included antioxidant properties of medicinal plants, enhancement of antioxidant defense (superoxid dismutase, catalase and glutathione peroxidase activity)[(1-2)], reduced peroxidation[(3-4)], reversed hepatic fibrosis via enhancement of the expression of matrix metalloproteinase and removal of collagen deposits, with attenuation of hepatic stellate cells activation[(5)], their antiinflammatory activity and attenuation of many inflammatory processes, antifibrotic properties of plants and stimulation of extracellular matrix degradation[(1)]. The current review discuss the medicinal plants possessed hepatoprotective activities in liver injury induced by many agents with explanation of their mechanism of action.

Medicinal plants with hepatoprotective effects:

Agrimonia eupatoria

The hepatoprotective effects of Agrimonia eupatoria water extract (AE) was studied in chronic ethanol-induced liver injury in rats. Animals were treated orally with AE at 10, 30, 100, and 300 mg/kg/day. After chronic consumption of ethanol, serum aminotransferase activities and pro-inflammatory cytokines markedly increased, and those increases were attenuated by AE. The cytochrome P450 2E1 activity and lipid peroxidation increased after chronic ethanol consumption, while reduced glutathione concentration decreased. Those changes were attenuated by AE. Chronic ethanol consumption also increased the levels of Toll-like receptor 4 (TLR4) and myeloid differentiation factor 88 protein expression, inducible nitric oxide synthase and cyclooxygenase-2 protein and mRNA expression, and nuclear translocation of nuclear factor-kappa B, which was attenuated by AE. The results revealed that AE ameliorates chronic ethanol-induced liver injury, and that protection is likely due to the suppression of oxidative stress and TLR-mediated inflammatory signaling[(6-7)].

Alhagi maurorum

The hepatroprotective effect of Alhagi maurorum aerial parts ethanol extract was studied using Wistar albino rats. Liver injury induced in rats by carbon tetrachloride. The normal appearance of hepatocytes and correction of serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and total bilirubin, indicated a good protection of the extract from carbon tetrachloride hepatotoxicity. The results were compared with silymarin, the reference hepatoprotective drug [(8)]. Administration of 660 mg/kg of the ethanolic Alhagi maurorum extract to mice, showed a significant decrease in the level of transaminases in animals treated with a combination of ethanolic Alhagi maurorum extract plus carbon tetrachloride (CCl_4) or acetaminophen as compared to animals receiving CCl_4 or acetaminophen alone. Histopatological investigation also confirmed that, Alhagi maurorum extract protects liver against damage-induced either by carbon tetrachloride or acetaminophen[(9-10)]. Alhagi maurorum extract (oral daily 100mg/kg

body weight) in rats protect liver enzymes, oxidation status (MDA and GSH), fucosidase tumor marker and risk lipid ratio[11-12].

Allium sativum

The antihepatic toxicity of garlic was investigated experimentally in rats, CrCl3 alone increased serum levels of AST and ALT. However , garlic inhibited the hepatotoxicity of CrCl3 , and the concomitant use of garlic and CrCl3 decreased the levels of AST and ALT when garlic used in a dose of 60 and 120 mg /kg and CrCl3 is 8 mg /kg[13-14].

Anchusa strigosa

The aqueous and ethanolic extracts of Anchusa strigosa were studied to inhibit aryl hydrocarbon hydroxylase activity (AHH) and 3H-benzo (a) pyrene (3H-BP) binding to rat liver microsomal protein. The 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

Burdock was shown to suppress the CCl_4 or acetaminophen-intoxicated mice as well as the ethanol plus CCl_4-induced rat liver damage. The underlying hepatoprotective ability of burdock could be related to the decrease of oxidative stress on hepatocytes by increasing glutathione (GSH), cytochrome P-450 content and NADPH-cytochrome C reductase activity and by decreasing malondialdehyde (MDA) content, hence alleviating the severity of liver damage based on histopathological observations[17-19].

Astragalus hamosus

The hepatoprotective activity of flavonoid rhamnocitrin 4'-β-D-galactopyranoside (RGP) obtained from leaves of Astragalus hamosus L. was documented against N-diethylnitrosamine (DENA)-induced hepatic cancer in Wistar albino rats[20-21].

Bauhinia variegata

The ethanolic extract of the stem of B. variegata showed chemoprevention against N-nitrosodiethylamine induced experimental liver tumor in rats. Ethanolic extract suppressed liver tumor induced by N-nitrosodiethylamine as revealed by decrease in N-nitrosodiethylamine induced elevated level of serum glutamate pyruvate transaminase, serum glutamate oxaloacetate transaminase, alkaline phosphatase, total bilirubin, gamma glutamate transpeptidase, lipid peroxidase, glutathione peroxidase and glutathione-S-transferase. The ethanolic extract of the stem bark of B. variegate (at the dose of 100 and 200 mg/kg orally) showed hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in rats, it decreased the level of AST, ALT, ALP and GGT[21-22].

Brassica nigra

The protective effect of the methanol extract of Brassica nigra leaves was investigated against D-galactosamine (D-GalN)-induced hepatic and nephrotoxicity in Wistar rats. The D-GalN-induced toxicity was evident from a significant increase ($p < 0.001$) in the serum and tissue inflammatory markers in toxic rats, when compared with the control (saline alone treated animals). The Brassica nigra pretreated groups (200 and 400 mg/kg bw) showed significant ($p < 0.001$) reduction in the DGalN-induced toxicity as obvious from biochemical parameters. Histopathological observations confirm the protective effect of Brassica nigra leaf extract by reduction in hepatic and renal tissue damage. Accordingly, the crude methanol extract of Brassica nigra leaf lacks inherent toxicity and exhibits hepatic and nephroprotective[23-24].

Brassica rapa

The pre-treatment of rats with Brassica rapa juice protected the rats against CCl_4-induced hepatotoxicity. The treatment significantly reduced the serum GOT, GPT, alkaline phosphatase (ALP) and bilirubin level at a dose of 16 ml/ kg bw. In addition, the juice was also replenished the lowered nonprotein sulfhydryl (NP-SH) concentration in the liver tissue after $CC1_4$ treatment[25]. The protective effect of turnip root ethanolic extract (TREE) on early hepatic injuries was studied in alloxan-induced diabetic rats. TREE treatment groups received TREE (200 mg/kg) daily for 8 weeks through the gavage. TREE significantly decreased the levels of serum biomarkers of hepatic injury. Furthermore, it significantly decreased the lipid peroxidation and elevated the decreased levels of antioxidant enzymes in diabetic rats. The study also showed that histopathological changes were in agreement with biochemical findings[26]. The effect of aqueous extract of Brassica rapa chinensis (250, 500 mg/kg, po) against the oxidative stress induced by Tertbutyl hydroperoxide (t-BHP) in rats. The treatment with aqueous extract of Brassica rapa chinensis 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. The results obtained were dose dependent with 500 mg/kg bw, dosage of Brassica rapa chinensis aqueous extract revealing more potential in curbing toxic insult of t-BHP[27-28]. The anti-fibrogenic and the therapeutic effect of turnip extracts was studied in thioacetamide (TAA)- induced liver fibrosis animal model. Anti-fibrogenic effect was demonstrated histopathologically and serologically after the animals fed with turnip extracts with synchronous TAA injections for 7 weeks. The animals fed with 20 mg/ml of turnip extracts showed the highest anti-fibrogenic effect[29]. The level of hepatic fibrosis induced by thioacetamide (TAA) was compared among TAA-turnip group, TAA group, and vehicle control group. Nodules-formed by TAA were observed; they were rarely shown in vehicle control group, observed in most area in TAA group, but only shown in periportal regions in TAA-turnip group. These results were confirmed through Masson's trichrom stain; fibrous structures increased in TAA group (fibrosis score: 4) but significantly decreased in TAA-turnip group (fibrosis score: 2-3)[39]. Isorhamnetin 3-O-glucoside, which was contained together with isorhamnetin 3,7-di-O-glucoside in the plant leaves, suppressed increases in the plasma ALT and AST activities of mice with liver injury induced by the injection of carbon tetrachloride, but no suppression by isorhamnetin 3,7-di-O-glucoside was apparent. This result indicates that the release of glucose at the 7-position in isorhamnetin 3,7- di-O-glucoside was very important to mitigating liver injury[30].

Bryonia dioica

The plant leaves extract was evaluated for its protective effect in hepatotoxicity induced in rats with CCl_4. Single oral dose of 250mg/kg of different fractions extract was given to rats for 7 days. Serum activities of transaminases (ALT and AST) were used as the biochemical marker of hepatotoxicity. Histopatholigical changes in rat's liver section were also examined. The results indicated that pretreatment of rats with Bryonia extract prior to induction of hepatotoxicity offered a hepatoprotective action[31-32].

Bryophyllum calycinum

The juice of the leaves and the ethanolic extract of the marc left after expressing were studied in rats against CCl_4-induced hepatotoxicity. It was found that they were effective hepatoprotective as evidenced by in vitro, in vivo and histopathological studies. The juice was found to be more effective than the ethanolic extract[33-34].

Caesalpinia crista

The hepatoprotective and antioxidant effect of the methanol extract of Caesalpinia crista was evaluated in albino rats. The methanolic extract of Caesalpinia crista at the doses of 50, 100 and 200 mg/kg and silymarin 25 mg/kg were administered to the CCl_4 treated rats. The effect of the methanol extract of Caesalpinia crista and silymarin on serum glutamyl pyruvate transaminase, serum glutamyl oxalacetic acid transaminase, serum alkaline phosphatase, bilirubin, uric acid and total protein were measured in the CCl_4 induced hepatotoxicity in rats. Furthermore, the effects of the extract on lipid peroxidation (LPO), enzymatic antioxidant (superoxide dismutase and catalase), and non enzymatic antioxidant (glutathione (GSH), vitamin C and vitamin E) were estimated. The methanol extract of Caesalpinia crista and silymarin 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]. The ameliorating effect of Caesalpinia crista Linn. (CCME) extract on iron-overload-induced liver injury was investigated. CCME attenuated the percentage increase in liver iron and serum ferritin levels when compared to control group. CCME also 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 were detected in CCME-treated group. In presence of CCME, the reductive release of ferritin iron was increased significantly. Furthermore, CCME exhibited DPPH radical scavenging and protection against Fe2+-mediated oxidative DNA damage[36-37].

Calendula officinalis

The hepatoprotective effect of calendula flowers and/or thyme leave extracts on aflatoxins (AFs)-induced oxidative stress, genotoxicity and alteration of p53 bax and bcl2 gene expressions were evaluated. Animals treated with the extracts 1 week before AFs treatment showed a significant decrease in oxidative damage markers, micronucleated cells, DNA fragmentation and modulation of the expression of pro-apoptotic genes[38]. The hydroalcohol extract of the flowers, when given to CCl_4-intoxicated liver in albino male Wistar rats at a dose of 10 ml/kg, resulted in a reduction of hepatocytolysis by 28.5 % due to reduction in glutamo-oxalate-transaminase (GOT) and glutamo-pyruvate-transaminase (GPT). Histoenzymology showed reduction of steatosis of lactate dehydrogenase (LDH), succinate dehydrogenase (SDH), cytochromoxidase (Cyox) and Mg2+-dependant adenosine triphosphatase (ATPase). The hot water extract of C. officinalis flowers 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[39-40].

Calotropis procera

An aqueous ethanolic extract of Calotropis procera flowers was tested for its hepatoprotective effect against paracetamol-induced hepatitis in rats. Paracetamol (2000 mg/kg) has been reported to enhance SGPT, SGOT, ALP, bilirubin and cholesterol levels and reduce serum levels of HDL and the tissue level of GSH while treatment with an aqueous ethanolic extract of C. procera flowers (200 mg/kg and 400 mg/kg) restored the altered levels of biochemical markers to almost normal levels in a dose dependent manner[41]. The possible hepatoprotective and nephroprotective activities of the ethanolic extract of C. procera root were investigated in female rats. Carbon tetrachloride (CCl_4) was used for induction of hepatotoxicity and nephrotoxicity with significant ($P<0.05$) increase in the level of serum enzyme markers of hepatotoxicity and nonenzyme markers of nephrotoxicity. Administration of 150 and 300 mg/kg body weight (bw) of the ethanolic extract of C. procera root did not protect the liver and kidney from CCl_4 -induced toxicity. Pretreatment with the extract rather potentiated the toxicity induced by CCl_4 . It is advised strongly that caution should be taken when ingesting alcoholic preparations of C. procera root[42]. The chloroform extract of Calotropis procera (100 and 200 mg/kg, po) showed remarkable hepatoprotective activity against paracetamol-induced hepatotoxicity as judged from biochemical parameters such as serum aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), total bilirubin, total protein, gamma glutamate transpeptidase (GGTP) and levels of lipid peroxides in liver, which was comparable to the activity exhibited by the reference standard Silymarin. Histopathological examination of the liver section of the rats treated with paracetamol showed intense centrilobular necrosis and vascuolisation. The rats treated with extracts with paracetamol showed sign of protection against paracetamol toxicity to considerable extent as evident from formation of normal hepatic cards and absence of necrosis and vascuoles[43-44].

Canna indica

The hepatoprotective activity of methanol extract of aerial parts of Canna indica L. plant was evaluated against carbon tetrachloride induced hepatotoxicity. Extract at doses (100 and 200mg/kg) restored the levels of all serum parameters like SGPT, SGOT, TB which were elevated in CCl_4 administrated rats. A 10% liver homogenate was used for estimation of catalase, GSH content, LPO level for in vivo antioxidant status of liver. All LPO, Reduced GSH and catalase levels were observed normal in extract treated rats. Histopathology demonstrated profound necrosis, lymphocytic infiltration was observed in hepatic architecture of carbon tetrachloride rats which were found to obtain near normalcy in extract plus carbon tetrachloride administrated rats[45-46].

Capparis spinosa

Ethanolic root bark extract of C. spinosa (100, 200 and 400 mg/kg) afford significant dose-dependent protection against CCl_4 induced hepatocellular injury. Blood samples from the animals treated with ethanolic root bark extracts showed significant decrease in the levels of serum markers, indicating the protection of hepatic cells[47]. Treatment of the paracetamol-induced liver damage in rats with aqueous extract of Capparis spinosa (25, 50, 100, 200 mg/kg of body weight) for 7, 14, 21 days 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 with dose dependent manner[48-49].

Capsella bursa-pastoris

Capsella bursa-pastoris showed hepatoprotective activity in toxicity induced by CCl_4 in rats. The serum levels of SGOT and bilirubin in the group of Capsella bursa -pastoris (Aerial parts) crude extract treated animals showed significant decreases by (26.9 and 31.7 %) respectively, at the dose of 500 mg/kg body weight ($p<0.05$) . The smaller dose of the extract, although it lowered the levels of all parameters, did not do so by a statistically significant amount[50-51].

Carthmus tinctorius

Hepatoprotective activity of methanolic extract of leaves of Carthmus tinctorius (MECT) was investigated against hepatotoxicity produced by administering a combination of two anti-tubercular drugs isoniazid and rifampicin for 24 days by oral route in rats. MECT were administered at two graded dose (200 and 300 mg/kg po) 45 min after anti-tubercular challenge for 24 days. MECT, in all doses caused significant decrease in AST, ALT, ALP, and total bilirubin levels and elevated the level of GSH[52]. The potential protective effect of HSYA was investigated in liver fibrosis induced by carbon tetrachloride (CCl_4)-induced in rats. HSYA was given in a daily dose of 5 mg/kg intraperitoneally with concurrent CCl_4. CCl_4 treatment induced

micronodular liver fibrosis with a pronounced deposition of collagen fibers. HSYA 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. This was accompanied by a decreased expression of transforming growth factor (TGF)-β1 and phosphorylation[53]. The effect of Safflower injection on the lipid peroxidation level and expression of heme oxygenase-1 of the rat liver with chronic hypoxia and hypercapnia was studied 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. In chronic hypoxia and hypercapnia for four weeks group, there were multiple dispersed immunoreactivity cells in liver, the immunoreactivity cells were significantly decreased in Safflower injection group. Histological study revealed that there were many hepatocytes with obvious adipose degeneration. Hepatic pathological damage in Safflower injection group was slighter than that in chronic hypoxia and hypercapnia for four weeks group[54-55].

Carum carvi

The renoprotective effect of aqueous extract of Carum carvi seeds was evaluated in experimentally induced diabetic nephropathy (DN) in rodents. The diabetic rats showed a variable increase in the serum levels of glucose, urea, creatinine, total urinary protein and microalbuminuric levels. Body weight decreased and urine volume increased in the diabetic groups. 30 and 60 mg/kg body weight of Carum carvi significantly decreased the levels of the biochemical parameters. High dose of Carum carvi aqueous seeds extract (60 mg/kg) showed renoprotection against STZ induced diabetic nephropathy in rats[56]. The renoprotective effect of Carum carvi essential oil (10 mg/kg of body weights orally) was also studied in diabetic rats. Diabetic rats showed an increase in the serum level of glucose, and decrease in glutathione peroxidase. 10 mg/kg body weight of Carum carvi oil significantly corrected these parameters. The morphological examination of untreated diabetic rats kidneys showed glomerular and tubular degeneration with massive cellular infiltration, hemorrhage in interstitial tissue and deformed renal tissue architecture. Whereas the kidney of Carum carvi essential oil treated rats showed marked improvement with minor pathological changes[57]. Essential oils of Carum carvi fruits were assayed for their hepatoprotective effect against carbon tetrachloride (CCl_4) damage. It exerted hepatoprotective effect and decreasing oxidative damage[58-59].

Cassia occidentalis

The nephroprotective activity of the 70% hydroalcoholic extract of Cassia occidentalis was tested against gentamicin induced nephrotoxicity in rats. The degree of protection was determined by estimating urinary creatinine, urinary glucose, urinary sodium, urinary potassium, blood urea, serum creatinine levels and body weight of the animals. The in-vivo antioxidant activity was determined by estimating the tissue levels of GSH, SOD, catalase and lipid peroxidation. The treatment with hydroalcoholic extract of Cassia occidentalis (200 and 400 mg/kg body weight) markedly reduced gentamicin induced elevation of urinary sodium, potassium electrolytes, urinary glucose, blood urea and creatinine levels. It also increased the body weights. The comparative histopathological study of kidney exhibited almost normal architecture as compared to control group. The deterioration in the antioxidant parameter associated with gentamicin induced nephrotoxicity in rats was also attenuated by 70% hydroalcoholic extract of Cassia occidentalis. 70% hydroalcoholic extract of Cassia occidentalis showed a dose dependent increase in the level of GSH. However, 200 mg/kg showed 23.3% increase and 400 mg/kg showed 51.4.7% increase in GSH levels. treatment with 70% hydroalcoholic extract of Cassia occidentalis significantly elevated the SOD ($p< 0.001$) and catalase ($p< 0.001$)[60-61]. The hepatoprotective effect of aqueous and aqueousethanolic extract (50% v/v) of leaves of Cassia occidentalis was studied on rat liver damage induced by paracetamol and ethyl alcohol by monitoring serum transaminase (aspartate amino transferase and serum alanine amino transferase), alkaline posphatase, serum cholesterol, serum total lipids and histopathological alterations. The extract of leaves of the plant produced significant hepatoprotection by restoring the liver functions[62-63]. Chrysophanol isolated from Cassia occidentalis (50 mg/kg bw) and methanol fraction (COLMF) (200 mg/kg bw) were administered to rats with paracetamol induced hepatotoxicity for seven days. Oral administration of chrysophanol and COLMF significantly normalized the values of SOD, CAT, GPx, GSH, Vit-C and Vit-E. The elevated serum enzymatic levels of AST, ALT, ACP and ALP were significantly restored towards normalization by pre-treatment with chrysophanol and COLMF ($p>0.05$). The histopathological studies also confirmedthe hepatoprotectiv e nature of the extracts. The results of this study strongly indicate that Cassia occidentalis has potent hepatoprotective action against paracetamol induced hepatic damage in rats[64]. The antimutagenic potential of aqueous extract of Cassia occidentalis against the chromosomal aberrations (CA) produced in vivo by benzo(a)pyrene (B(a)P) and cyclophosphamide (CP) in mice was investigated. Male mice were treated with three doses of plant extract (50 mg/kg, 250 mg/kg and 500 mg/kg) for 7 days prior to the administration of single dose of mutagens (B(a)P 125 mg/kg oral; CP 40 mg/kg ip). The results indicated that C. occidentalis was not genotoxic per se and exerted no

other toxic signs and symptoms in treated animals. The chromosomal aberrations produced by B(a)P and CP were significantly reduced ($p<0.001$) by C. occidentalis pre-treatment. Furthermore, animals treated with plant extract showed a reduced level of cytochrome P450 and elevated levels of glutathione S-transferase activity and glutathione content in the liver[65-66].

Casuarina equisetifolia

The nephroprotective activity of methanolic extract of Casuarina equisetifolia leaves was studied in gentamicin induced nephrotoxicity in Wistar rats. Subcutaneous injection of rats with gentamicin (80 mg/kg body weight/day) for six consecutive days induced marked acute renal toxicity, manifested by a significant increase in serum urea, creatinine and uric acid levels, along with a significant depletion of serum potassium level. Also oxidative stress was noticed in renal tissue as evidenced by a significant decrease in glutathione level, superoxide dismutase, glutathione-S-transferase activities, with a significant increase in malondialdehyde and nitric oxide levels when compared to control group. Administration of plant extract at a dose of 300 mg/kg once daily for 4 weeks restored normal renal functions and attenuated oxidative stress. Casuarina equisetifolia leaves extract ameliorates gentamicin-induced nephrotoxicity and oxidative damage by scavenging oxygen free radicals, decreasing lipid peroxidation and improving intracellular antioxidant defense[67]. The methanol extracts of Casuarina equisetifolia were studied for hepatoprotective activity against liver damage induced in Swiss albino rats by carbon tetrachloride (CCl_4). It was found that the methanol extract of C. equisetifolia at a dose of 500 mg/kg body weight exhibited moderate protective effect by lowering the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol to a significant extent. The hepatoprotective activity was also supported by attenuatation of the histopathological changes associated with CCl_4 induced hepatotoxicity[68-69].

Celosia cristata

A new triterpenoid saponin, semenoside A, was isolated from Semen Celosia cristatae. The hepatoprotective activity of semenoside A with an oral dose of 1.0, 2.0 and 4.0mg/kg, respectively, were investigated by carbon tetrachloride (CCl_4)-induced hepatotoxicity in mice. The results indicated that it had significant hepatoprotective effects ($p < 0.01$)[70]. Cristatain saponin exhibited significant hepatoprotective effect on carbon tetrachloride (CCl_4) - and N, N-dimethylformamide (DMF)-induced hepatotoxicity in mice, which were evidenced by significant decreases in the values of asparate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) of serum and histopathological examinations compared to controls[71-72].

Chenopodium album

The antioxidant and hepatoprotective efficacy of Chenopodium album extract (300 mg/kg and 450 mg/kg) was evaluated in carbon tetrachloride (CCl_4) induced hepatotoxicity in rats. Chenopodium album extract was found to exhibit excellent antioxidant and free radical scavenging activity, when compared with ascorbic acid, in in vitro studies, Chenopodium album extract at a dose of 450 mg/kg showed inhibition of elevated biochemical parameters associated with induction of hepatotoxicity by CCl_4. It was also attenuated histopathologic effects of CCl_4[73]. Alcoholic and aqueous extracts of the aerial parts of Chenopodium album at the doses of 200 and 400 mg/Kg were evaluated for hepatoprotective activity against 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. Aqueous and alcoholic extract did not show any sign of toxicity up to oral dose of 5 g/Kg in mice[74]. The hepatoprotective activities of dried whole plant of Chenopodium album Linn, acetone and methanol extracts in ratio of (50:50), was also evaluated against 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

The hepatoprotective activity of petroleum ether, methanol and aqueous extracts of aerial parts (except fruits) of Cicer arietinum L was studied against CCl_4 induced hepatotoxicity in rats. The plant extracts were administered to the experimental rats (200 and 400 mg/kg/day po for 20 days). The Hepatoprotective activity of these extracts was evaluated by liver function biochemical parameters (serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, serum alkaline phosphatase, total bilirubin, lipid peroxidation, superoxide dismutase, catalase, reduced glutathione) and histopathological studies of liver. 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 treated animals. Histology of liver sections of the animals treated with the extracts showed the presence of normal hepatic cords, absence of necrosis and fatty infiltration[77-78].

Cichorium intybus

The hepatoprotective activity of aqueous-methanolic extract of Cichorium intybus seeds was investigated against acetaminophen and CCl_4-induced hepatic damage. Acetaminophen produced 100% mortality at the dose of 1 g/kg in mice while pretreatment of animals with plant extract (500mg/kg) reduced the death rate to 30%. Acetaminophen at the dose of 640 mg/kg produced liver damage in rats as manifested by the significant ($p< 0.01$) rise in serum levels of alkaline phosphatase (ALP), GOT and GPT to 393 ± 28, 767 ± 215 and 692 ± 191 IU/l respectively, compared to respective control values of 198 ± 15, 76 ± 07 and 39 ± 09 IU/l. Pretreatment of rats with plant extract (500 mg/kg) significantly lowered ($p<0.01$) the respective serum ALP, GOT and GPT levels to 228 ± 16, 68 ± 10 and 41 ± 08 IU/l. Similarly, a hepatotoxic dose of CCl_4 (1.5 ml/kg; orally) significantly raised ($p<0.01$), the serum ALP, GOT and GPT levels to 312 ± 20, 503 ± 98 and 407 ± 109 IU/l respectively, compared to respective control values of 215 ± 16, 79 ± 18 and 49 ± 10 IU/l. The same dose of plant extract (500 mg/kg) was able to prevent significantly ($p<0.05$) the CCl_4-induced rise in serum enzymes, the estimated values of ALP, GOT and GPT were 222 ± 27, 114 ± 23 and 68 ± 14 IU/l respectively. Moreover, it prevented CCl_4-induced prolongation in pentobarbital sleeping time which further confirmed hepatoprotectivity[79].

The natural root and root callus extracts of Cichorium intybus were studied for their anti-hepatotoxic effects in Wistar strain of Albino rats against carbon tetrachloride induced hepatic damage. The increased levels of serum enzymes (aspartate transaminase, alanine transaminase) and bilirubin observed in rats treated with carbon tetrachloride were very much reduced in the animals treated with natural root and root callus extracts and carbon tetrachloride. The decreased levels of albumin and proteins observed in rats after treatment with carbon tetrachloride were found to increase in rats treated with natural root and root callus extracts and carbon tetrachloride. These biochemical observations were confirmed by histopathological examination of liver sections[80].

Esculetin, a phenolic compound found in Cichorium intybus was investigated for its possible protective effect against paracetamol and CCl_4-induced hepatic damage. Paracetamol produced 100% mortality at the dose of 1 g/ kg in mice while pre-treatment of animals with esculetin (6 mg/ kg) reduced the death rate to 40%. Oral administration of paracetamol (640 mg/ kg) produced liver damage in rats as manifested by the rise in serum enzyme levels of alkaline phosphatase (ALP) and aminotransferases (AST and ALT). Pretreatment of rats with esculetin (6 mg/ kg) prevented the paracetamol-induced rise in serum enzymes. The hepatotoxic dose of CCl_4 (1.5 ml/ kg; orally) also raised serum ALP, AST and ALT levels. The same dose of esculetin (6 mg/ kg) was able to prevent the CCl_4-induced rise in serum enzymes. Esculetin also prevented CCl_4-induced prolongation in pentobarbital sleeping time confirming hepatoprotectivity[81].

The hepatoprotective effect of ginger, chicory and their mixture against carbon tetrachloride intoxication was investigated in rats. Carbon tetrachloride treatment significantly elevated the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase activities and the serum triglycerides and cholesterol concentration as compared to control group. It also increased RBCs counts, Hb concentration, total and differential leucocytes counts. However it decreased platelet counts, platelet distribution width, mean platelet volume, platelet larger cell ratio. 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. No toxic symptoms were reported in doses up to 5 g/kg[82].

The possible potential therapeutic and protective effects of Cichorium intybus (chicory) against oxytetracyclin-induced fatty liver was studied in rats. Fatty liver groups showed high significant increase in serum glucose, cholesterol, triglycerides, LDL cholesterol, ALAT, ASAT, GGT, LDH, urea, creatinine and albumin level to globulin level ratio. Total protein, albumin, globulin and HDL cholesterol were significantly decreased compared to control group. These biochemical changes were accompanied with fatty liver histopathological alterations. 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].

The hepatoprotective activity of aqueous-ethanolic (30:70 %) extract of fresh dried leaves of Cichorium intybus at the doses of 100, 200 and 300 mg/kg body weight po, was compared with Silymarin (25 mg/kg, po) treated animals. The significant changes in biochemical parameters (increases in serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alanine phosphatase (ALP) and serum tolal bilirubin (TB) level) in Nimesulide intoxicated rats, were restored towards normal values in

Cichorium intybus leaves extract (100 mg/kg, 200 mg/kg and 300 mg/kg, po) treated animals. Histopathological examination of liver tissues further substantiated these findings[84].

Cichotyboside isolated from the seeds of Cichorium intybus exhibited a significant anti-hepatotoxic activity against CCl_4 induced toxicity in Wistar rats, wherein it reduced the elevated levels of liver enzymes such as serum glutamate oxaloacetate transaminase (SGOT) by 52 units/ml; SGPT 38 units/ml; ALKP 24.97 units/ml, with 7.54 g/dl, 5.48 g/dl increase in total protein and albumin, respectively. It was observed that cichotyboside decreased the level of ALKP comparable with that of standard drug silymarin, exhibiting an 88% decrease in comparison to silymarin (92%) and increased the level of total albumin 85% in comparison to silymarin (89%) against intoxicated control. Whereas, the levels of SGOT and SGPT were also decreased considerably in comparison to standard and intoxicated control[85].

Cichorium root extract therapy normalized some morphofunctional liver features (decreases glycogen content and necrosis and increases the number of cells with pronounced protein synthesis activity in rats with CCl_4-induced hepatitis[86].

The effects of Cichorium intybus root extracts at different doses were tested against CCl_4 induced rats liver toxicity. The elevated serum markers and liver tissue microvesicular steatosis were significantly reduced in Cichorium intybus groups at 150-450 or 200-500 mg/kg/day[87-88].

The effect of chicory (Cichorium intybus L.) seed extract was evaluated in hepatic steatosis caused by early and late stage diabetes in rats, and induced in HepG2 cells (in vitro) by BSA-oleic acid complex (OA). Different dosages of Cichorium intybus seed extract (1.25, 2.5 and 5 mg/ml) were applied along with OA (1 mM) to HepG2 cells, simultaneously and non-simultaneously; and without OA to ordinary non-steatotic cells. Cellular lipid accumulation and glycerol release, and hepatic triglyceride (TG) content were measured. 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. In non-simultaneous treatment, Cichorium intybus seed extract up-regulated the expression of both genes and restored the normal levels of the corresponding proteins; with a greater stimulating effect on PPARα, Cichorium intybus seed extract acted as a PPARα agonist. Cichorium intybus seed extract released glycerol from HepG2 cells, and targeted the first and the second hit phases of hepatic steatosis[89-90].

Cistanche tubulosa

The methanolic extract from fresh stems of Cistanche tubulosa possessed hepatoprotective effects against D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced liver injury in mice. 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[91].

The hypocholesterolemic effect of the aqueous ethanol extract (CTE) from the roots of Cistanche tubulosa was evaluated using gene chip and RT-PCR analysis of the livers of mice given CTE (400 mg/kg) for 14 days. The administration of CTE (400 mg/kg) for 14 days significantly suppressed serum cholesterol elevation in high cholesterol diet-fed mice. The mRNA expressions of VLDL receptor and cytochrome P450 SCC were significantly enhanced. In addition, acteoside, a major constituent of CTE, was found to enhance the mRNA expressions of apolipoprotein B, VLDL receptor, and cytochrome P450 SCC in HepG2 hepatocytes[92].

Three among acylated phenylethanoid oligoglycosides isolated from stems of Cistanche tubulosa were found to inhibit D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes[93].

Citrullus colocynthis

The protective effect of methanolic extract of Citrullus colocynthis fruits (MECC) was studied in nitrosodiethylamine induced hepatic damage in male rats. Rats received DEN/PB showed elevated levels of cholesterol ($p<0.05$), triglycerides (TG, $p<0.01$), free fatty acids (FFA, $p<0.01$), low density lipoprotein (LDL, $p<0.01$), very low density lipoprotein (VLDL, $p<0.05$) and decreased level of high density lipoprotein (HDL), urea and creatinine. Administration of MECC 200,400 mg/kg to rats orally for 28 days significantly reduced the biochemical alterations induced by DEN/PB[94-95].

***Citrus* species**

The cytoprotective effects of Citrus aurantifolia was evaluated against Aflatoxin B1 (AFB1)-induced liver injury in rat model. Wistar albino rats were divided into five groups. Group I served as the control. Group II treated with vehicle, dimethyl sulfoxide (DMSO) a single intraperitoneally intraperitoneally on day 5. Group III received AFB1-alone (1mg/Kg body weight) intraperitoneally in DMSO as a single dose on day 5. Group

IV and V received Citrus aurantifolia methanolic extract (MeCA) and Citrus aurantifolia aqueous extract (AqCA) (500mg/Kg body weight, per oral) for 5 days and AFB1 (1mg/kg body weight) intraperitoneally in DMSO as a single dose on day 5. At the end of the 8th day, the livers were collected and used to determine the hepatoprotective activity. Genomic DNA fragmentation was observed by agarose gel electrophoretic pattern in the rat livers. The ultra-structure of the liver cells was studied by electron microscopy. Citrus aurantifolia treatment significantly protected nucleic acid. 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].

The ethanol extract of Citrus limon fruits was evaluated for its effects on experimental liver damage induced by carbon tetrachloride. The ethyl acetate soluble fraction of the extract of Citrus limon. fruits was evaluated on HepG2 cell line. The ethanol extract normalized the levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total and direct bilirubin, which were altered due to carbon tetrachloride intoxication in rats. In the liver tissue, treatment significantly raised the levels of antioxidant enzymes superoxide dismutase and catalase. It improved the reduced glutathione (GSH) levels in treated rats in comparison with CCl_4-intoxicated rats. In the histopathologic studies, treated animals exhibited restoration of the liver architecture toward normal. Three doses of ethanol extract (150, 300, and 500 mg/kg) were evaluated. The results obtained were dose dependent, and the effect of the highest dose was almost equal to the standard silymarin. 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 treated with different concentrations of ethyl acetate soluble fraction of the ethanol extract. The highest percentage viability of HepG2 cells was observed at a concentration of 100 µg/ml[97-98].

The hepatoprotective activity of orange essential oils was evaluated in carbon tetrachloride-induced hepatotoxicity in rats. Orange essential oils significantly reduced the serum ALT level when compared to CCl_4 group, while it did not affect the serum AST level. The histopathological findings did not show any significant difference between the orange essential oils treated and CCl_4 groups[99].

Clerodendron inerme

The ethanolic extract of Clerodendron inerme leaves were screened for its hepatoprotective activity in paracetamol induced liver damage in Swiss albino rats at a dose of 200 mg/kg bw. The ethanolic extract exhibited a significant protective effect by lowering serum levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase and total bilirubin[100-101].

Clitoria ternatea

Petroleum ether, chloroform, and methanol extracts of roots of blue and white flowered varieties of Clitoria ternatea (CT) were studied for their hepatoprotective potential against carbon tetrachloride (CCl_4) induced hepatotoxicity in rats. The hepatoprotective activity was assessed using various biochemical parameters like serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum alkaline phosphatase and total bilirubin along with histopathological studies of liver tissues. The substantially elevated serum enzymatic levels of serum transaminases, alkaline phosphatase and total bilirubin were significantly restored towards normalization with the treatment of CT. The biochemical improvement were confirmed by histopathological examination of liver sections[102-103].

Convolvulus arvensis

The hepatoprotective activity of Convolvulus arvensis was studied in paracetamol-induced hepatotoxicity in mice. The results showed that ethanolic extract of Convolvulus arvensis (200 and 500 mg/kg) produced significant ($p<0.05$) decrease in paracetamol induced increased levels of liver enzymes and total bilirubin. Histopathological investigation supported the hepato-protective effects of Convolvulus arvensis[104-105].

Cordia myxa

The hepatoprotective effect of Cordia myxa. (CM) extracts was studied in rats. Oxydative liver damage in rats was induced by two agents, carbon tetrachloride (CCl_4) and thioacetamide (TA). Oxydative damage was evaluated by a measurement of aspartate transaminase (AST), glutamate transaminase (ALT) and alkaline phosphatase (ALP) in sera of the rats. Several extracts of Cordia myxa were prepared and were fed to experimental animals over a period of two weeks. Liver recovery was assessed by re-measuring the hepatic enzymes and their comparison with the control group. CCl_4 and TA induced comparable oxidative liver damage as measured through hepatic enzymes. A significant ($p = 0.05$) liver recovery was noticed when animals treated with CCl_4/TA were fed with CM extracts[106-107].

The protective role of Cordia myxa (CM) extracts (50-500mg/kg) against liver fibrosis induced by carbon tetrachloride or thioacetamide (TA) was investigated in rats. The serum aspartate transaminase (AST), glutamate transaminase (ALT) and alkaline phosphatase (ALP) were significantly improved in rats after administration of (CCl_4) + CM, or (TA) + CM as compared to rats treated alone with CCl_4 or TA[108].

Coriandrum sativum

The administration of paracetamol caused a significant increase in plasma alanine amino transferase, aspartate amino transferase, alkaline phosphates, gamma glutamyl transferase, bilirubin, urea and creatinine with significant decrease in plasma total proteins, albumin and some antioxidant biomarkers (plasma total antioxidant capacity, catalase and glutathione peroxidase) compared to normal rates. Statistical analysis indicated that rats which supplemented with aqueous extract of Coriandrum sativum and then administrated paracetamol showed significant improvement in all biochemical parameters, which become near to control, the results were confirmed by histopathological examination of the liver tissue of control and treated animals[109-110]. The antioxidant activity of Coriandrum sativum was evaluated in CCl_4 treated oxidative stress in rats. CCl_4 injection induced oxidative stress by a significant rise in serum marker enzymes and thiobarbituric acid reactive substances (TBARS) along with the reduction of antioxidant enzymes. In serum, the activities of enzymes, ALP, ACP and protein and bilirubin were evaluated. Pretreatment of rats with different doses of plant extract (100 and 200mg/kg) 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. Histopathological examinations showed extensive liver injuries, characterized by extensive hepatocellular degeneration/necrosis, inflammatory cell infiltration, congestion, and sinusoidal dilatation in CCl_4 trated rats. Oral administration of the leaf extract at a dose of 200mg/kg bw significantly reduced the histological effects induced by CCl_4. The activity of leaf extract at the dose of 200mg/kg was comparable to the standard drug, silymarin[111].

The hepatoprotective activity of Coriandrum sativum against carbon tetrachloride was studied, with estimation of serum glutamyl oxaloacetic acid transaminase, serum glutamyl pyruvate transaminase, alkaine phosphatase and bilirubin. Coriandrum sativum possessed hepatoprotection by reducing the liver weight, activities of SGOT, SGPT, and ALP, and direct bilirubin of CCl_4 intoxicated animals. These results were confermied be histological effects, administration of Coriandrum sativum extract at 300 mg/kg dose resulted in disappearance of fatty deposit, ballooning degeneration and necrosis[112].

Essential oils of Coriandrum sativum were assayed for their in vitro and in vivo antioxidant activity and hepatoprotective effect against carbon tetrachloride damage. The in vitro antioxidant activity was evaluated as a free radical scavenging capacity (RSC), measured as scavenging activity of the essential oils on 2,2-diphenyl-1-picrylhydrazyl (DPPH) and OH radicals and effects on lipid peroxidation (LP) in two systems of induction. Liver biochemical parameters were determined in animals pretreated with essential oils and later intoxicated with CCl_4 to assess in vivo hepatoprotective effect. The essential oils were able to reduce the stable DPPH in a dose-dependent manner and to neutralize H_2O_2, with IC_{50} values of 4.05 microl/ml[113].

Crocus sativus

The protective effects of saffron extract and crocin was evaluated in chronic - stress induced oxidative stress damage of the brain, liver and kidneys in rats. Rats were injected with a daily dose of saffron extract (30 mg/kg, ip) or crocin (30 mg/kg, ip) during a period of 21 days following chronic restraint stress (6 h/day). In order to determine the changes of the oxidative stress parameters following chronic stress, the levels of the lipid peroxidation product, malondialdehyde (MDA), the total antioxidant reactivity (TAR), as well as antioxidant enzyme activities glutathione peroxidase (GPx), glutathione reductase (GR) and superoxide dismutase (SOD) were measured in the brain, liver and kidneys tissues after the end of chronic stress. In the stressed animals that receiving saline, the levels of MDA, and the activities of GPx, GR, and SOD were significantly higher ($p< 0.0001$) and the TAR capacity was significantly lower than those of the non-stressed animals ($p< 0.0001$). 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 of the brain, liver and kidneys[114-115].

The protective effects of hydroalcoholic extract from Crocus sativus petals (CSP) against Acetaminophen (APAP) -induced hepatotoxicity was evaluated in male rats. Rats were treated with either low dose (10 mg /kg) or high dose (20 mg/kg) of CSP before receiving APAP (600 mg/kg, iv). The APAP treatment resulted in higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, along with lower total protein and albumin concentration than the control group. The administration of CSP with a dose of 20 mg/kg resulted in lower levels of AST, ALT and bilirubin, with a significant higher concentration of total protein and albumin. The histopathological results regarding liver pathology, revealed cell swelling, severe inflammation and necrosis in APAP-exposed rats, which was quiet contrasting compared to the

control group. The pre-treated rats with low doses of CSP showed hydropic degeneration with mild necrosis in centrilobular areas of the liver, while the same subjects with high doses of CSP appeared to have only mild hepatocyte degeneration. It was appeared that the antioxidant property of CSP resulted in reducing the oxidative stress complications of toxic levels of APAP in intoxicated rats, and 20 mg/kg of CSP ameliorates APAP-induced acute liver injury in rats[116].

The potential protective effect of saffron ethanol extract (SEE) in a rat model upon hepatic ischemia-reperfusion (IR) injury was studied. Caspases 3 and terminal deoxynucleotidyl transferase-mediated dUTP biotin nick end labeling (TUNEL) results showed increased cell death in the IR samples; reversely, minor apoptosis was detected in the SEE/IR group. 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. Proteome tools revealed that 20 proteins were significantly modulated in protein intensity between IR and SEE/IR groups. Particularly, SEE administration attenuate the carbonylation level of several chaperone proteins[117].

The protective effect of ethanolic extract of Crocus sativus stigma (EECSL.S) was evaluated against rifampin-induced hepatotoxicity in the rats in comparison with standard drug silimarin. Male Wistar rats with were randomly assigned into 5 groups. Group I as normal control received normal saline (10 ml/kg) and group II as toxicant control received rifampin (500 mg/kg). Group III as positive control received silymarin plus rifampin (500 mg/kg) and groups IV and V (50 mg/kg) received EECSL.S at 40 and 80 mg/kg plus rifampin, respectively. All the treatments were given through gavage for 1 month. At the end of experiment, levels of liver function marker enzymes (aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase), total bilirubin, albumin and total proteins were assessed in serum of the rats. In rifampin-treated rats, silymarin and EECSL.S (40 and 80 mg/kg) were significantly decreased the levels of serum biomarker of hepathic injury and total bilirubin and elevated the levels of albumin and total proteins. Histopathologically, silymarin and EECSL.S ameliorated rifampin induced hepatic injury[118].

Crocin possessed hepatoprotective effects against aflatoxin B1 hapatotoxicity via the reduction of hepatic (AST, ALT, ALP and γ-GGT) and via its antioxidant activity in rats[119].

Crotalaria juncea

The petroleum ether extract of Crotalaria juncea seed at low and high dose (100 and 500mg/kg) were tested for its efficacy against thioacetamide induced acute hepatic damage in rats. The different groups of rats were administered with thioacetamide (100mg/kg, sc). Drug Silymarin (100 mg/kg,) was used as reference standard. The rats were monitored for biochemical changes of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum alkaline phosphatase, and bilirubin (total and direct). Activity of antioxidant enzymes such as superoxide dismutase and catalase in liver tissue homogenate and Histopathological changes were observed. According to the results, it was proved that the crotalaria juncea seed extract (CJSE) 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

The effect of Cuminum cyminum (Cumin) on kidney exposed to profenofos was evaluated in female swiss albino mice. The results showed that cumin was effective in normalizing the uric acid and creatinine level[122-123].

Depression in growth, hepatotoxicity and nephrotoxicity were observed in rats that had been given paracetamol at 500 mg/kg orally for 4 weeks. These findings were accompanied by leucopenia, macrocytic normochromic anemia and alterations of serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase activities and concentrations of cholesterol, urea and other serum constituents. Serum bilirubin did not change. In rats given the mixture of paracetamol 500 mg/ kg plus 6% Cuminum cyminum fruit for 4 weeks, the recovery of paracetamol hepatotoxicity was evidenced by increase in body weight, absence of hepatocellular fatty vacuolation and significant improvement of serbiochemical and hematological parameters[124].

Cupressus sempervirens

The Cupressus sempervirens extract was investigated for its therapeutic effect against CCl_4 hepatotoxicity by biochemical (serum total proteins, albumin**,** urea, creatinine, LDH) and histopathological evaluations. A single intraperitoneal dose of 10% CCl_4 in olive oil (1 ml/kg body weight) was administered to a group of female Wister rats as the injury group. The other group was given CCl_4 and administered with Cupressus sempervirens extract three times per week for six weeks and a further group administered CCl_4 was left for six weeks to allow self-recovery. At the end of experiment, the rats from all groups were sacrificed for sampling for biochemical and histological analysis. Remarkable disturbances were observed in the levels of all

tested parameters. On the other hand, rats injected with the toxic agent and left for one and a half month to self recover showed moderate improvements in the studied parameters. Treatment with herbal extract ameliorated the levels of the disturbed biochemical parameters. The Cupressus sempervirens group also showed histopathological liver & kidney profiles close to those of the control group[125-126].

Pre-treatment with either hydroethanolic extract (250 mg/kg/day, po) or silymarin (50 mg/kg/day, po) for 4 weeks has good safety profile in normal rats and exhibited a marked hepatoprotection against single toxic dose of paracetamol (4 g/.kg bw, po) as proved from marked decline in the DNA fragmentations and inhibition in the percentage of chromosomal aberrations in bone marrow cells[127].

Cuscuta planiflora

The in vivo hepatoprotective activity of methanolic extract of whole plant was studied in carbon tetrachloride (CCl_4) induced hepatotoxicity animal model using albino rats. The results showed that, the methanolic extract exerted significant hepatoprotective activity against CCl_4 induced hepatotoxicity by suppressing CCl_4 induced cellular oxidative stress. Furthermore, these results confirmed by enzymatic and histological study[128].

Cynodon dactylon

The methanolic extract of roots of Cynodon dactylon was screened for its hepato-protective activity in diethyl nitrosamine (DEN) induced liver cancer in Swiss albino mice. The plant extract at a dose of 50 mg/kg was administered orally once a week, up to 30 days after DEN administration. Diethyl nitrosamine treated group showed low significant elevation ($p< 0.05$) in liver GST activity with respect to control, whereas the control, DEN + Cynodon dactylon, DEN + tamoxifen treated animals did not shown any alteration. 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, whereas saline and DEN + Tamoxifen treated animals did not showed any significant alteration[129].

The hepatoprotective activity of roots of Cynodon dactylon in CCl_4 induced hepatotoxicity was studied in albino rabbits. Alcoholic extracts of roots of Cynodon dactylon was administered orally for 20 days in a doses of 100mg/kg/day. Cynodon dactylon extract was able to bring down the level of serum transaminase, serum alkaline phosphatase, serum bilirubin and increased in serum albumin significantly ($p< 0.001$), when compared with untreated group[130].

Cyperus rotuntdus

The effects of Cyperus rotundus rhizome on cellular lipogenesis and non-alcoholic/diet-induced fatty liver disease, and the molecular mechanism of these actions were studied. It appeared that the hexane fraction of Cyperus rotundus rhizome 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. The SREBP-1c gene was a master regulator of lipogenesis and a key target of LXRα. CRHF inhibited not only the LXRα-dependent activation of the synthetic LXR response element (LXRE) promoter, but also the activation of the natural SREBP-1c promoter. Moreover, the hexane fraction of Cyperus rotundus decreased (i) the recruitment of RNA polymerase II to the LXRE of the SREBP-1c gene; (ii) the LXRα-dependent up-regulation of various lipogenic genes; and (iii) the LXRα-mediated accumulation of triglycerides in primary hepatocytes. Furthermore, the hexane fraction of Cyperus rotundus ameliorated fatty liver disease and reduced the expression levels of hepatic lipogenic genes in high sucrose diet (HSD)-fed mice. CRHF did not affect the expression of ATP-binding cassette transporter A1, another important LXR target gene that was required for reverse cholesterol transport (RCT) and protected against atherosclerosis. Accordingly, these results suggested that the hexane fraction of Cyperus rotundus might be a novel therapeutic remedy for fatty liver disease through the selective inhibition of the lipogenic pathway[131-132].

***Datura* species**

The effectiveness of pretreatment with Datura seed extract (DSE) to increase the survival following organophosphate (OP) poisoning was evaluated in rats. Datura stramonium seeds were collected, crushed, and then heated in water to make a 2mg/ml atropine solution (100 seeds contain approximately 6 mg of atropine or 0.007 mg/seed). Male rats were pretreated with 7.5 mg/kg DSE given as a single intraperitoneal injection 5 minutes prior to a subcutaneous injection of 25 mg/kg of dichlorvos. The endpoint was time to death recorded by a blinded observer. The 24-hour survival rate was 90% (95% CI = 56% to 100%) for the DSE-pretreated group and 10% (95% CI = 0% to 45%) for the control group. A statistically significant longer survival for the

Datura-treated animals (p = 0.0002). Median survival time was 22 minutes 30 seconds for the control group and greater than 24 hours for the DSE-pretreated group[132].

The protective role of Datura stramonium leaves ethanolic extract against acute carbaryl toxicity was studied in in rats. The animal with toxic dose of carbaryl showed mainly cholinergic effect, while those with toxic dose of Datura stramonium extract showed mainly anticholinergic effect symptom. The result of isobolographic analysis showed that the sort of interaction was highly antagonism .There was increase in the combined LD_{50} of carbaryl and Datura stramoinum extract nearly double that of each one alone , this was due to high tropane alkaloids contents of Datura stramonium that abolish carbaryl cholinergic toxic effect by blocking the muscarinic receptors of parasympathetic nerve ending[133-134].

Daucus carota

The renoprotective activity of Daucus carota root extract was studied in renal ischemia reperfusion injury in rats. Renal pedicles of rats were occluded for 45 minutes followed by 24 hours reperfusion. Six days prior to induction of I/R, groups of rats received petroleum ether extract, fractional methanolic extract and methanolic extract of Daucus carota root (250 & 500 mg/kg, orally). Renal ischemia reperfusion caused significant impairment of kidney function. Six day administration of Daucus carota, minimized this effect. Rats with renal I/R only showed significantly decreased activity of superoxide dismutase, catalase, and reduced glutathione compared with the sham operated rats. These declining trends were significantly less in the group treated with petroleum ether, fractional methanolic and direct methanolic extract of Daucus carota root compared with those in I/R group. Renal I/R produced a significant increase in malondialdehyde level, while pretreatment with Daucus carota extracts was associated with a significantly lower malondialdehyde level. Accordingly, Daucus carota extracts exerted renoprotective activity probably by the free radical scavenging activity[135-136].

The nephroprotective effects of ethanolic root extract of Daucus carota (200 mg/kg and 400 mg/kg. po) was studied against gentamicin-induced nephrotoxicity in Albino Wistar rats. Nephrotoxicity was induced in rats by intraperitoneal administration of gentamicin (100 mg/kg/day) for 8 days. Gentamicin intoxication induced elevated serum urea, BUN, uric acid, and creatinine levels which was found to be significantly ($p< 0.01$) decreased in a dose-dependent manner in groups received Daucus carota. The nephroprotective effects of Daucus carota were further confirmed by histological observations[137].

The protective and curative potential of Daucus carota root extract was investigated in renal ischemia reperfusion injury in rats. Renal pedicles of rats were occluded for 45 min and allowed for reperfusion period. In protective and curative studies, 14 days prior and 14 days after the induction of ischemia/reperfusion (I/R), rats received petroleum ether extract (PEE 250 and 500 mg/kg), fractional methanol extract (FME 250 and 500 mg/kg) and direct methanol extract (DME 250 and 500 mg/kg) of Daucus carota root, orally, once daily. PEE at a dose of 500 mg/kg significantly ($p< 0.001$) reduced the levels of serum creatinine (0.853-3.090 mg/dl), uric acid (1.300-3.500 mg/dl) and urea (58.26-132.00 mg/dl) compared to disease control. FME at a dose of 500 mg/kg body weight significantly ($p < 0.001$) reduced the levels of serum creatinine (0.960-3.090 mg/dl), uric acid (1.700-3.500 mg/dl) and urea (77.17-132.00 mg/dl) compared to disease control. DME at a dose of 500 mg/kg body weight significantly ($p < 0.001$) reduced the levels of serum creatinine (1.173-3.090 mg/dl), uric acid (2.267-3.500 mg/dl) and urea (84.75-132.00 g/dl) compared to disease control[138].

The hepatoprotective and antioxidant activity of methanolic extract of Daucus carota (D. carota) seeds was studied in experimental rats. Oxidative stress were induced in rats by thioacetamide 100 mg/kg sc, in four groups of rats (two test, standard and toxic control). Two test groups received D. carota seeds extract (DCSE) at doses of 200 mg/kg and 400 mg/kg. Standard group received silymarin (25 mg/kg) and toxic control received only thioacetamide. Control group received only vehicle. On the 8^{th} day animals were sacrificed and liver enzyme, serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase (ALP) were estimated in blood serum and antioxidant enzyme, superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GRD), glutathione peroxidase (GPX), glutathione-S-transferase (GST) and lipid peroxidation (LPO) were estimated in liver homogenate. A significant decrease in SGPT, SGOT and ALP levels was observed in all drug 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 all drug treated groups as compared with thioacetamide group. However, a significant ($p< 0.001$) reduction in LPO was observed as compared to toxic control group[139].

The effect of carrot extract on carbon tetrachloride (CCl_4)-induced acute liver damage was evaluatedin mice. The extracts significantly lowered the serum levels of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, sorbitol and glutamate dehydrogenase elevated by CCl_4-induction. Extract also decreased the elevated serum bilirubin and urea. 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].

The hepatoprotective effect of kaempferol (100 and 200 mg/kg bw) isolated from Daucus carota leaves was tested in paracetamol induced liver damage of albino 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

The hepatoprotective effect of the polyphenolic fraction of Desmostachya bipinnata root (PFDB) was studied in liver damage induced in female Sprague-Dawley rats. A dose-dependent increase in percentage viability was observed when ethanol-exposed BRL3A cells were treated with PFDB. Both the treatment groups upon pretreatment with PFDB exhibited a significant ($p\leq 0.05$) protective effect by lowering serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, triglycerides, cholesterol, urea, uric acid, bilirubin and creatinin levels and improving protein level in serum in dose-dependent manner, which was comparable to that of silymarin group. In addition, PFDB prevented elevation of reduced glutathione, glutathione peroxidase, superoxide dismutase and catalase in the tamoxifen-intoxicated rats in concentration-dependent manner and significantly ($p< 0.05$) reduced the lipid peroxidation in the liver tissue. The biochemical observations were confirmed by histopathological studies, which showed the attenuation of hepatocellular necrosis[142].

The hepatoprotective potential of dried powdered roots of Desmostachya bipinnata (100mg/kg and 200mg/kg, orally for 7 days) was studied against paracetamol- induced liver damage in wistar rats. Animals before treatment with aqueous extract of D. bippinata 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. D.bipinnata showed good hepatoprotective and antioxidant activity when compared to Silymarin[143].

***Digitalis* species**

Four different glycosides (acteoside, purpureaside A, calceolarioside B and plantainoside D) were isolated from the leaves of Digitalis purpurea and studied their abilities to induce glutathione S-transferase (GST) and their protective efficiencies against aflatoxin B1-induced cytotoxicity in H4IIE cells. Of these four glycosides, 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[144-145].

The neuroprotective action of cardiac glycoside neriifolin was evaluated on in ischemic stroke. Neriifolin provided significant neuroprotection in a neonatal model of hypoxia/ischemia and in a middle cerebral artery occlusion model of transient focal ischemia[146].

The heart protective effects of ouabain against ischemia-reperfusion injury, through activation of the Na^{+},K^{+}-ATPase/c-Src receptor complex, was studied. In Langendorff-perfused rat hearts, a short (4 min) administration of ouabain 10 muM followed by an 8-minute washout before 30 min of global ischemia and reperfusion, improved cardiac function, decreased lactate dehydrogenase release and reduced infarct size by 40%. Western blot analysis revealed that ouabain activated the cardioprotective phospholipase C gamma1/protein kinase Cepsilon (PLC-gamma1/PKCepsilon) pathway. Pre-treatment of the hearts with the Src kinase family inhibitor 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolol(3,4-d)pyrimidine (PP2) blocked not only ouabain-induced activation of PLC-gamma1/PKCepsilon pathway, but also cardiac protection. The protection was also blocked by a PKCepsilon translocation inhibitor peptide (PKCepsilon TIP)[147].

Dodonaea viscosa

The inhibitory effect of crude leaves of Dodonaea viscosa was studied on lead acetate induced synthesis of glycoproteins and sialic acid in liver and plasma. Enhanced synthesis of glycoproteins (protein - bound hexose and protein - bound hexosamine) and sialic acid levels were found in liver and plasma of the lead acetate poisoned rats. Administration of crude leaves of D.viscosa (100 mg/100 g bw orally) effectively suppressed the synthesis of glycoproteins and sialic acid in liver and thereby controlling the concentration in plasma. The authors concluded that D.viscosa may exert its membrane protection effect by inhibiting the synthesis of glycoproteins and sialic acid induced by lead acetate[148-149].

Dolichos lablab

The hepatoprotective effects and underlying mechanism of Dolichos lablab water extract (DLL-Ex) were assessed using an in vitro cellular model in which nonalcoholic fatty liver disease (NAFLD) was

simulated by inducing excessive FFA influx into hepatocytes. HepG2 cells were treated with DLL-Ex and FFAs for 24 h. DLL-Ex inhibited expression of CD36 in HepG2 cells, which regulates fatty acid uptake, as well as BODIPY-labeled fatty acid uptake. Additionally, DLL-Ex significantly attenuated FFA-mediated cellular energy depletion and mitochondrial membrane depolarization. Furthermore, DLL-Ex enhanced phosphorylation of AMPK, indicating that AMPK is a critical regulator of DLL-Ex-mediated inhibition of hepatic lipid accumulation, possibly through its antioxidative effect[150-151].

***Ephedra* species**

The hepatroprotective effect of Ephedra foliate was studied in Wistar albino rats. Liver injury induced in rats using carbon tetrachloride. The biochemical parameters; serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and total bilirubin were estimated as reflection of the liver condition. The hepatoprotective effect offered by E. foliate (whole plant) crude extract at 500 mg/kg doses, was found to be significant in all parameters studied with 42.6, 39.5, 21.2 and 46.2% reduction in SGOT, SGPT, ALP and bilirubin, respectively. At the lower doses (250 mg/kg) the extract resulted in a significant reduction in SGOT, ALP and bilirubin ($p< 0.05$)[152-153].

Equisetum arvense

Hepatoprotective activity-guided fractionation of the MeOH extract of Equisetum arvense showed that onitin and luteolin isolated from the methanolic extract of Equisetum arvense possessed hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying EC_{50}) values of 85.8 ±9.3 microM and 20.2 ± 1.4 microM, respectively, while, Silybin, used as a positive control, showed the EC_{50} value of 69.0 ±3.3 microM[154-155].

Eupatorium cannabinum

F. cannabinum aqueous extract (125, 250, 500, 1000 mg/kg) possessed anti-necrotic properties against $CC1_4$-induced hepatotoxicity . Pretreatment (30 min before $CC1_4$), with E. cannabinum showed a significant decrease of GPT levels at 250, 500, and 1000 mg/kg[156-157].

An aqueous extract of the plant exhibited anti-necrotic activity against carbon tetrachloride-induced hepatotoxicity in rats. The effect is attributed to the presence of flavonoids, rutoside, hyperoside and quercetin; phenolic acids, caffeic and chlorogenic; and not due to the presence of eupatoriopicrin. Acrylic acid and the lactic,malic and citric acids, present in the plant, also exhibited protective effect against acute toxicity induced by ethanol in mice[158].

Euphorbia hirta

The antihepatotoxic effect of hydroalcoholic extract of whole Euphorbia hirta extracts was evaluated in experimental models of liver injury in rats induced by CCl_4 or paracetamol. E.hirta showed hepatoprotective activities at doses 125 mg/kg and 250 mg/kg, since serum levels of alanine aminotransferase and aspartate aminotransferase in rats given the extracts were significantly lower ($p< 0.05$ and 0.01 respectively) compare to control CCl_4 or paracetamol-injured rats[159-160].

The in vivo antimalarial activity of the Euphorbia hirta extract doses (200, 400 and 800 mg/kg body weight) was studied against P. berghei infected mice. Te results showed that te extract had significant ($p<0.05$) suppressive activity of 51 – 59 % and prophylactic activity of 25 – 50 % when compared with chloroquine that gave 95 and 81 % suppressive and prophylactic antiplasmodial activities respectively. The antiplasmodial action of the extract was not related to the oxidation of red blood cell membrane lipids as increasing extract concentration results in the reduction of the enzymatic activities of SOD and GPx, and concentrations of GSH and TBARS[161].

Foeniculum vulgare

The potential protective effect of anise and fennel essential oils was studied against carbon tetrachloride (CCl_4) induced fibrosis in rats. Administration of CCl_4 (1.5ml/kg /kg bw) intrapretoneally in olive oil (1:7 dilution) for 7 successive weeks resulted in liver damage manifested by significant increase in serum AST, ALT, ALP, decreased total protein and increased triglycerides, total cholesterol, LDL and decreased the HDL level. Rats treated orally with essential oil of Pimpinella anisum (Anise, 125 &250mg/kg) or Foeniculum vulgare (Fennel, 200 &400kg/bw) for 7 successive weeks and intoxicated with CCl_4 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. These protective effects were further confirmed by histopathological examination[162].

The effect of whey protein concentrate (WPC) (0.5g/kg/day) or fennel seed extract (FSE) (200mg/ kg/day) was evaluated on paraoxonase-1 activity (PON1) and oxidative stress in liver of tienilic acid (TA)

treated rats. TA administration significantly increased ALT and AST, total- and direct bilirubin levels, serum tumor necrosis factor-α and nitric oxide levels. Furthermore, serum PON1, and hepatic reduced glutathione, glutathione-S-transferase and Na^+/K^+-ATPase values were diminished matched with a significant rise in the level of hepatic lipid peroxidation. Triglycerides, total- and LDL-cholesterol levels were significantly elevated while HDL-cholesterol was unchanged. The administration of either WPC or FSE to TA-treated animals 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; where WPC showed the strongest protection effect[163].

The nephroprotective effects of different oral doses of aqueous extract of Foeniculum vulgare seeds 250 mg/kg, Solanum nigrum 500 mg/kg fruit and their mixture (of 250 and 500 mg/kg/oral respectively) were studied in gentamicin induced nephrotoxicity in albino rabbits. All the treatments were continued for 21 days. Blood samples were taken from all groups at day 21 to determine serum urea, creatinine, albumin, plasma malondialdehyde and catalase. Histopathological parameters of kidneys were also examined at day 21. Gentamicin induced oxidative stress and caused structural changes in the kidneys. The aqueous extract of Foeniculum vulgare seeds, Solanum nigrum fruit and their mixture significantly prevented renal damage by normalizing increased levels of renal markers. Mixture of both plants at high doses exhibited improved nephroprotective and antioxidant activities[164].

The renoprotective effect of the aqueous extract of Foeniculum vulgare (150 mg/kg bw) was studied in experimental PCOS female rats. The mean values of blood urea nitrogen in PCOS rats treated with low dose of extract of Foeniculum vulgare and estradiolvalerate and non-treated, was significantly ($p< 0.05$) increased compared with non-PCOS and PCOS rats treated with high dose of extract of Foeniculum vulgare. Moreover, histopathological changes of kidney samples were comparable in PCOS rats with respect to treated groups with extract of Foeniculum vulgare[165].

The protective effect of fennel essential oil (250, 500, and 1000 mg/kg/day, for 10 days) as a phytoestrogen source was studied against cisplatin -induced nephrotoxicity in rats. The serum levels of blood urea nitrogen (BUN) and creatinine (Cr), kidney tissue damage score (KTDS), and kidney weight (KW) and body weight changes in CDDP-treated groups increased significantly ($p< 0.05$). Fennel essential oil did not reduce the levels of BUN and Cr, KTDS, and KW and body weight changes. Also, the serum and tissue levels of nitrite were not altered significantly by fennel essential oil[166].

Fumaria officinalis

Hepatoprotective activity of ethanolic extract of Fumaria officinalis was in carbon tetrachloride (CCl_4) induced liver damage in rats. The ethanolic extract at a dose of 200 and 500 mg/ kg orally 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, triglycerides. Ascorbic acid in rat's urine and histophathological studies further conform the hepatoprotective activity of Fumaria officinalis when compared to the CCl_4 treated control groups[167].

Fumaria parviflora

The hepatoprotective effect of the ethanol extract of the aerial part of Fumaria parviflora (250 mg/kg daily 5 days prior to the experiments till 2 days after injection of CCl_4) was evaluated in carbon tetrachloride 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 carbon tetrachloride hepatotoxicity[168].

The protective effect of Fumaria parviflora on nimesulide induced cell death was investigated in primary rat hepatocyte cultures. Fumaria parviflora extract treated cells showed increased viability as compared to nimesulide stressed cells as assessed by MTT assay. LDH leakage increased significantly at 500microM nimesulide, and the data suggested that apoptosis was the predominant mechanism responsible for cell death. Nimesulide induced apoptosis was further confirmed by DNA fragmentation and chromatin condensation. Nimesulide exposure increased intracellular ROS, translocation of Bax and Bcl2 followed by mitochondrial depolarization and cytochrome c (Cyt c) release along with caspase-9/-3 activity confirming involvement of mitochondria in nimesulide induced apoptosis. Events like membrane depolarization of mitochondria, expression of Bax, Bcl2, and externalization of phosphatidyl serine were substantially reversed by the pre-treatment of of Fumaria parviflora extract. These results indicated that of Fumaria parviflora extract modulates critical events regulating pro and anti-apoptotic proteins in mitochondria dependent apoptosis induced by nimesulide[169].

The hepatoprotective potential of Fumaria parviflora extract was evaluated against nimesulide induced oxidative stress in rats, and regulation of critical events in mitochondria mediated apoptosis. Pre-treatment with

Fumaria parviflora extract for 5 days significantly reduced the impact of nimesulide induced toxicity as evident from the serum biomarkers of liver damage and histopathology. It also modulated mRNA expression and antioxidant enzymes (SOD, glutathione peroxidase, glutathione reductase) and reduced lipid peroxidation during nimesulide toxicity. Nimesulide exposure decreased GSH content (92.9%) and increased reactive oxygen species (9.29 fold) which was attenuated in Fumaria parviflora extract treated rats. Fumaria parviflora extract pre-treatment significantly altered key apoptotic events like Bcl2 and Bax translocation, inhibited mitochondrial depolarization, prevented cytochrome c release, caspase-9/caspase-3 activation and DNA damage[170].

The hepatoprotective activity of an aqueous-methanolic extract of Fumaria parviflora was investigated against paracetamol- and CCI4-induced hepatic damage. Pretreatment of animals with the plant extract (500 mg/kg; orally) reduced the death rate from 100 to 50%. 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 CCI_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].

The protective effect of ethanolic extract of F. parviflora was investigated against lead-induced testicular oxidative stress in rats. Adult Wistar rats were treated with 0.1% lead acetate in drinking water with or without 200 mg kg/ day F. parviflora extract via gavage for 70 days. Lead acetate treatment resulted in significant reduction in testis weight, seminiferous tubules diameter, epididymal sperm count, serum testosterone level, testicular content of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Moreover, significant elevation was observed in content of malondialdehyde (MDA) in lead-treated rats. Co-administration of Fumaria parviflora extract showed a significant increase the reproductive parameters in lead-treated rats[172].

Galium aparine

The hepatoprotective effects of mixture of Berberis lycium, Galium aparine and Pistacia integerrima were evaluated in carbon tetrachloride (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. These medicinal plants were more curative than preventive treatment[173].

Galium verum

A hepatoprotective activity of Galium verum (I and II dry extracts, 25 mg/kg) , was studied against carbon tetrachloride-induced acute hepatitis in rats. The hepatoprotective effect of I and II extracts at the dose of 25 mg/kg is characterized by a decreased activities of serum enzymes, Serum Alanine Aminotransferase (ALT) decreased 2.7-3.5 fold, Serum Aspartate Aminotransferase (AST) decreased 2.4-3.4 fold and ALP decreased 1.2-1.3 fold; whereas the activity of cholinesterase increased 1.3-1.4. The administration of the I extract decreased Thiobarbituric acid Reactive Substances (TBARS) levels 1.4 fold in the serum and 1.8 fold in the liver homogenate. The administration of the II extract decreased TBARS levels 1.6 fold in the serum and 2.0 fold in the liver homogenate . The histopathological analysis of the liver material of the experimental group showed neither degenerative-dystrophic changes nor significant hemodynamic changes in comparison with the control group. The hepatoprotective effect of the II extract was more pronounced than that of the I extract and was comparable to the hepatoprotective activity of the reference drug Silibor[174].

The protective effects of diosmetin extracted from Galium verum on the thymus of U14-bearing mice were investigated using flow cytometry, peripheral blood lymphocytes were characterized based on the expression of surface markers for T helper cells ($CD4^+$) and T suppressor cells ($CD8^+$). Serum levels of tumor necrosis factor α (TNF-α), interleukin-2 (IL-2), IL-10, and transforming growth factor β1 (TGF-β1) and a cell proliferation assay were determined with an enzyme-linked immunosorbent assay. The expression of Fas and Fas ligand (FasL) on the thymus was determined by Western blotting. The results showed that diosmetin inhibited tumor growth and significantly increased the thymus weight compared with the control. Diosmetin also elevated serum levels of IL-2 and significantly reduced levels of TNF-α, TGF-β1, and IL-10 in a dose-dependent manner. Histological study and terminal dUTP nick end labeling staining results showed that diosmetin protected thymus tissue against the onslaught of tumor growth by inhibiting thymus lymphocyte apoptosis. The cell proliferation assay revealed that diosmetin might promote more thymus lymphocytes towards proliferation. The ratio of $CD4^+/CD8^+$ T lymphocytes was significantly increased from 0.69 to 2.29 by treatment with diosmetin. Immunoblotting analyses revealed that the expression of Fas and FasL on the thymus was lower in mice in the diosmetin treatment group than in the control mice[175].

Geum urbanum

A-Hepatica is an herbal combination (contained ten herbs included Geum urbanum (Clove root- 6.5 ml) was used for detoxification of the liver and gallbladder. A-Hepatica was said to be 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

The hepatoprotective potential of aqueous (QGG) and ethanol extract of G. glabra (EGG) and their possible mechanism were studied in rats hepatotoxicity.For acute hepatopathy, rats were intraperitoneally injected with CCl_4 at a dose of 1.0 ml/kg as a 50% olive oil solution. The rats were orally given the aqueous and ethanol extract of G. glabra at doses of 250, 500 mg/kg after 6 h of CCl_4 treatment. At 24 h after CCl_4 injection, samples of blood and liver were collected and then biochemical parameters and histological studies were carried out. The results revealed that both extracts inhibited significantly the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which elevated by CCl_4 and increased the activity of superoxide dismutase which decreased by CCl_4[177].

The hepatoprotective effect of aqueous extract (2gm/kg/day orally for 7 days) of Glycyrrhiza glabra roots was investigated in rabbit models with acute liver injury induced by Carbon tetrachloride at a dose of 1.25 ml/kg. Aqueous extract of G. glabra had a significant effect in amiolerating liver functions as well as restoring hepatic tissue in acute liver diseases[178].

The hepatoprotective and antioxidant potential of Glycyrrhiza glabra hydromethanolic root extract were investigated against carbon tetra chloride induced oxidative-stress mediated hepatotoxicity in liver tissue of Swiss albino mice. The results suggest that, the crude extract of root of G. glabra at the doses of 300 and 600mg/kg body wt for 7 days possessed significant hepatoprotective potential against CCl_4 induced oxidative stress mediated hepatotoxicity ($p< 0.05$) at dose dependent manner[179].

The protective effect of three medicinal plants, Nigella sativa, Glycyrrhiza glabra and Zingiber officinale, and their combination was studied against doxorubicin (DOX) -induced apoptosis and death in H9c2 cells. The cells were incubated with different concentrations of each extract or their combination for 4 hr and continued in the presence or absence of 5μM doxorubicin for 24 hr. Treatment with doxorubicin increased ROS generation, enhanced malondialdehyde (MDA) formation, and induced apoptosis. Co-treatment of the cells with each herb extract increased viability of cells dose-dependently with a maximum protection effect of about 30%, and their potencies were Nigella sativa > Glycyrrhiza glabra > Zingiber officinale. The combination of the threshold dose of each extract produced a similar effect, which was increased dose-dependently to a maximum protection of 70%. These effects were correlated with the effects of the combination on ROS and MDA[180].

The efficacy of intravenous glycyrrhizin in decreasing alanine aminotransferase level in the early stage of acute onset acute onset autoimmune hepatitis was studied clinically. Thirty-one patients defined as acute onset of autoimmune hepatitis based on a uniform criteria, were enrolled in study. 17 patients were treated with (100 ml/day) of intravenous glycyrrhizin at an early stage and 14 patients of severe disease were treated with intravenous glycyrrhizin and corticosteroids. Treatment response, clinical and biochemical parameters were evaluated. The alanine aminotransferase level could be controlled at an early stage using intravenous glycyrrhizin with no significant difference compared with glycyrrhizin and corticosteroids. Recovery rate was higher in the intravenous glycyrrhizin group than in the glycyrrhizin and corticosteroids group. The authors concluded that introduction of sufficient doses of intravenous glycyrrhizin might prevent disease progression in patients with acute onset autoimmune hepatitis[181].

The effect of Glycyrrhiza glabra on the metabolism of acetaminophen was examined in male rats. The pretreatment with the methanol extract of Glycyrrhiza glabra roots (1 g/kg, po) for 6 days 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. In order to study the effect of Glycyrrhiza glabra on the glucuronidation in rat liver, the enzymatic activity of p-nitrophenol UDP-glucuronosyltransferase (UGT), which is also called UGT1A, and intracellular concentrations of hepatic UDP-glucuronic acid were examined upon the administration of Glycyrrhiza glabra (1 g/kg, po) or glycyrrhizin (23 mg/kg, po), a major component of Glycyrrhiza glabra, for 6 days. 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

The nephroprotective activity of alcoholic and aqueous root extracts of Gossypium herbaceum was investigated in gentamicin induced nephrotoxicity in rats. Both alcoholic and aqueous extract at the dose of 250 and 500 mg/kg body weight showed significant nephroprotective activity asevident by increase in urine output,

with decrease in elevated serum creatinine and serum urea. The protective effect was further confirmed by histopathological study[183].

The protective effect of Gossipium hirsutum extracts was 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[184].

Hedera helix

α-Hederin exerted an antimutagenic effect against the clastogenicity of doxorubicin. The possible antimutagenic mechanisms of this compound included induction of metabolic enzymes which inactivated doxorubicin[185-186].

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 (5 µl) using a modified liquid incubation technique of the Salmonella/microsomal assay[187].

Helianthus annuus

The hepatoprotective activity of ethanolic and aqueous extracts of Helianthus annus flowers was studied in CCl_4 induced hepatotoxicity in wistar rats. Treatment with the Helianthus annus flower extracts significantly ($p< 0.001$) reduced elevated serum enzymatic level of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase and total bilirubin in CCl_4 induced rats treated with 200mg/kg bw. The biochemical effects of the ethanolic and aqueous extracts of Helianthus annus flowers were further confirmed by histopathological examinations of liver[188-189].

The effect of aqueous and ethanolic extracts (500 mg each for 10 days) of Helianthus annuus leaves on calcium oxalate nephrolithiasis was studied in male rats. Ethylene glycol and ammonium chloride feeding resulted in hyperoxaluria as well as increased renal excretion of calcium and phosphorus. The increased deposition of stone forming constituents in the kidneys of calculogenic rats was significantly lowered by treatment with aqueous and ethanolic extracts[190].

Oil of Helianthus annuus (Sunflower) at doses of 20 mg/kg for two weeks, protected New Zealand rabbits from myocardial infarction induced by epinephrine[191].

Applying 12% sunflower seed oil in rat food pellet for 4 weeks, decreased the incidence of reperfusion-induced ventricular fibrillation both after 6 min (2/15 vs. 7/11) and 12 min (0/11 vs. 2/8) of myocardial ischemia and the incidence of other arrhythmias was also decreased. The number of animals developing no arrhythmias during reperfusion was increased (8/15 after 6 min of ischemia, 4/11 after 12 min of ischemia vs. 0/11 and 0/8 in controls, respectively)[192].

Heliotrpium undulatum

The hapatoprotective effect of n-BuOH extract of Heliotrpium undulatum (HUBE) was evaluated in Acetylhydrazide (ACHD) induced hepatotoxicity in rats. Hepatic damage was induced by administration of ACHD (300 mg/Kg op). HUBE (200 mg/Kg op) administered for 14 days before ACHD administration, caused a decrease in LPO levels and in the transaminase and ALP levels and restored the GSH and its related enzymes (GPx, GST, GR) (50-62 %). Simultaneous administration of HUBE afforded a partial protection in hepatic GSH[193].

Hibiscus cannabinus

The hepatoprotective activity of a daily oral dose (1.6 g/ kg bw) of aqueous leaf extract of H. cannabinus was investigated over a two week period in albino rats. Liver damage in rats was induced by Carbon tetrachloride and Paracetamol . The induction was confirmed by increased plasma transaminases activities, total bilirubin concentration and Thiobarbituric Acid Reactive substance (TBRs, a measure of lipid peroxidation). Histopathological examinations substantiated this liver damage with fatty deposits, severe inflammation and severe necrosis. The aqueous leaf extract of H. cannabinus possessed significant ($p< 0.05$) hepatoprotective activity against hepatic damage represented by lowering the plasma transaminases and bilirubin concentration significantly ($p< 0.05$), absents of necrosis in liver cells of rats pretreated with extrac and inhibition of lipid peroxidation[194-195].

Hibiscus rosa-sinensis

Hibiscus rosa sinensis sinensis petal partially purified anthocyanin extract possessed a hepato protective effects against carbon tetrachloride-induced lipoperoxidation[196-197].

The methanolic extract of Hibiscus rosa sinensis flowers exhibited statistically significant ($p< 0.005$) haemoprotective activity against phenylhydrazine induced haematotoxicity in Charles foster rats[198].

The hepatoprotective potential of Hibiscus rosa sinensis flower extracts (HRS) (acute :80m 160 and 240 mg / kg bw orally, once a day for 5 days, and chronic: the same doses for 30 days chronic) was investigated in 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. Increase in blood MDA level were seen in hypercholesterolaemic groups and significantly reduced ($p> 0.05$) in HRS flower extract treated animals[(199)].

The protective effect of the alcoholic leaf extract of Hibiscus rosa-sinensis (AEH) (30 mg/kg bw for 15 days orally), was investigated against piroxicam-induced toxicity in mice. The results indicated that treatment with piroxicam alone (6.6 mg/kg bw for 15 days), resulted in a significant increase in the activities of aspartate transaminase, alanine transaminase, and alkaline phosphatase with profound hepatic lipid peroxidation as evidenced by a marked increment in the level of thoibarbituric acid reactive substances along with a distinct diminution in reduced glutathoine content and various antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in the liver. 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)].

The neuroprotective potential of the methanol extract of Hibiscus rosa sinensis (100, 200, 300 mg/kg/day for 6 days, po) was investigated in a bilateral common carotid artery (BCCA) occlusion model of global cerebral ischemic reperfusion. The bilateral common carotid artery occlusion resulted in increase in lipid peroxidation, and reduction in superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GSH) activity. The extract attenuated the ischemic reperfusion-induced increase in lipid peroxidation and fall in SOD, CAT, and GSH levels. The cerebral hypoperfusion caused a propensity towards anxiety and was accompanied by deficits of learning and memory. The extract ameliorated anxiety and improved learning and enhanced memory[(201)].

Hibiscus sabdariffa

The effects of the water extract of the dried flowers of Hibiscus sabdariffa and Hibiscus anthocyanins (HAs) were evaluated in paracetamol-induced hepatotoxicity in rats. The water extract was given in drinking water for 2, 3 or 4 consecutive weeks, and the HAs were given orally at doses of 50, 100 and 200 mg/Kg for five consecutive days. The extract for 4 weeks (but not for 2 or 3 weeks significantly improved some of the liver function tests, but did not alter the histology of the paracetamol-treated 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 extracts (1-5% for 9weeks) were tested for hepatoprotective effects against liver fibrosis induced by carbon tetrachloride (CCl_4) in rats. HSE significantly reduced the liver damage including steatosis and fibrosis in a dose dependent manner. HSE also significantly decreased the elevation in plasma aspartate aminotransferase and alanine aminotransferase and restored the decrease in glutathione content and inhibited the formation of lipid peroxidative products during CCl_4 treatment[(203)].

Pretreatment of rats with aqueous extractof H. sabdariffa resulted in significantly less hepatotoxicity than with Cd alone as measured by plasma ALT and liver ALT and AST activities. The extract also protected the rats against Cd-induced liver, prostate, and testis lipoperoxidation as evidenced by significantly reduced MDA values in these organs, as well as reduced prostatic acid phosphatase activity in the prostate, when compared to the Cd-only exposed rats[(204)].

The hepatoprotective effect of the anthocyanin-rich extract of H. sabdariffa calyces (HSARE, 100 mg/kg/d for 4 weeks) was studied examination thioacetamide (TAA)-induced hepatotoxicity in rats. Compared to the TAA-intoxicated group, HSARE significantly reduced the serum levels of alanine aminotransferase, aspartate aminotransferase and hepatic malondialdehyde by 37.96, 42.74 and 45.31%, respectively. It also decreased hepatic inflammatory markers, including tumour necrosis factor alpha, interleukin-6 and interferon gamma (INF-γ), by 85.39, 14.96 and 70.87%, respectively. In addition, it decreased the immunopositivity of nuclear factor kappa-B and CYP2E1 in liver tissue, with an increase in the effector apoptotic marker (caspase-3 positive cells), restoration of the altered hepatic architecture and increases in the activities of superoxide dismutase (SOD) and glutathione by 150.08 and 89.23%, respectively[(205)].

The effect of Hibiscus sabdariffa extract (HSE) on acetaminophen (AAP)-induced liver injury was investigated in mice. Mice were fed orally with 200, 400 or 600 mg/kg HSE for 2 weeks and then injected with 1000 mg/kg AAP. Pretreatment with HSE decreased lipid peroxidation and increased catalase activity and glutathione level. It also decreased AAP-induced liver injury, accompanied by decreased expression of pJNK, Bax and tBid in the liver[(206)].

The possible protective mechanism of the polyphenol extract of Hibiscus sabdariffa (HPE) against acetaminophen (AAP)-caused liver damage was studied in mice. Mice were orally fed with HPE (100, 200 or

300 mg/kg) for two weeks prior to an ip injection of 1000 mg/kg of AAP. 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. An in vitro assay revealed that HPE reduced AAP-induced death of BABL/c normal liver cells (BNLs), reversed the lost mitochondrial potency and improved the antioxidative status[207].

CCl_4 in rats elevated aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total protein, globulin levels significantly ($p< 0.05$) while albumin was reduced. CCl_4 significantly reduced sperm count, viability and motility ($p< 0.05$), while sperm head abnormality increased. However, administering of H. sabdariffa extract at the doses of 300 and 600 mg/kg caused the reversal of these effects significantly[208].
The protective effect of extract of H. sabdariffa was studied against SGD-induced PC12 cells injury. Cells were pretreated with different concentrations of H. sabdariffa extract (HSE) for 2 hr, and then exposed to SGD condition for 6, 12 and 18 hr. SGD caused a major reduction in cell viability after 6, 12, and 18 hr as compared with control cells ($p< 0.001$). Pretreatment with HSE (30-500 μg/ml) significantly increased cell viability following SGD insult for 6, 12 and 18 hr. A significant increase in cell apoptosis was seen in cells under SGD condition after 12hr as compared with control cells ($p< 0.001$). Pretreatment with HSE significantly decreased cell apoptosis subsequent SGD conditionafter12hr[209].

Flavonoid-rich aqueous fraction of methanolic extract of Hibiscus sabdariffa calyx was evaluated for anti-hepatotoxic activities in streptozotocin-induced diabetic wistar rats. The ameliorative effects of the extract on STZ-diabetes induced liver damage was evident from the histopathological analysis and the biochemical parameters evaluated in the serum and liver homogenates. Reduced levels of glutathione, catalase, superoxide dismutase and glutathione peroxidase in the liver of diabetic rats were restored to a near normal level in the Hibiscus sabdariffa -treated rats. Elevated levels of aspartate amino transferase, alanine amino transferase and alkaline phosphatase in the serum of diabetic rats were also restored in Hibiscus sabdariffa -treated rats. Histologically, hepatic fibrosis and excessive glycogen deposition in the diabetic rats were ameliorated in the extract-treated rats[210].

The ameliorative effect of co-administration of aqueous extract of Hibiscus sabdariffa (HS) and vitamin E was evaluated on sub-chronic carbamazepine (CBZ)-induced alterations in semen characteristics in rats. The result showed that mean sperm counts in the CBZ-treated alone group was lower than in groups with HS, Vitamin E, and HS and vitamin E ($p< 0.05$) when compared to the control groups. There was significant decrease in mean progressive sperm motility with an increase in the means non-progressive motility and non-motile sperm cells of the CBZ-treated group as compare to the control group ($p< 0.05$). While there were significant increases in mean progressive sperm motility with a decrease in non-progressive motility and non-motile sperm cell of the groups treated with CBZ in combination with HS, vitamin E, and HS and vitamin E as when compared to the CBZ-treated alone and control groups ($p< 0.05$) .There was no considerable statistically significant different in abnormal sperm cells in the treatment groups[211].

The antigenotoxic property of Hibiscus sabdariffa dry calyx extracts was in vestigated in mice. The dried calyx extracts of Hibiscus sabdariffa were administered to male albino mice at doses of 50, 100, and 150 mg/kg bw for 7 days followed by a single dose of interperitoneal injection of sodium arsenite (2.5 mg/kg bw). The calyx extract inhibited the DNA damage induced by sodium arsenite in a dose dependent manner[212].

***Hyoscyamus* Species**

The hepatoprotective activity of methanolic extracts of leaves of Hyoscyamus albus was studied against hepatotoxicity induced by CCl_4. The extract protected the liver from the toxicity of CCl_4 and significantly ($p\leq 0.05$) reduced the 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

The possible protective effect of Hypericum triquetrifolium (HT) was investigated against cyclophosphamide (CP) -induced hepatotoxicity. The results revealed that 25, 50 and 100 mg/kg HT, caused an important decrease in the (CP) toxicity. In the groups given both CP plus HT, there was a rise in serum total anti-oxidant status levels, while the levels of AST, ALT, ALP, LDH, TOS and OSI showed a remarkable decrease. Liver histological gave further evidence for the protective effect of Hypericum triquetrifolium[214-215].

Juglans regia

The protective effect of Juglans regia extract was studied in a rat model of Bleomycin (BLM)-induced pulmonary toxicopathy. Methanolic extract 150mg/kg bw was given per os to Wistar rats for 14days prior to BLM exposure. A single intratracheal injection of BLM (10U/kg bw) was administered on the eleventh day of

the treatment. BLM caused marked increase in the hydroxyproline level, lipid peroxidation, nitric oxide production, and in the activities of xanthine oxidase and myeloperoxidase in the lung tissue compared to control animals. BLM also decreased the activities of antioxidant enzymes such as glutathione reductase and catalase and increased the lung inflammation and apoptosis by upregulating the NF-κB signaling pathway and caspase-3 expression. Treatment with walnut extract attenuated these changes in a significant manner, it significantly modulated the lung injury as measured by markers of cellular injury such as lactate dehydrogenase and alkaline phosphatase, total cell count, total protein and reduced glutathione in bronchoalveolar lavage fluid. Histological findings supported the protective effects of walnut extract against BLM-induced lung injury[216].

The polyphenol-rich fraction (WP, 45% polyphenol) prepared from the kernel pellicles of walnuts was assessed for its hepatoprotective effect in mice. A single oral administration of WP (200 mg/kg) significantly suppressed serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) elevation in liver injury induced by carbontetrachloride, while it did not suppress d-galactosamine (GalN)-induced liver injury. However , of the isolated constituents, only ellagitannins with a galloylated glucopyranose core, such as tellimagrandins I, II, and rugosin C, suppressed CCl_4-induced hepatocyte damagesignificantly[217].

The protective effects of Juglans regia kernel extract against cigarette smoke extract (CSE)- induced lung toxicities was studied in Wistar rats. Prophylactic treatment of methanolic extract of J. regia kernel at the doses of 50 mg/kg b.wt. and 100 mg/kg b.wt was given by gavage to Wistar rats for 1 week prior to CSE exposure. J. regia extract significantly decreased the levels of LDH, total cell count, total protein and increased the GSH level, it also significantly restored the levels of GR, catalase and reduced the XO activity in lung tissue[218].

The modulatory effects of walnut extract on the toxicity of an anticancer drug, cyclophosphamide (CP) was evaluated in mice. Plant extract+CP group animals showed restoration in the level of cytochrome P450 (CYP) content and in the activities of glutathione S-transferase (GST), glutathione peroxidase (GP) and catalase (CAT) in both liver and kidneys. But plant extract restored the activity of superoxide dismutase (SOD) and the level of reduced glutathione (GSH) in the kidneys only when compared with CP-treated animals. Plant extract treatment alone caused significant reduction in the content of CYP in the kidneys mainly. The extract showed a significant increase in the level of GSH and in the activities of GP in both the tissues and CAT in liver only, whereas no significant change was observed in the activities of GST and SOD. The extract+CP showed a significant decrease in the LPO in liver and kidneys when compared with the CP-treated group[219].

The antioxidant effect of aqueous extractof walnut bark and its modulatory effect on cyclophosphamide (CP)-induced urotoxicity were studied in Swiss albino male mice. Walnut bark extract treatment (150 mg/kg po for 10 days) resulted in protective restoration of decreased antioxidants in CP-treated animals. CP treatment caused decreases in the activities of catalase (CAT), glutathione peroxidase (GP), glutathione reductase (GR) and glutathione S-transferase (GST) and in the glutathione (GSH) content in urinary bladder and a significant concomitant increase in lipid peroxidation (LPO). Administration of extract restored all the antioxidants significantly and lowered the elevated LPO in the bladder[220].

Thirty minutes after ip administration of extract 62.5, 125 and 250 mg/kg to mice, NaF (150 mg/kg) was applied ip to each mouse and the antihypoxic activity was estimated in minutes as the latent time of evidence of hypoxia. A statistically significant antihypoxic activity of the extract was established in the experimental model of haemic and circulatory hypoxia in mice. The effects were found to be dose-dependent[221].

Juniperus communis

The hepatoprotective activities of the of ethyl acetate fraction (EAF) of Juniperus communis leaves were investigated against PCM-Paracetamol-induced hepatic damage in Wistar albino rats. It was found that EAF treated group shows remarkable decrease in serum Aspartate aminotransferase, serum Alanine aminotransferase, total bilirubin, direct bilirubin, and alkaline phosphatase level in treatment group as compared to the hepatotoxic group[222-223].

The combination of ethanolic fruits extract of Solanum xanthocarpum (SX) and Juniperus communis (JC) was evaluated against Paracetamol (PCM) and Azithromycin (AZM) induced liver toxicity in rats. Liver toxicity was induced by combine oral administration of PCM (250 mg/kg) and AZM (200 mg/kg) for 7 days in Wistar rats. Fruit extract of SX (200 and 400 mg/kg) and JC (200 and 400 mg/kg) were administered daily for 14 days. A combine administration of AZM and PCM significantly produced liver toxicity by increasing the serum level of hepatic enzymes, oxidative parameters in liver, and histopathological. Chronic treatment of SX and JC extract significantly and dose-dependently attenuated the liver toxicity by normalizing the biochemical factors and histopathological changes in rats[224].

Jussiaea repens

Elevated serum levels of both alanine transferase (ALT) and gamma glutamyl transferase (GGT) on infection with Schistosoma mansoni were significantly reversed in comparison to praziquantel, which in turn means the improvement of liver functions. Also, elevation of malondialdehyde (MDA) and glutathione (GSH) levels in liver homogenate (6- and 2-folds, respectively) was significantly reduced by 50% and 41% on treatment with the low dose of EA-extract (100mgkg bw). The percentage of this reduction was increased at the high dose (200mgkg bw) in comparison with silymarin. This was an evidence of the strong antioxidant and consequently hepatoprotective effect of this extract, which could be attributed to its high flavonoids content[(225)].

II. CONCLUSION

The current review discussed the medicinal plants possessed hepatoprotective effects against carbon tetrachloride, D-galactosamine (D-GalN), D-galactosamine (D-GalN)/ lipopolysaccharide (LPS), N, N-dimethylformamide (DMF), oxytetracyclin thioacetamide (TAA), nitrosodiethylamine, paracetamol, rifampin, INH, aflatoxins, iron-overload and oxidative stress induced hepatotoxicity and against hepatic cancer induced chemically.

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