Review Article

REVIEW ON HEPATOPROTECTIVE PLANTS

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ABSTRACT

Liver diseases are a major problem of worldwide proportions and liver damage is very common since liver has the capacity to detoxicate toxic substances. In this review some of the plants with their extract studied for protective effect in liver diseases were summerised. The varios isolated compounds studied herein are Andrographolide, neo-andrographolide, bacoside-A, colchicine, populnin, naringenin, echinacoside, kolaviron, ternatin, indigtona, rubiadin, bacicalein, baicalin, wogonin, punicalagin, punicalin for their hepatoprotective activity. There are several chemicals have been known to induce heptotoxicity by producing reactive species which cause depletion in tissue thiol, lipid peroxidation, plasma membrane damage like carbontetrachloride, paracetomol, thioacetamide, antituberculer drugs, D galactosamine, liposachharide and arsenic etc.

Keywords: Hepatoprotective, Heptotoxicity, Medicinal plants, Antioxidants.

INTRODUCTION

Liver damage is very common since liver has to detoxicate lot many toxic substances. Most of the hepatotoxic chemicals damage liver cells primarily by producing reactive species which form covalent bond with the lipids of the tissue. Due to excessive exposure to hazardous chemicals, sometimes the free radicals generated are so high that they overpower the natural defensive system leading to hepatic damage and cause jaundice, cirrhosis and fatty liver. Production of the reactive species depletion manifests in tissue thiol depletion, lipid peroxidation, plasma membrane damage etc., culminating into severe hepatic injury[1]**.** Hepatic response to insults by chemicals depends upon the intensity of the insult, the population of cells affected, and whether the exposure is acute or chronic. Acute poisoning with carbon tetrachloride causes rapid lipid accumulation, before necrosis becomes evident. Some chemicals produce a very specific type of damage, others, notably ethanol produces sequential types of damage or combinations of damage. Hepatitis, a commonly encountered disorder of varying severity can lead to cirrhosis, liver failure and death. If acute liver disorders are not promptly treated then the disorder advances to chronic forms characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which tends to progress to cirrhosis and liver failure. The prominence of extrahepatic features of autoimmunity as well as seroimmunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis[2]**.**

HEPATOTOXICITY INDUCING AGENT

Several chemicals have been known to induce hepatotoxicity. Carbontetrachloride (CCl_4), Galactosamine, *d-Galactosamine /Lipopolysachharide (GalN/LPS)*, Thioacetamide, antitubercular drugs, paracetamol, arsenic etc are used to induce experimental hepatotoxicity in laboratory animals. Liver injury due to CCl_4 in rats was first reported in 1936[3] and has been widely and successfully used by many investigators[4,5]**.** Carbontetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of $CCl_3O^{\cdot}$, a reactive oxidative free radical, which initiates lipid peroxidation[6,7]**.**

$$CCl_4 \rightarrow CCl_3O^{\cdot} + O^{\cdot}$$

Administration of a single dose of CCl_4 to a rat produces, within 24 hrs, a centrilobular necrosis and fatty changes[3]**.** The poison reaches its maximum concentration in the liver within 3 hrs of administration. Thereafter, the level falls and by 24 hrs there is no CCl_4 left in the liver[8]**.** The development of necrosis is associated with leakage of hepatic enzymes into serum. Dose of CCl_4 that induces hepatotoxicity ranges from 0.1 to 3 ml/kg administered intraperitoneally.

Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylate nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes Galactosamine decrease the bile flow and it's content i.e. bile salts, cholic acid and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption. Dose of D-Galactosamine is 400 mg/kg, intraperitoneally[9]**.**

Lipopolysachharide activates liver Kuffer cells, releases several inflammatory mediators such as tumor necrosis factor alpha, nitric oxide, prostaglandins, leukotrienes & interleukins, causing hepatocellular damage & apoptosis, while d-GalN specifically inhibits hepatic protein synthesis by depleting cellular stores of uridine nucleotides. When co-administration with LPS, d-GalN inhibit the hepatic cytoprotective protein synthesis, thus potentiating the hepatotoxic effects of LPS[10].

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide (perhaps s-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and it's content i.e. bile salts, cholic acid and deoxycholic acid. Dose of thioacetamide is 100 mg/kg, S.C[9].

Liver is among the organs most susceptible to the toxic effects of ethanol. Alcohol consumption is known to cause fatty infiltration, hepatitis and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Hepatitis and cirrhosis may occur because of enhanced lipid peroxidative reaction during the microsomal metabolism of ethanol. It is generally accepted that alcohol can induce *in vivo* changes in membrane lipid composition and fluidity, which may eventually affect cellular functions. Among the mechanisms responsible for effects of alcohol, an increase in hepatic lipid peroxidation leads to alteration in membrane phospholipid composition. The effects of ethanol have been suggested to be a result of the enhanced generation of oxyfree radicals during its oxidation in liver. The peroxidation of membrane lipids results in loss of membrane structure and integrity. These results in elevated levels of γ-glutamyl transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decrease the activity of catalase, superoxide dismutase, along with increase in levels of glutathione in liver. The decrease in activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol[11]. Alcohol pre-treatment stimulates the toxicity of CCl_4 due to increased production of toxic reactive metabolites of CCl_4, namely trichloro-methyl radical by the microsomal mixed function oxidative system. This activated radical binds covalently to the macromolecules and induces peoxidative degradation of membrane lipids of endoplasmic reticulum rich in polyunsaturated fatty acids. This lipid peroxidative degradation of biomembranes is the principle cause of hepatotoxity[12].

Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl-P-benzoquinoneimine, an oxidative product of paracetamol to sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver. Dose of Paracetamol: 1 gm/kg P.O[12,4].

Antitubercular drugs pose a major problem since they are required to be administered over a prolonged period. Adverse effects of antitubercular therapy are sometimes potentiated by multiple drug regimens. Thus, though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is further enhanced. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P_{450} leading to hepatotoxicity. Patients on concurrent rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to rifampicin-induced cytochrome P_{450} enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half life of AcHz (metabolite of INH) is shortened by rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and rifampicin in combination. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. Pharmacokinetic interactions exist between rifampicin and pyrazinamide in tuberculosis patients, when these drugs are administered concomitantly. Pyrazinamide decrease the blood level of rifampicin by decreasing its bioavailability and increasing its clearance. Pyrazinamide, in combination with INH and rifampicin, appears to be associated with an increased incidence of hepatotoxicity[13].

Arsenicals are widespread in the environment as a result of natural or anthropogenic activities. Nearly 50 million people in Bangladesh and parts of West Bengal in India are drinking toxic level of arsenic daily knowingly or unknowingly. Arsenic is the first metalloid to be identified as a human carcinogen. Exposure to arsenic contaminated drinking water causes several health problems, Blackfoot disease, hypertension, diabetes mellitus, disturbances in nervous system, cancers of liver, kidney, lung and bladder in humans. Arsenic forms strong complexes with various sulfhydryl groups and exert its toxicity by generating reactive oxygen species (ROS) such as superoxide, hydroxyl and peroxyl radicals during its metabolism in cells. Arsenic exposure was shown to depress the antioxidant defense system leading to oxidative damage to cellular macromolecules including DNA, proteins, lipids, in biological system by tissue damage**,** altering biochemical compounds and corroding cell membranes. As the oxidative stress plays a central role in liver pathogenesis and progression, the use of

antioxidants has been proposed as therapeutic agents as well as drug coadjuvants to counteract liver damages and to protect the cellular machinery from peroxidative injury inflicted by ROS. Reports showed the protective efficacies of *Mentha piperita, Spirulina fusiformis* and *Oscimum sanctum* against sodium arsenite and mercuric chloride induced oxidative stress[14].

Table 1: Medicinal plants having hepatoprotective activity

S. No	Name of plant	Family	Part used	Extract	Animal Model	Hepatotoxic agent used	Remark	Ref. No.
1	*Aerva lanata*	Amaranthaceae	Whole plant	Petroleum ether extract	Sprague Dawley rats	CCl_4	Reduce SGOT, SGPT, and ALP; enhance antioxidant enzyme activities, reduced hepatic LPO and increased the serum total protein and albumin/globulin (A/G) ratio.	**14**
			Fresh plants	Hydroalcoholic extract	Rats	PA	Reduced in serum enzymes ALT, AST, ALP and bilirubin.	**15**
2	*Aphanamixis polystachya*	Meliaceae	Leaves	Ethanolic extract	Rats	CCl_4	Inhibits the enhanced AST, ALT, ALP, ACP and LDH activities .It also improved the depressed value of serum albumin and the enhanced value of TB in plasma	**16**
3	*Alternanthera sessilis*	Amaranthaceae	-	-	Mice & Rats	CCl_4 /APAP & D(+)-GalN	Reduced elevated SGOT and SGPT levels, microscopic and histopathological examinations including centrilobular necrosis, eosinophilic bodies, pyknotic nuclei, microvesicular degeneration of hepatocytes.	**17**
4	*Alnus japonica*	Betulaceae	Stem bark	EtOAc and BuOH fraction	Rats	APAP	Pretreatment led increase in free radical scavenging activity and a decrease in inhibition of LPO, SOD & CAT which prevent hepatoxicity.	**18**
5	*Acathopanax senticosus*	Araliaceae	Root & rhizome	Crude Powder extacts	Rats	CCl_4 /APAP	Reduced levels of AST and ALT. Histopathological observation were also favourable.	**19**
6	*Amaranthus spinosus*	Amaranthaceae	Whole plant	(50%) Ethanolic extract	Rats	CCl_4	SGOT, SGPT, ALP and TB. The presence of flavonoids and phenolics compound may be responsible.	**20**
7	*Aegiceras corniculatum*	Aegiceritaceae	Stems	n-hexane, ethyl acetate	Rats	CCl_4	Pretreatment.of animal with ethyl acetate extract showed corresponding decline in serum ALT level whereas level of AST was reduced in the presence of n-hexane extract significant inhibition in ALT & AST level were observed a relatively higher dose.	**21**
8	*Achillea millefolium*	Asteraceae	Aerial parts	70% Aqueous methanol extract	Mice	d-GalN and LPS	Pre-treatment reduced plasma ALT and AST levels in the dose dependent manner and reduced mortality. Histopatological study also provided favourable results.	**10**
9	*Aloe barbadensis*	Liliaceae	Dried aerial parts	Aqueous extract	Mice	CCl_4	Restore of SGOT, SGPT, ALP, bilirubin,TG, LPO, GSH, glucose-6-phosphatase and microsomal aniline hydroxylase and amidopyrine *N*-demethylase towards normal. Supportive Histopathological findings.	**22**
10	*Aquilegia vulgaris*	Ranunculaceae		Ethanol and ethyl acetate extract	Rats	Aflatoxin B_1	Restored the GSH concentration up to the basal level. Decreased TBARS level & reduced the GST activity.	**23**
11	*Berberis aristata*	Berberidaceae	Fruit	Fruit extract	Rats	PA/ CCl_4	Pre-treatment prevented rise in SGOT and SGPT. Reduced mortality.	**24**
12	*Boerhavia diffusa*	Nyctaginaceae	Whole plant	Alcoholic extract	Rats & mice	CCl_4	-	**25**
			Root	Aqueous extract	Rats	Thioacetamide	Decreased the level of SGOT, SGPT, ACP and ALP. Aqueous form of the drug has more hepatoprotective activity than the powder form, probably due to better absorption of the liquid form.	**26**
13	*Beta vulgaris*	Chenopodiaceae	Root	Ethanolic extract	Rats	CCl_4	Significantly prevented serum markers viz. cholesterol, TG, ALT & ALP	**27**
14	*Curcuma xanthorrhiza*	Zingiberaceae	-	-	Rats	β-D-GalN	Reduced SGOT and SGPT levels; showed favorable histopathological changes.	**28**

15	*Calotropis procera*	Asclepiadaceae	Flower	Hydro-ethanolic extract (70%)	Rats	PA	Reversed the enhance SGPT, SGOT, ALP, bilirubin and cholesterol levels; reduce the serum levels of HDL and tissue level of GSH.	**29**
16	*Camellia oleifera*	Theaceae	Seed	Oil	Male SD rats	CCl_4	Pre-treatment significantly lowered the serum levels of AST, ALT & LDH, reduced the content of the peroxidation product MDA, and elevated the content of GSH. Pre-treatment increased the activities of glutathione peroxidase, reductase and S transferase in liver.	**30**
17	*Chrysanthemum balsamita*	Asteraceae	Herba	Hydroalcoholic extract	Albino male wistar rats	CCl_4	Reduced hepatocytolysis, SGPT; histological modification; enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis .	**31**
18	*Calendula officinalis*	Asteraceae	Flos	Hydroalcoholic extract	Albino male wistar rats	CCl4	Reduced hepatocytolysis; histological; enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis	**31**
19	*Corylus avellana*	Betulaceae	Folium	Hydroalcoholic extract	Albino male wistar rats	CCl_4	Reduced hepatocytolysis ; histological ;enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis	**31**
20	*Daucus carota*	Apiaceae	-	-	Rats	Lindane	decreasing the level of serum enzymes (AST, ALT/ALP, TBARS, cholesterol, TG and LDL-cholesterol	**32**
21	*Decalepis hamiltonii*	Asclepiadaceae	Root	Aqueous extract	Rat	Ethanol	Pretreatment significantly prevented increase in activities of the serum enzymes AST, ALT, ALP & LDH in a dose dependent manner. Also suppressed LPO and protein carbonylation and maintain levels of antioxidant enzymes and GSH.	**33**
22	*Eclipta alba*	Asteraceae	-	Alcoholic extract	Rats & mice	CCl_4	Parameter like hexobarbitone-induced sleep, zoxazolamine-induced paralysis, bromosulphalen (BSP) clearance, serum levels of transaminases, bilirubin and protein. Loss of hepatic lysomal acid phosphatase and alkaline phosphatase was significantly restored by the ethanol/water (1:1) extract.	**34**
23	*Eclipta prostrate*	Asteraceae	Whole plant	Aqueous powder extract	Mice	CCl_4 or APAP	Significantly inhibited the acute elevation of serum transaminases (SGOT and SGPT)	**35**
					Rats	β-D-GalN		
24	*Epaltes divaricata*	Compositae	Whole plant	Aqueous extract	Mice	CCl_4	Pretreatment significantly reduced the serum levels of ALT, AST, ALP and significantly increased liver reduced glutathione level	**36**
25	*Emblica officinalis*	Euphorbiaceae	Fruit	50% Hydroalcoholic extract	Rats	Rifampicin, isoniazide & pyrazinamide	Reversal of serum enzyme activity i.e (AST, ALT, ALP, bilirubin) & LPO & recovery of GSH content. CAT & GSH-Px activities were restored. Histopathological examination provided favourable results.	**37**
					Adult Swiss albino mice	$NaAsO_2$	According histopathology study reduced karyolysis, karyorrhexis, necrosis and cytoplasmic vacuolization. Combined treatment of *Emblica* and arsenic (pre and post) declined the serum transaminases and LPO content; significant increase in SOD, CAT, GST and serum ALP activities.	**38**
26	*Echinacea pallid*	Asteraceae	In toto	Hydroalcoholic extract	Albino male wistar rat	CCl_4	Reduced hepatocytolysis; histological; enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis	**31**
27	*Fumaria indica*	Fumariceae	Whole plants	Petroleum ether extract	Albino Rats	CCl_4	Reductions in the elevated levels of some of the serum biochemical parameters	**39**
				Total aqueous extract		PA		
				Methanolic extract		Rifampicin		

28	*Glycosmis arborea*	Rutaceae	Aerial parts	Butanol extract	Albino Rats	GalN hydrochloride & PA & CCl4	Lowered the levels of SGPT, ALP and increased level of SOD in serum. Altered TBARS generation in liver. Necrosis of liver was reversed.	**40**
29	*Ganoderma lucidum (fungi)*	Ganodermataceae	-	Water extract	Mice	d-GalN	Pretreatment with peptides reversed the significant increase in the activities of enzymes (AST, ALT) and MDA level and significant decrease in activity of SOD and GSH level. histopathological observation also provide favourable result.	**41**
30	*GRAPE SEED OIL*	-	Seed	Seed oil	Male Wistar rats	CCl_4	reduced serum AST, ALT, ALP level, liver MDA, hyperperoxide and significant improvement in GSH, SOD, CAT, TP.	**42**
31	*Hypericum perforatum*	Clusiaceae	Dried aerial parts	50% Alcoholic extract	Male albino mice	CCl_4	Increased the bile secretion and shortens the barbiturate sleeping time.	**43**
32	*Hedyotis corymbosa*	Rubiaceae	Whole plant	Methanolic extract	Wistar rats	PA	Significantly decreased GOT, GPT, ALP and bilirubin in serum, almost normal histology of the liver, shorten hexobarbitone-induced sleeping time.	**44**
33	*Hyssopus officinalis*	Labiatea	Herba	Hydroalcoholic extract	Albino wistar rats	CCl4	Reduced hepatocytolysis ; histological & enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis.	**31**
34	*Lygodium flexuosum*	Lygodiaceae	Leaves	*n*-hexane extract	Wistar rats	CCl_4 /d-GalN	Pretreatment prevented the elevation of serum AST, ALT, LDH and liver lipid peroxides. Post-treatment normalised AST, ALT, LDH and MDA levels. significantly hepatic glutathione levels increased & Histopathological changes were reduced. Saponins, triterpenes, sterols and bitter principles could be responsible for the possible hepatoprotective action.	**45** **46**
35	*Moringa oleifera*	Moringaceae	-	-	Male Sprague Dawley rats	APAP	Pretreatment led to reduction in the level of ALT, AST, ALP, & GSH. histopathological analysis provided favourable result.	**47**
			Fruit	Aqueous & alcoholic extract	Rats	CCl4	SGPT, SGOT level decrease significantly	**48**
36	*Mamordica subangulata*	Cucurbitaceae	Leaf	Aqueous suspension	Male wistar rats	PA	Prevent elevation in SGOT, SGPT, ALP and stimulate bile flow in normal rats	**49**
37	*Oenothera biennis*	Oenotheraceae	Semen	Fatty oil	Albino male wistar rats	CCl_4	Reduced hepatocytolysis; histological & enzyme modification (LDH, SDH, CyOx, ATP-ase) & steatosis.	**31**
38	*Pluchea indica*	Compositae	Roots	Methanol fraction of pteroleum ether extract	Rats & mice	CCl_4	Significantly reduced the elevated serum enzyme levels (AST, ALT, LDH and ALP) and serum bilirubin content in acute liver injury, significant increase of reduced serum TP, albumin and albumin/ globulin ratio, reduced the prolonged pentobarbitone-induced sleeping time, plasma prothrombin time and reduction of the increased bromosulphalein retention.	**50**
39	*Polygala arvensis*	Polygalaceae	Leaves	Chloroform extract	Wistar albino rats	d-GalN	normalizing the levels of SGOT, SGPT, ALP, TB, LDH, total cholesterol ,TG, albumin, TP.	**51**
40	*Pergularia daemia*	Asclepiadaceae	Areial parts	Acetone sub fraction of ethanolic fraction	wistar albino rats	CCl_4	Significant decrease in all the elevated SGOT, SGPT, ALP, TB and Cholesterol levels; and significant increase in reduced total protein and albumin levels. Flavonoid compounds in the ethanolic subfraction of alcohol extract may be responsible for hepatoprotective properties.	**52**
41	*Pterocarpus santalinus*	Fabaceae	Stem bark	Aqueous Ethanol extracts	Male Wistar albino rats	CCl_4	Decreased in serum levels of bilirubin, AST, ALT & ALP with a increase in total protein level	**53**

42	*Phyllanthus maderaspatensis*	Phyllanthaceae	-	Hexane extract	Rats	CCl_4 and Thioacetamide	Prevented the elevation of serum AST, ALT and LDH and liver lipid peroxides. Hepatic glutathione levels significantly increased. Histopathological changes were also significantly reduced	**54**
43	*Phyllanthus emblica*	Euphorbiaceae	Fruit	50% Ethanol extract	Rats	Ethanol	Enhanced liver cell recovery by bringing the levels of AST, ALT, interleukin -1beta back to normal. Histopathological studies also provide favourable results.	**55**
44	*Phyllanthus urinaria*	Euphorbiaceae	Whole plant	Alcohol extract	Wistar albino rats	CCl_4	Pretreatment cause significant reversal of the elevated SGOT and SGPT level.	**56**
45	*Phyllanthus niruri*	Euphorbiaceae	Whole plant	Alcohol extract	Wistar albino rats	CCl_4	Pretreatment cause significant reversal of the elevated SGOT and SGPT level.	**56**
46	*Phyllanthus amarus*	Euphorbiaceae	Leaf	Methanolic extract	Male Wistar albino rats	Ethanol	Significantly enhanced level of GSH, SOD, and CAT & reduced GST, LPO level in the liver, Also increased the activities of hepatic ALT, AST & ALP.	**57**
47	*Rubia cordifolia*	Rubiaceae	Root	Aqueous-methanol extract	Mice	APAP/CCl4	Pretreatment with extract reduced the death rate to 30%, also prevented CCl_4-induced prolongation in pentobarbital sleeping time & lowered the SGOT & SGPT level.	**58**
48	*Rumex patientia*	Polygonaceae	Root	Ethanolic extract	Mice	Fe-NTA	Restored hepatic antioxidant armory architecture close to normal.	**59**
49	*Rhazya stricta*	Apocynanaceae	-	Lyophilized extracts	Mice	PA	Significantly improved the liver function tests	**60**
50	*Strychnos potatorum*	Loganiaceae	Seed	Aqueous extract	-	CCl_4	Reduce the serum marker enzymes like (SGOT, SGPT & elevated levels of ALP, serum bilirubin) Reduced enzymic and nonenzymic antioxidant levels and elevated lipid peroxide levels.	**61**
51	*Swertia chirata*	Gentianaceae	Whole plant	Methanol extract Chloroform soluble fraction	Rats	PA and GalN	The butanol soluble fraction, rich in bitter secoiridoids, was devoid of significant activity observed by biochemical and histopathological parameters.	**62**
52	*Sarcostemma brevistigma*	Asclepiadaceae	Stem	Ethyl acetate extract	Rats	CCl_4	Decreased serum bilirubin due to presence of flavonoids.	**63**
53	*S. miltiorrhiza polysaccharides (SMPS)*	Lamiaceae	-	-	Mice	Bacille-Calmette-Guerin (BCG) and LPS	Effectively improve liver, spleen and thymus index; reduced the serum levels of AST, ALT and nitric oxide; and restored liver homogenate contents of tumor necrosis factor-alpha and interleukin-1beta.	**64**
54	*Termnalia arjuna*	Combretacea	Bark	Aqueous extract	Mice	CCl_4	Prevented the rise in serum levels of GPT, ALP, TBARS; whereas decreased GSH, SOD, CAT and GST levels in the liver and kidney tissue homogenates.	**65**
55	*Tridax procumbens*	Compositae	Aerial part	Chloroform insoluble fraction from ethanolic extract	Rats	d-GalN/LPS	Pretreatment altered increase in the activities of marker enzymes (AST, ALT, ALP, LDH and gamma glutamyl transferase) and bilirubin level in serum and lipids.	**66**
56	*Taraxacum officinale*	Asteraceae	Root	Hydro-alcoholic acid extract	Rats	CCl_4	Improved level of SOD, CAT, GSH & LPO.	**67**
57	*Trianthema portulacastru m*	Aizoaceae	Whole plant	Ethanol extract	Mice	CCl_4	Dose-dependently decrease in the activities of SGOT, SGPT, LDH, ALP, GDH & SDH as well as serum levels of bilirubin and urea. Normalization of increase activities of plasma membrane enzymes GGT and 5'NTD and lysosomal enzymes acid phosphatase and acid ribonuclease in hepatic tissue. Inhibition of hepatic microsomal enzyme glucose-6-phosphatase also restored. The attenuated activities of mitochondrial succinate dehydrogenase and adenosine 5'-triphosphatase remained unaltered.	**68**

58	*Vitis vinifera*	Vitaceae	Leaves	*n*-BuOH fraction from ethanolic extract Ethanolic extract	Rats	CCl_4	Reduce plasma and liver tissue MDA, transaminase enzyme levels in plasma AST, ALT and liver GSH levels. Histopathological studies also provide favourable result.	**69**
59	*Vitex trifolia*	Verbenaceae	Leaves	Aqueous & ethanolic extact	Rats	CCl_4	Significant reduction in TB & serum markar enzyme; increase in total protein level; histological study also provide favourable results.	**70**
60	*Veronica officinalis*	Scrophulariaceae	Herba	Pressed juice	Albino male wistar rat	CCl_4	Reduced histological & enzyme modification (LDH, SDH.CyOx, ATP-as) & steatosis.	**31**
61	*Withania frutescens*	Solanaceae	Leaves	Ethanolic extract	Rat or mice	CCl_4	Alteration in the modification of Nembutal-induced sleep, bile flow, serum transaminase and hepatic fatty acids levels and histopathological study	**71**
62	*Zingiber officinale*	Zingiberaceae	Rhizome	Ethanolic extract of essential oil	Rats	CCl_4 /APAP	Lowered the elevation of ALP, AST, ALT, LDH, SDH & GDH / direct bilirubin level in dose dependent manner. Histopathology study also provides favourable result.	**72**

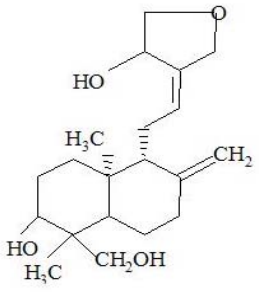
SOME SCIENTIFIC STUDIES

Anoectochilus formosanus

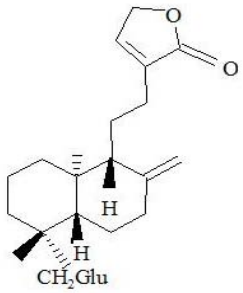
Aqueous Extracts (AFEW-2) of fresh whole plant of *Anoectochilus formosanus* (Orchidaceae) at dose 130 mg/kg showed inhibition of chronic hepatitis (induced by CCl_4) in mice by reducing SGPT & hepatic hydroxyproline level. It also diminished the hypoalbuminemia & splenomegaly. In an *in vitro* study, the LD_{50} values for H_2O_2-induced cytotoxicity in normal liver cells were significantly higher after kinsenoside (isolated from AFEW-2) pretreatment at the dose 20-40 ug/ml[73].

Andrographis paniculata

Andrographolide (active constituent of *Andrographis paniculata*, fam: Acanthaceae) antagonized the toxic effects of paracetamol on certain enzymes (SGOT, SGPT and ALP) in serum as well as in isolated hepatic cells as tested by trypan blue exclusion and oxygen uptake tests, in a significant dose dependent (0.75 - 12 mg/kg p.o. x7 days) manner[74]. Neoandrographolide increase GSH, glutathione 5-transferase, glutathione peroxidase and SOD and LPO level[26].



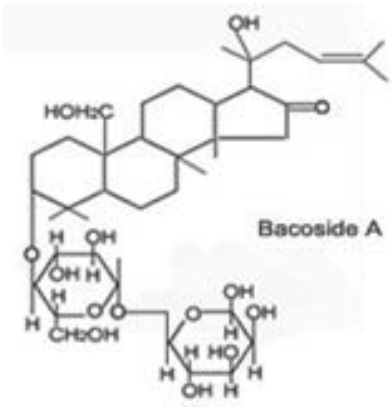
Andrographolide



Neoandrographolide

Bacopa monniera

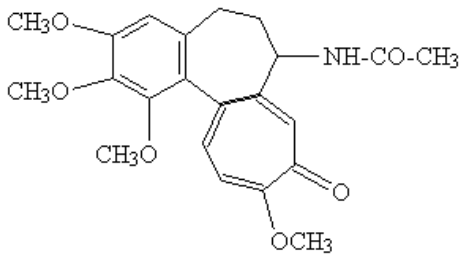
Bacoside-A (B-A) pretreatment with (isolated from *Bacopa monniera* Linn; Fam: scrophulariaceae). For 21 days in dose of 10 mg/kg of body weight once daily on oral administration. B reduces the elevated levels of serum ALT, AST, ALP, GGT, LDH, which was induced by d-GalN in rats[75].



Bacoside-A (levorotatery)

Colchicum autumnale

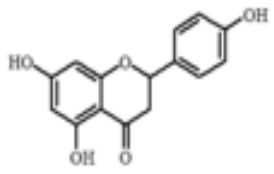
Colchicine, the major alkaloid in *Colchicum autumnale (fam: Colchicaceae)* protects the liver of experimental animals against several hepatotoxins i.e D-galactosamine & paracetamol by its ability to bind microtubule protein. A colchicine derivative, trimethylcolchicinic acid (TMCA) that does not bind tubulin i.e tested on chronic liver damage induced by CCl4 and by bile duct ligation (BDL). So, both compounds were equally potent but that TMCA could be administered at larger doses than colchicine without side effects and better hepatoprotective actions[76].



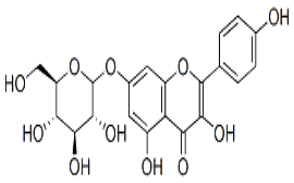
Colchicine

Cudrania cochinchinensis

Three flavonoids (25 mg/kg), wighteone, naringenin in the Ethyal acetate fraction and populnin (kaempferol-7-glucoside) in *n*-BuOH fraction obtained from the ethanol extract of *Cudrania cochinchinensis* var. *gerontogea* (fam: Moraceae) exhibited hepatoprotective effects on CCl_4-induced liver injury by reversing the SGOT and SGPT and preventing the development of hepatic lesions, including liver centrilobular inflammation, cell necrosis, fatty change, ballooning degeneration[77].



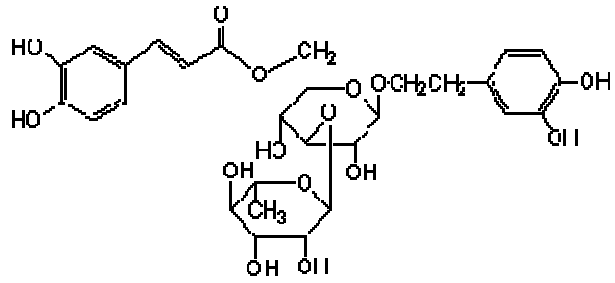
Naringenin



Populnin

Cistanches salsa

Echinacoside, (50 mg/kg, i.p) is a phenylethanoid isolated from the stems of *Cistanches salsa* (fam: Orobanchaceae), in carbon tetrachloride-induced hepatotoxicity showed significant result by reducing serum ALT, AST levels, hepatic MDA content, ROS production, and hepatic SOD activity and GSH content were restored remarkably in rats. Moreover, the histopathological damage of liver and the number of apoptotic hepatocytes were also significantly ameliorated by echinacoside treatment[78].



Echinacoside

Egletes viscosa

Ternatin (25 and 50 mg/kg) a tetramethoxyflavone isolated from dried flower buds of *Egletes viscosa* L (fam: Asteraceae) prevent significantly APAP (300 mg/kg) induced acute increase (by a 29-, 23- and 7-fold) in serum enzymes ALT, AST, LDH and MDA concentration in liver homogenates; the severity of histological alterations (centrilobular necrosis and cellular infiltration) were greatly diminished in male swiss mice that received ternatin[79].

Garcinia kola

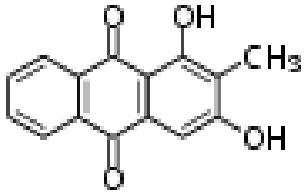
One hour prior treatment with kolaviron, a biflavonoid extract from seeds of *Garcinia kola (fem: Clusiaceae)* in dose500 mg/kg, i.p. in CCl4 (2 mL/kg per day i.p., for 3 days) induced liver damage, show significantly alterations in GOT, GPT, SDH and GLDH in serum and concentrations of hepatic GSH and TG in liver[80].

Indigofera tinctoria

A bioactive fraction, indigtone (12.5-100mg/kg p.o) characterized as trans-*tetracos*-15-enoic acid (TCA), obtained by fractionation of a petroleum ether extract of the aerial parts of *Indigofera tinctoria (fam: leguminosae)*, showed significant dose dependent hepatoprotective activity against PA (200mg/kg i.p) & CCl_4 (0.5ml/kg p.o mixed with liquid paraffin 1:1) induced liver injury in rats and mice. Pretreatment reduced Hexobarbitone induced 'sleeptime', and zoxazolamine induced "paralysis time'. Pre & post treatment reduced levels of transaminases, bilirubin, TG, LPO & restored the depleted GSH in serum[81].

Rubia cordifolia

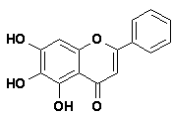
Rubiadin (isolated from *Rubia cordifolia* Linn, (Fam: Rubiaceae) at a dose of 50, 100 and 200 mg/kg was administered orally once daily for 14 days in rats. The substantially elevated serum enzymatic activities of serum GOT, GPT, ALP and GGT; decreased activities of glutathione *S*-transferase and glutathione reductase were restored towards normalization in dose dependent manner which were induce by CCl4 treatment in rats. It also significantly prevents the elevation of hepatic MDA formation and depletion of reduced GSH content in the liver[82].



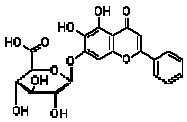
Rubiadin

Scutellaria rivularis

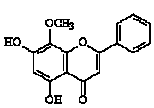
Baicalein, Baicalin and Wogonin, three major components isolated from entire plant of *Scutellaria rivularis* Benth (fam: labiatae); Wogonin (5 mg/kg i.p), exhibit best effect in CCl4 & D-GalN treated rats. Baicalein & Baicalin at the dose 20 mg/kg i.p in D-GalN & APAP; at dose 10 mg/kg i.p in CCl4 treated rats exhibit best effect. Protective effects were seen by comparing the serum GOT, GPT and histopathologic examination (hepatic lesions) [83].



Baicalein



Baicalin



Wogonin

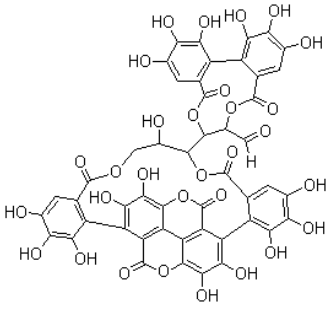
Solanum xanthocarpum (Sx) & Solanum nigrum (Sn)

The total extracts and steroidal saponins isolated with aqueous – methanol (40:60) from whole plants of Sx and Sn (fam:solanaceae); which at the doses of 100mg and

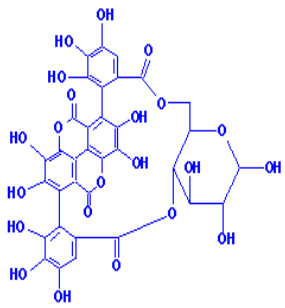
200mg/kg showed significant dose dependent attenuation of elevated levels of SGOT, SGPT, ALP, TB contents with a concomitant increase in TP content & significantly inhibited the increase in MDA levels. Glutathione, SOD and CAT levels were significantly and dose dependently increased in the test compound treated groups. The adverse effects were due to paracetamol induced hepatotoxicity in rats[1].

Terminalia catappa

Punicalagin and Punicalin isolated from the leaves of *Terminalia catappa* L., (Fam: Combretaceae) reduced hepatitis by reducing levels of AST and ALT which increased by APAP administration in rats[84].



Punicalagin



Punicalin

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