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HEPATOPROTECTIVE MEDICINAL HERBS AND ANIMAL MODELS FOR THEIR SCREENING - A REVIEW

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ABSTRACT: The liver is a vital solid organ in the upper abdomen that helps in digestion, detoxification and has other synthetic, metabolic and storage functions. Liver diseases are a major problem worldwide; viral hepatitis, alcohol, malnutrition, autoimmune and drugs being most important causes. Currently there is no way to compensate for the absence of liver function in the long term and liver transplant is the only option for those with irreversible loss of hepatic function. The scientific basis for the statement that plants and their active constituents play an important role in the prevention of diseases is continuously advancing. In this review some of the plants with their phyto-constituents studied for protective effect in liver diseases are reviewed.

INTRODUCTION: The liver plays an astonishing array of vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. And it functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. The bile secreted by the liver has, among other things, plays an important role in digestion. Therefore, maintenance of a healthy liver is essential for the overall well being of an individual [1].

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Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide, chronic alcohol consumption and microbes are common. Enhanced lipid per oxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis [2].

Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. Since time immemorial, mankind has made the use of medicinal plants in the treatment of various ailments. Recently, various medicinal plants and their phytoextracts/active bioactive compounds have shown plenty of medicinal properties including antioxidant [3, 4], anti-inflammation[5], anti-cancer [5], anti-microbial [6, 7], anti-diabetes [5, 8], anti-

nociceptive action [9] etc. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases.

One of the important and well documented uses of plant products is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent[10]. In spite of tremendous strides in modern medicine, there are hardly any drugs that stimulate liver function, offer protection to the liver from damage or help regeneration of hepatic cell. Many formulations containing herbal extracts are sold in the Indian market for liver disorders [11]. But management of liver disorders by a simple and precise herbal drug is still an intriguing problem. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder. Some of these plants have already been reported to posse's strong antioxidant activity [12, 13].

The nature has bestowed some plants with the property to prevent, treat and cure hepatic disturbances with interception of fewer side effects. Hepatoprotectives are a class of therapeutic agents that includes synthetic as well as natural product which offer protection to liver from damage or help in regeneration of hepatic cells. Medicinal herbs are significant source of hepatoprotective drugs. It has been reported that about 170 phytoconstituents isolated from 110 plants belonging to 55 families do possess hepatoprotective activity.[14] Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, curcuminoids, lignans, essential oils and terpenoids. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. Only a small portion of hepatoprotective plants as well as formulations used in traditional medicine are pharmacologically evaluated for its efficacy.[14]

According to world health organization (WHO) more than 80% of the world's population relies on traditional medicines for their primary health care needs[15]. In India, about 40 polyherbal commercial formulations reputed to have hepatoprotective action are being used. It has been reported that 160 phytoconstituents from 101 plants have hepatoprotective activity.[16, 17] Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthines.[18]

Modern medicines have little to offer for alleviation of hepatic diseases and it was chiefly the plant based preparations, which were employed for their treatment of liver disorders. But there was not much drug available for the treatment of liver disorders[19, 20]. Therefore; many folk remedies from plant origin were tested for its potential antioxidant and hepatoprotective liver damage in experimental animal model.

Liver Functions: [21]

Various functions of liver are as follows:

1. A large part of amino acid synthesis.

2. The liver performs several roles in carbohydrate metabolism:

a. Gluconeogenesis (the synthesis of glucose from certain amino acids, lactate or glycerol)
b. Glycogenolysis (the breakdown of glycogen into glucose)
c. Glycogenesis (the formation of glycogen from glucose)(muscle tissues can also do this)
d. The liver is responsible for the mainstay of protein metabolism, synthesis as well as degradation

3. The liver also performs several roles in lipid metabolism:

a. Cholesterol synthesis
b. Lipogenesis, the production of triglycerides (fats).

4. The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX,

5. X and XI, as well as protein C, protein S and antithrombin.

6. In the first trimester foetus, the liver is the main site of red blood cell production. By the 32nd week of gestation, the bone marrow has almost completely taken over that task.

7. The liver produces and excretes bile (a yellowish liquid) required for emulsifying fats.

8. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.

9. The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.

10. The liver is a major site of thrombopoietin production. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by the bone marrow.

11. The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years' supply), vitamin D (1–4 months' supply), vitamin B_{12} (1-3 years' supply), iron, and copper.

12. The liver is responsible for immunological effects- the reticulo-endothelial system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.

13. The liver produces albumin, the major osmolar component of blood serum.

14. The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure.

Breakdown of Chemical Constituents: [21]

1. The liver helps in the breakdown of insulin and other hormones.

2. It breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin).

3. It modifies toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This sometimes results in toxicities, when the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine.

4. The liver converts ammonia to urea.

List of Hepatotoxic Agents: [21]

a. Various Cshemical agents those causes hepatotoxicity are shown in **Table 1** below.

TABLE 1: VARIOUS CHEMICAL AGENTS THOSE CAUSES HEPATOTOXICITY.

Inorganic Chemical agents	**Metals and metalloids:** Antimony, Arsenic, Beryllium, Bismuth, Boron, Cadmium, Chromium, Cobalt, Copper, Iron, Lead, Manganese, Mercury, Gold, Phosphorous, Selenium, Tellurium, Thallium, Zinc, Hydrazine derivative, Iodides[22, 23].
Organic Chemical agents	**Natural : Plant toxins** Albitocin, Cycasin, Nutmeg, Tannic acid, Icterogenin, Pyrrolidizines, Saferole, Indospicine. **Mycotoxins:** Aflatoxins, Cyclochlorotine, Ethanol, Luteoskyrin, Griseofulvin, Sporidesmin, Tetracycline and Other Antibiotics. **Bacterial toxins:** Exotoxins (C.diphtheria, Clostridium botulinus), Endotoxins, Ethionine. **Synthetic:** Haloalkanes and Haloolephins, Nitroalkanes, Chloroaromatic compounds, Nitro-aromatic compound, Organic Amines, Azo compounds, Phenol and derivatives, Various other organic compounds.

b. Various Medicinal agents those causes hepatotoxicity are shown in **Table 2** below

TABLE 2: VARIOUS MEDICINAL AGENTS THOSE CAUSES HEPATOTOXICITY.

Category of Drugs	Examples
Neuropsychotropics	Hydrazine, Tranylcypromine, Anticonvulsants, Antidepressants.
Anti-inflammatory and anti-muscle spasm agents	Cinchopen, Cholchicine, Ibuprofen, Salicylates, Indomethacin.
Hormonal derivatives and other drugs used in endocrine disease	Acetohexamide, Azepinamide, Carbutamide, Tolbutamide.
Antimicrobials	Clindamycin, Novobiocin, Penicillin, Tetracycline, Sulfonamide, Amodiaquine, Isoniazid, Rifampin.
Antineoplastic	L-Asparaginase, Azacytidine, Methotrexate, 6-Mercaptopurine, Chlorambucil, Clavicin[24]

The **Table 3** shows Various Medicinal/Herbal plants having Hepatoprotective Activity.

TABLE 3: VARIOUS MEDICINAL/HERBAL PLANTS HAVING HEPATOPROTECTIVE ACTIVITY [25]

Plant Name & Family	Part Used	Extract	Hepatotoxic Model	Exp. Animal	Remarks	Ref
Aerva lanata Fam: Amaranthaceae	Whole plant	Petroleum ether	CCl_4	Sprague Dawley rats	Reduce SGOT, SGPT, & ALP; enhance antioxidant enzyme activities, reduced hepatic LPO & increased the serum total protein & albumin/globulin (A/G) ratio.	**26**
	Fresh plants	Hydro-alcoholic	PA	Rats	Reduced in serum enzymes ALT, AST, ALP & bilirubin.	**27**
Aphanamixis Polystachya Fam: Meliaceae	Leaves	Ethanolic	CCl_4	Rats	Inhibits the enhanced AST, ALT, ALP, ACP & LDH activities .It also improved the depressed value of serum albumin and the enhanced value of TB in plasma.	**28**
Alternanthera sessilis Fam : Amaranthaceae	Herb	-	CCl_4 /APAP & D-Galactosamine	Mice & Rats	Reduced elevated SGOT & SGPT levels, microscopic & HPE including centrilobular necrosis, eosinophilic bodies, pyknotic nuclei, microvesicular degeneration of hepatocytes.	**29**
Alnus japonica Fam: Betulaceae	Stem bark	EtOAc & BuOH fraction	APAP	Rats	Pretreatment led increase in free radical scavenging activity & a decrease in inhibition of LPO, SOD & CAT which prevent hepatoxicity.	**30**
Acathopanax senticosus Fam: Araliaceae	Root & rhizome	Crude Powder	CCl_4 /APAP	Rats	Reduced levels of AST and ALT. HPE were also favourable.	**31**
Amaranthus spinosus Fam: Amaranthaceae	Whole plant	50% Ethanolic	CCl_4	Rats	SGOT, SGPT, ALP & TB. The presence of flavonoids & phenolics compound may be responsible.	**32**
Aegiceras corniculatum Fam: Aegiceratacea	Stems	n-hexane, ethyl acetate	CCl_4	Rats	Pre-treatment 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.	**33**
Achillea millefolium Fam: Asteraceae	Aerial parts	70% Aqueous methanol	D-Galactosami-ne & LPS	Mice	Pre-treatment reduced plasma ALT & AST levels in the dose dependent manner & reduced mortality. HPE also provided favourable results.	**34**
Aloe barbadensis Fam: Liliaceae	Dried aerial parts	Aqueous	CCl_4	Mice	Restore of SGOT, SGPT, ALP, bilirubin, TG, LPO, GSH, glucose-6- phosphatase & microsomal aniline hydroxylase & amidopyrine N-demethylase towards normal. Supportive HPE findings.	**35**
Aquilegia vulgaris Fam: Ranunculaceae	-	Ethanol and ethyl acetate	Aflatoxin B1	Rats	Restored the GSH concentration up to the basal level. Decreased TBARS level & reduced the GST activity.	**36**

Berberis aristata Fam: Berberidaceae	Fruit	Fruit	PA/ CCl_4	Rats	Pre-treatment prevented rise in SGOT & SGPT. Reduced mortality.	**37**
Boerhavia diffusa Fam: Nyctaginaceae	Whole plant	Alcohol	CCl_4	Rats & mice	-	**38**
	Root	Aqueous	Thioacetamide	Rats	Decreased the level of SGOT, SGPT, ACP & ALP. Aqueous form of the drug has more hepatoprotective activity than the powder form, probably due to better absorption of the liquid form.	**39**
Beta vulgaris Fam: Chenopodiaceae	Root	Ethanol	CCl_4	Rats	Significantly prevented serum markers viz. cholesterol, TG, ALT & ALP	**40**
Curcuma xanthorrhiza Fam: Zingiberaceae	-	-	D-Galactosami-ne	Rats	Reduced SGOT & SGPT levels; showed favourable HPE changes.	**41**
Calotropis procera Fam: Asclepiadaceae	Flower	70% Hydro-ethanolic	PA	Rats	Reversed the enhance SGPT, SGOT, ALP, bilirubin & cholesterol levels; reduce the serum levels of HDL and tissue level of GSH.	**42**
Camellia oleifera Fam: Theaceae	Seed	Oil	CCl_4	Male SD rats	Pre-treatment significantly lowered the serum levels of AST, ALT & LDH, reduced the content of the peroxidation product MDA & elevated the content of GSH. Pretreatment increased the activities of glutathione peroxidase, reductase & S transferase in liver.	**43**
Chrysanthemum balsamita Fam: Asteraceae	Herba	Hydro alcoholic	CCl_4	Albino male wistar rats	Reduced hepatocytolysis, SGPT; histological modification; enzyme modification (LDH, SDH.CyOx, ATPase) & steatosis .	**44**
Calendula officinalis Fam: Asteraceae	Flos	Hydro alcoholic	CCl_4	Albino male wistar rats	Reduced hepatocytolysis; histological; enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis	**44**
Corylus avellana Fam: Betulaceae	Folium	Hydro alcoholic	CCl_4	Albino male wistar rats	Reduced hepatocytolysis; histological; enzyme modification (LDH, SDH.CyOx, ATP-ase) & steatosis	**44**
Daucus carota Fam: Apiaceae	-	-	Lindane	Rats	Decreasing the level of serum enzymes (AST, ALT/ALP, TBARS, cholesterol, TG and LDL-cholesterol	**45**
Decalepis hamiltonii Fam: Asclepiadaceae	Root	Aqueous	Ethanol	Rat	Pretreatment significantly prevented increase in activities of the serum enzymes AST, ALT, ALP & LDH in a dose dependent manner. Also suppressed LPO & protein carbonylation & maintain levels of antioxidant enzymes & GSH.	**46**
Eclipta alba Fam: Asteraceae	Fresh leaves	Alcoholic	CCl_4	Rats & mice	Parameter like hexobarbitone induced sleep, zoxazolamine induced paralysis, bromosulphalen (BSP) clearance, serum levels of transaminases, bilirubin & protein. Loss of hepatic lysomal acid phosphatase & alkaline phosphatase was significantly restored by the ethanol/water (1:1) extract.	**47**
Eclipta prostrate Fam: Asteraceae	Whole plant	Aqueous powder	CCl_4 or APAP D-Galactosami-ne	Mice Rat	Significantly inhibited the acute elevation of SGOT & SGPT	**48**
Epaltes divaricata Fam: Compositae	Whole plant	Aqueous	CCl_4	Mice	Pretreatment significantly reduced the serum levels of ALT, AST, ALP & significantly increased liver reduced glutathione level.	**49**
Emblica officinalis	Fruit	50% Hydro-alcoholic	Rifampicin, isoniazide & pyrazinamide	Rats	Reversal of serum enzyme activity i.e (AST, ALT, ALP, bilirubin) & LPO & recovery of GSH content. CAT &	**50**

Fam: Euphorbiaceae					GSH-Px activities were restored. HPE provided favourable results.	
			$NaAsO_2$	Adult Swiss albino mice	According HPE reduced karyolysis, karyorrhexis, necrosis and cytoplasmic vacuolization. Combined treatment of *Emblica* & arsenic (pre and post) declined the serum transaminases & LPO content; significant increase in SOD, CAT, GST & serum ALP activities.	**51**
Echinacea pallid Fam: Asteraceae	In toto	Hydro-alcoholic	CCl_4	Albino male wistar rat	Reduced hepatocytolysis; histological; enzyme modification (LDH, SDH.CyOx, ATP-ase) & Steatosis	**44**
Fumaria indica Fam: Fumariceae	Whole Plants	Petroleum Ether Total aqueous	CCl4 PA	Albino Rats	Reductions in the elevated levels of some of the serum biochemical parameters	**52**
Glycosmis arborea Fam: Rutaceae	Aerial parts	Methanol Butanol extract	Rifampicin D-galactosamine hydrochloride & PA & CCl_4	Albino Rats	Lowered the levels of SGPT, ALP & increased level of SOD in serum. Altered TBARS generation in liver. Necrosis of liver was reversed.	**53**
Ganoderma lucidum (fungi) Fam: Ganodermataceae		Aqueous	D-galactosamine	Mice	Pretreatment with peptides reversed the significant increase in the activities of enzymes (AST, ALT) & MDA level and significant decrease in activity of SOD & GSH level. HPE also provide favourable result.	**54**
Grape seed oil	Seed	Seed oil	CCl_4	Male Wistar rats	Reduced serum AST, ALT, ALP level, liver MDA, hyperperoxide & significant improvement in GSH, SOD, CAT, TP.	**55**
Hypericum perforatum Fam: Clusiaceae	Dried aerial parts	50% Alcoholic	CCl_4	Male albino mice	Increased the bile secretion & shortens the barbiturate sleeping time.	**56**
Hedyotis corymbosa Fam: Rubiaceae	Whole plant	Methanol	PA	Wistar rats	Significantly decreased GOT, GPT, ALP & bilirubin in serum, almost normal histology of the liver, shorten hexobarbitone-induced sleeping time.	**57**
Hyssopus officinalis Fam: Labiatea	Herba	Hydro-alcoholic	CCl_4	Albino wistar rats	Reduced hepatocytolysis; histological & enzyme modification (LDH, SDH. CyOx, ATP-ase) & steatosis.	**44**
Lygodium flexuosum Fam: Lygodiaceae	Leaves	n-hexane	CCl_4 / D-galactosamine	Wistar rats	Pre-treatment prevented the elevation of serum AST, ALT, LDH & liver lipid peroxides. Post-treatment normalised AST, ALT, LDH & MDA levels. Significantly hepatic glutathione levels increased & Histopathological changes were reduced. Saponins, triterpenes, sterols & bitter principles could be responsible for the possible hepatoprotective action.	**58,59**
Moringa oleifera Fam: Moringaceae	Leaves Fruit	Ethanol Aqueous & alcoholic	APAP CCl_4	Male Sprague Dawley rats Rats	Pretreatment led to reduction in the level of ALT, AST, ALP, & GSH. HPE provided favourable result. SGPT, SGOT level decrease significantly	**60** **61**
Mamordica subangulata Fam : Cucurbitaceae	Leaf	Aqueous suspension	PA	Male wistar rats	Prevent elevation in SGOT, SGPT, ALP and stimulate bile flow in normal rats	**62**
Oenothera biennis Fam: Oenotheraceae	Semen	Fatty oil	CCl_4	Albino male wistar rats	Reduced hepatocytolysis; histological & enzyme modification (LDH, SDH, CyOx, ATP-ase) & steatosis.	**44**
Pluchea indica	Roots	Methanol fraction of	CCl_4	Rats & mice	Significantly reduced the elevated serum enzyme levels (AST, ALT, LDH	**63**

Fam: Compositae		pteroleum ether extract			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.	
Polygala arvensis Fam: Polygalaceae	Leaves	Chloroform	D-galactosami-ne	Wistar albino rats	Normalizing the levels of SGOT, SGPT, ALP, TB, LDH, total cholesterol ,TG, albumin, TP.	**64**
Pergularia daemia Fam: Asclepiadaceae	Areial parts	Acetone sub fraction of ethanolic fraction	CCl_4	wistar albino rats	Significant decrease in all the elevated SGOT, SGPT, ALP, TB & Cholesterol levels; and significant increase in reduced total protein and albumin levels. Flavonoid compounds in the ethanolic sub-fraction of alcohol extract may be responsible for hepatoprotective properties.	**65**
Pterocarpus santalinus Fam: Fabaceae	Stem bark	Aqueous Ethanol	CCl_4	Male Wistar albino rats	Decreased in serum levels of bilirubin, AST, ALT & ALP with a increase in total protein level	**66**
Phyllanthus maderaspatensis Fam: Phyllanthaceae	Whole plant	Hexane	CCl_4 & Thioacetamide	Rats	Prevented the elevation of serum AST, ALT and LDH & liver lipid peroxides. Hepatic glutathione levels significantly increased. HPE changes were also significantly reduced	**67**
Phyllanthus emblica Fam: Euphorbiaceae	Fruit	50% Ethanol	Ethanol	Rats	Enhanced liver cell recovery by bringing the levels of AST, ALT, interleukin -1beta back to normal. HPE also provide favourable results.	**68**
Phyllanthus urinaria Fam: Euphorbiaceae	Whole plant	Alcohol	CCl_4	Wistar albino rats	Pretreatment cause significant reversal of the elevated SGOT & SGPT level.	**69**
Phyllanthus niruri Fam: Euphorbiaceae	Whole plant	Alcohol	CCl_4	Wistar albino rats	Pretreatment cause significant reversal of the elevated SGOT & SGPT level.	**70**
Phyllanthus amarus Fam: Euphorbiaceae	Leaf	Methanol	Ethanol	Male Wistar albino rats	Significantly enhanced level of GSH, SOD, and CAT & reduced GST, LPO level in the liver. Also increased the activities of hepatic ALT, AST & ALP.	**71**
Rubia cordifolia Fam: Rubiaceae	Root	Aqueous-methanol	APAP/CCl_4	Mice	Pretreatment with extract reduced the death rate to 30%, also prevented CCl_4-induced prolongation in pentobarbital sleeping time & lowered the SGOT & SGPT level.	**72**
Rumex patientia Fam: Polygonaceae	Root	Ethanol	Fe-NTA	Mice	Restored hepatic antioxidant armory architecture close to normal.	**73**
Rhazya stricta Fam: Apocynanaceae	-	Lyophilized extracts	PA	Mice	Significantly improved the liver function tests	**74**
Strychnos potatorum Fam: Loganiaceae	Seed	Aqueous	CCl_4	Rats	Reduce the serum marker enzymes like (SGOT, SGPT & elevated levels of ALP, serum bilirubin) Reduced enzymic & nonenzymic antioxidant levels & elevated lipid peroxide levels.	**75**
Swertia chirata Fam: Gentianaceae	Whole plant	Methanol Chloroform soluble fraction	PA & D-galactosamine	Rats	The butanol soluble fraction, rich in bitter secoiridoids, was devoid of significant activity observed by biochemical and histopathological parameters.	**76**
Sarcostemma brevistigma Fam: Asclepiadaceae	Stem	Ethyl acetate	CCl_4	Rats	Decreased serum bilirubin due to presence of flavonoids.	**77**

S. miltiorrhiza polysaccharides (SMPS) Fam : Lamiaceae	-	-	Bacille-Calmette-Guerin (BCG) and LPS	Mice	Effectively improve liver, spleen & thymus index; reduced the serum levels of AST, ALT & nitric oxide; & restored liver homogenate contents of tumor necrosis factor-alpha & interleukin-1beta.	**78**
Termnalia arjuna Fam: Combretacea	Bark	Aqueous	CCl_4	Mice	Prevented the rise in serum levels of GPT, ALP, TBARS; whereas decreased GSH, SOD, CAT & GST levels in the liver and kidney tissue homogenates.	**79**
Tridax procumbens Fam: Compositae	Aerial part	Chloroform insoluble fraction from ethanolic extract	D-galactosamine /LPS	Rats	Pretreatment altered increase in the activities of marker enzymes (AST, ALT, ALP, LDH & gamma glutamyl transferase) & bilirubin level in serum and lipids.	**80**
Taraxacum officinale Fam: Asteraceae	Root	Hydro-alcoholic	CCl_4	Rats	Improved level of SOD, CAT, GSH & LPO.	**81**
Trianthema portulacastrum Fam:Aizoaceae	Whole plant	Ethanol	CCl_4	Mice	Dose-dependently decrease in the activities of SGOT, SGPT, LDH, ALP, GDH & SDH as well as serum levels of bilirubin & urea. Normalization of increase activities of plasma membrane enzymes GGT and 5'NTD & lysosomal enzymes acid phosphatase & acid ribonuclease in hepatic tissue. Inhibition of hepatic microsomal enzyme glucose-6-phosphatase also restored. The attenuated activities of mitochondrial succinate dehydrogenase & adenosine 5'-triphosphatase remained unaltered.	**82**
Vitis vinifera Fam: Vitaceae	Leaves	n-BuOH fraction from ethanolic extract	CCl_4	Rats	Reduce plasma & liver tissue MDA, transaminase enzyme levels in plasma AST, ALT & liver GSH levels. HPE also provide favourable result.	**83**
Vitex trifolia Fam: Verbenaceae	Leaves	Aqueous & Ethanol Ethanol	CCl_4	Rats	Significant reduction in TB & serum markar enzyme; increase in total protein level; HPE also provide favourable results.	**84**
Veronica officinalis Fam: Scrophulariaceae	Herba	Pressed juice	CCl_4	Albino male wistar rat	Reduced histological & enzyme modification (LDH, SDH.CyOx, ATPas) & steatosis.	**44**
Withania frutescens Fam: Solanaceae	Leaves	Ethanol	CCl_4	Rat or mice	Alteration in the modification of Nembutal-induced sleep, bile flow, serum transaminase & hepatic fatty acids levels & HPE	**85**
Zingiber officinale Fam: Zingiberaceae	Rhizome	Ethanolic extract of essential oil	CCl_4 /APAP	Rats	Lowered the elevation of ALP, AST, ALT, LDH, SDH & GDH / direct bilirubin level in dose dependent manner. HPE also provides favourable result.	**86**
Tubers of *Amorphophallus campanulatus* Roxb.	Tubers	Ethanol	CCl_4	Albino Rat	Biochemical normalisation. HPE shows significant results.	**87,88**
Baliospermum montanum	Roots	Methanol	CCl_4	Albino Rat Culture of rat hepotocytes	Normalisation of elevated enzyme levels. Biochemical parameters were restored significantly by fraction of ethyl methyl ketone.	**89**
Bacopa monniera Linn Fam: Scrophulariaceae	-	-	D-galactosamine	Albino Rat	Raised Serum ALT, AST, ALP, GGT, LDH levels reduced.	**90**
Colchicum	-	-	PA/ D-	-	Better hepatoprotective effects.	**91**

autumnale Fam: Colchicaceae			galactosamine			
Cudrania cochinchinensis var. *gerontogea* Fam: Moraceae	-	n-BuOH fraction from Ethanol	CCl_4	-	Reversing the SGOT & SGPT & preventing the development of hepatic lesions, including liver centrilobular inflammation, cell necrosis, fatty change, ballooning degeneration.	**92**
Cistanches salsa (fam: Orobanchaceae)	Stems	Echinacoside, (50 mg/kg, i.p)	CCl_4	Albino Rat	Reducing serum ALT, AST levels, hepatic MDA content, ROS production, & hepatic SOD activity & GSH content were restored remarkably in rats. HPE showed number of apoptotic hepatocytes were also significantly ameliorated by echinacoside treatment.	**93**
Capparis deciduas	Stems	Aqueous & Methanol	CCl_4	Albino Rat	Slight to mild changes in hepatocytes were observed in rats dosed by aqueous extract & higher dose of methanolic extract, whereas the lower dose of methanolic extract revealed more severe lesions than the higher dose.	**94**
Calotropis procera	Flower	Hydro-ethanolic 70%	PA	Albino Rat	Lowered the altered levels of biochemical markers to the near normal levels in the dose dependent manner.	**95**
Cudrania tricuspidata Bureau (Moraceae)	Root bark	MeOH	Tacrine induced cytotoxicity	-	*In vitro* study, furnished four isoprenylated xanthones, cudratricusxanthone A (1), cudraxanthone L (2), cudratricusxanthone E (3), & macluraxanthone B (4). All of these compounds showed the significant hepatoprotective effect on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells. Compounds 1, 2, & 4 also exhibited the significant hepatoprotective effect on nitrofurantoin-induced cytotoxicity in human liver-derived Hep G2 cell.	**96**
Cassia fistula (Fabaceae)	Leaves	n-heptane	PA	Albino Rat	Significant protective effect by lowering the serum levels of SGOT, SGPT, bilirubin & ALP.	**97**
Curcuma longa	-	-	PA	Albino Rat	Significant decrease in serum ALT, AST & ALP.	**98,99**
Embelia ribes	-	-	PA	Swiss mice	showed a dose dependent fall of 41 % 47 % & 66 % to the serum SGPT level as compared to PA treated group. HPE revealed liver mice revealed 67 %, 70 % & 80 % normal liver.	**100**
Egletes viscosa L (fam: Asteraceae)	dried flower buds	-	APAP	Swiss mice	diminished serum enzymes ALT, AST, LDH in male swiss mice that received ternatin. HPE revealed diminished alterations centrilobular necrosis and cellular infiltration	**101**
Launaea intybacea (Asteraceae)	-	Aqueous/ ethyl acetate	CCl_4	Albino Rat	shown very significant hepatoprotection by reducing serum total bilirubin, direct bilirubin, SGPT & SGOT levels	**102**
Leucas ciliata (Lamiaceae)	-	Ethabnol	CCl_4	Albino Rat	Inhibited the increase in biochemical markers	**103**
Phyllanthus-polyphyllus (Euphorbiaceae)	-	Methanol	APAP	Albino Rat	Showed a remarkable hepatoprotective and antioxidant activity as judged from the serum marker enzymes and antioxidant levels in liver tissues.	**104**
*Phyllanthus reticula*tus (Euphorbiaceae)	Ariel Part	-	CCl_4	Albino Rat	Significant changes in serum levels of SGPT, SGOT, SALP & bilirubin	**105**
Ptrospermum acerifolium (Sterculiaceae)	Leaf	Ethanol	CCl_4	Albino Rat	The toxicity effect of carbon tetrachloride was controlled significantly by restoration of the levels of serum	**106**

					bilirubin & enzymes.	
Piper nigrum (piperaceae)	Root	Aqueous/ ethanol/ chloroform	CCl_4	Albino Rat	Ethanol extract exhibits the highest hepatoprotective activity ($p < 0.05$).	**107**
Sesamum indicum Linn. (Pedaliaceae)	Seed	Ethanol	CCl_4	Albino Rat	Elevated serum enzymatic level of SGOT, SGPT, ALP, ACP, Total Protein, Albumin and Total Bilirubin were restored towards normalization significantly.	**108**
Spermacoce hispida. (Rubiaceae)	-	Ethanol	CCl_4	Albino Rat	The serum biochemical analysis results exhibited significant protective effect from hepatic damage. HPE studies revealed its hepatoprotective activity.	**109**
Tinospora cordifolia (Menispermaceae)	-	-	CCl_4	Albino Rat	The treatment of Tinospora cordifolia significantly recovers all the serum and liver parameters like normal levels.	**110**
Terminalia catappa Fam: Combretaceae	Leaves	-	APAP	Albino Rat	Reduced hepatitis by reducing levels of AST and ALT which increased by administration in rats	**111**

The **Table 4** shows Various Phytoconstituents showing Hepatoprotective Activity below.

TABLE 4: VARIOUS PHYTOCONSTITUENTS SHOWING HEPATOPROTECTIVE ACTIVITY[112]

Phytoconstituents	Liver protective drug	Part used
Phenols	1. *Arnica Montana* Linn.[113]	Plant
	2. *Cichorium intybus* Linn.[114,115]	Plant
	3. *Picrorriza kurroa* Royle[116]	Root
	4. *Syzygium aromaticum* Linn.[117]	Plant
Coumarin	1. *Armillaria tabescens* Scop.[118]	Fungus
	2. *Artemisiae capillaries* herba[119]	Plant
	3. Hemidesmus indicus[120]	Roots
Lignans	1. *Schisandra chinensis* Turcz.[121]	Fruit
	2. *Schisandra sphenanthera*[122]	Fruit
	3. *Silybum marianum* Gaertn[123, 124]	Seed
	4. *Thujopsis dolabrata* [125]	Leaves
Essential oil	1. *Anethum graveolens* Linn.[126]	Fruit
	2. *Apium graveolens* Linn.[127, 128]	Seed
	3. *Azadirachta indica* [139]	Leaves
	4. *Carapa guianensi* Aublet[130]	Seed
	5. *Cynara scolumus* Linn.[131]	Leaves, Flower
	6. *Foenuculum vulgare* Mill.[132,133]	Plant
	7. *Petroselinum sativum* Hoffm.[134]	Plant
	8. *Pimpinella anisum* Linn.[135]	Plant
Monoterpens	1. *Murraya koenigii* Linn.[136]	Rhizome
Sesquiterpens	1. *Atractylodis lanceae* Rhizoma[137]	Root
	2. *Lindera strychnifolia* (Sieb. & Zucc.)[138]	Leaves
Diterpens	1. *Andrographis paniculata* Nees[139,140]	Whole plant
Triterpens	1. *Glycyrrhiza glabra* Linn.[141,142]	Root
	2. *Hedyotis corymbosa* Linn.[143]	Whole plant Trunkwood
	3. *Protium heptaphyllum* Aubl.[144]	Plant
	4. *Sambucus chinesis* Lindley[145]	Leaves
	5. *Tetrapanax papyriferus*[146]	
Carotenoids	1. *Gardenia florida*[147]	Fruit
Glycosides	1. *Aloe barbadensis* Mill[148]	Leaves
	2. *Dianthus superbus* Linn.[141]	Plant
	3. *Panax ginseng*[141]	Rhizome
	4. *Polygonum cuspidatum*[149]	Root
	5. *Polygonum multiflorum* Thunb.[149]	Root
Flavonoids	*1. Acacia catechu* Willd.[150]	Hard wood
	2. Aegiceras corniculatum[151]	Stem
	3. Artemisia capillaries Thunb.[118]	Plant
	4. Calotropis gigantean R. Br.[152]	Leaves
	5. Canscora decussate Roxb.[153]	Plant and Juice
	6. Cassia occidentals Linn.[154]	Leaves
	7. Clausena dentate Willd.[155]	Plant

	8. Garcinia kola Heckel[156]	Inflorescences
	9. Helichrysum arenarium Linn.[157]	Plant
	10. Mentha longifolia Linn.[158]	Leaves
	11. Phyllanthus emblica Linn.[159]	Leaves
	12. Scrophularia grossheimi[155]	Plant
	13. Tagetes patula Linn.[156]	Seeds
	*14. Uncaria gambir (Hunter)*Roxb[156]	Heartwood
Alkaloids	*1. Aristolochia clematis*[160]	Plant
	2. Fumaria parviflora Lam.[161]	Plant
	3. Fumaria officinalis Linn.[161]	Plant
	4. Herniaria glabra Linn.[162]	Whole Plant
	5. Peumus boldus Molina.[163]	Plant
	6. Physalis peruviana[164]	Plant
Xanthines	*1. Coffea Arabica*[165]	Seed
	2. Thea sinensis[166]	Leaves

The **Table 5** shows Medicinal Plants in Ayurveda showing Hepatoprotective activity below.

TABLE 5: MEDICINAL PLANTS IN AYURVEDA SHOWING HEPATOPROTECTIVE ACTIVITY[112].

Scientific Name	Family	Parts Used
Achille millefolium Linn.	Compositae	Plant
Aconitum herterophy llum wall.	Ranunculaceae	Root
Aegal marimelos Corr.	Rutaceae	Leaves
Aegiceras corniculatum	Aegiceritaceae	Stem
Allium sativum Linn.	Liliaceae	Bulb
Aloe barbadensis Mill.	Ranunculaceae	Plant
Aloe perry Baker.	Ranunculaceae	Plant
Andrographic paniculata Nees.	Acanthaceae	Plant
Aphanamixis polystachya Wall. Parkar	Meliaceae	Bark
Apium graveolens Linn.	Umbelliferae	Seeds
Asteracantha longifolia Nees.	Acanthaceae	Leaves, root & seeds
Azadirachta indica A. Juss	Meliaceae	Exudates
Berberis lycium Royle.	Berberidaceae	Leaves
Boerhaavia diffusa Linn.	Nyctaginaceae	Root
Bryonia alba Linn.	Cucurbitaceae	Root
Calotropis gigantea (Linn)R.Br.	Asclepiadaceae	Latex, Flower, Stem
Canavalia ensiformis DC	Leguminosae	Root
Carapa Guianensis Aublet.	Meliaceae	Seed
Carthamus tinctorius Linn.	Compositae	Flower
Cephaelis ipecacuanha Rich.	Rubiaceae	Draught
Cichorium intybus Schard.	Compositae	Plant
Citrullus colocynthis Schrad.	Cucurbitaceae	Root
Clausena dentate Willd.	Rutaceae	Stem bark
Colchicum luteum Baker.	Liliaceae	Corma
Coptis teeta Wall.	Ranunculaceae	Rhizome
Cosmpstigma racemosa Weight.	Asclepidaceae	Root, Bark
Croton oblongifolius Roxb.	Euphorbiaceae	Bark
Cuscita reflexa Roxb.	Convolvulaceae	Stem
Cyprus pertunuis	Cyperanceae	Plant
Delphinium zalil Atich & Hemse	Ranunculaceae	Plant
Desmodium biflorum Linn.	Fabaceae	Whole plant
Eclipta alba Hassk.	Compositeae	Plant juice
Emblica officinalis Gaertn.	Euphorbiaceae	Fruit
Euphorbia neriifolia Linn.	Euphorbiaceae	Fruit
Ferula alliaceae boiss.	Umbelliferae	Gum resin
Ficus asperrima Roxb.	Moraceae	Juice, Bark
Ficus benjamina Linn.	Moraceae	Bark juice
Ficus carica Linn.	Moraceae	Fruit
Ficus hetrrophylla Linn. F.	Moraceae	Root juice
Flacoutia indica Merr.	Flacourtiaceae	Bilangra
Fumaria officinalis Linn.	Fumariaceae	Whole plant

Gentiana kurroo Royld.	Gentianaceae	Root
Garcinia indica chois.	Guttiferae	Fruit
Fumaria parviflora Lam.	Fumariaceae	Whole plant
Garcinia kola Heckel.	Guttiferae	Seeds
Gymnema sylvestre R. Br	Asclepiadaceae	Leaves
Hedyotis corymbosa Linn.	Rubiaceae	Whole plant
Hemidesmus indicus	Asclepiadaceae	Roots
Hermodactylus gol	Colchicaeae	Tubers
Herniaria glabra Linn.	Caryophyllaceae	Flowers
Hygrophila spinosa T. Anders	Acanthaceae	Leaves, Roots, Stem, Seeds
Hyssopus officinalis Linn.	Labiatae	Plant
Jatropha gossypifolia Linn.	Euphorbiaceae	Leaves
Lawsonia inermis Linn.	Lythraceae	Bark
Luffa echinata Roxb.	Cucurbitaceae	Fruit, Seed
Lycopersicon esculentum Mill.	Solanceae	Fruit
Mentha longifolia Linn.	Labiatae	Leaves
Momordica cochimchinesis spreng.	Cucurbitaceae	Fruit
Moringa oleifera Lam.	Moringaceae	Root
Murraya koenigii Linn.	Rutaceae	Leaves
Myristica fragrans Houtt.	Myristicaeae	Seed
Nelumbo mucifera Gaertn.	Nymphaceae	Flower
Paeonia emodi Wall.	Ranunculaceae	Tubers
Phyllanthus niruri Linn.	Euphorbiaceae	Plant
*Picrorhiza kurro*a Royle.	Scrophulariaceae	Root
Pinus roxburghii Sargent	Pinaceae	Volatile oil
Podophyllum emodi Wall.	Berberidaceae	Rhizome
Portulaca oleracea Linn.	Potulacaceae	Herb
Protium heptaphyllum March.	Burseraceae	Trunk wood
Prunus armeniaca Linn.	Rosaceae	Fruit
Pyrenthrum indicum DC.	Compositae	Flowers
Rhem emodi Wall.	Polygonaceae	Rhizome
Rumex crispus Linn	. Polygonaceae	Root
Solanum dulcamara Linn.	Solanaceae	Berries
Solanum indicum Linn.	Solanaceae	Fruit, Plant
Symplocos racemosa Roxb.	Symplocaceae	Bark
Sphaeranthus hirtus Willd.	Compositae	Herb
Solanum nigrum Linn.	Solanaceae	Dried fruit
Swertia chirata BuchHam.	Gentianaceae	Plant
Taraxacum officinale Weber.	Compositae	Root
Terminalia chebula Retz.	Combretaceae	Fruit
Tinospora cordifolia Willd.	Menispermaceae	Stem
Trichosanthes cordata Roxb.	Cucurbitaceae	Root
Trigonella foenumgraececum Linn.	Leguminosae	Seed
Triticum sativum Lam.	Gramineae	Roots
Vitex negundo Linn.	Verbenaceae	Plant
Woodfordia fruticosa Kurz.	Lythraceae	Flower
Zinziber officinale Rose.	Zingiberaceae	Rhizome

The **Table 6** shows Database of retrospective studies on Medicinal herbs showing hepatoprotective activity below.

TABLE 6: DATABASE OF RETROSPECTIVE STUDIES ON MEDICINAL HERBS SHOWING HEPATOPROTECTIVE ACTIVITY.[167]

Scientific Name	Part Used	Extract Solvent	Hepatotoxic Model	Ref.
Adoxaceae Viburnum tinus L	Leaves	Aqueous / Methanol	Carbon tetrachloride	5
Aegle marmelos	Leaves	Ethanol	Alcohol	168
Aframomum longiscapum	Seed	Aqueous	Sodium Arsenite & Ethanol	169
Allium paradoxum	Aerial parts/ Bulbs	-	Carbon tetrachloride	170
Amomum xanthioides	Whole part	Aqueous	Dimethyl nitrosamine	171
Andropogon muricatus	Roots	Methanol	Bile duct ligation-induced liver fibrosis	172

Andrographis lineate	Leaves	Aqueous / Methanol	Carbon tetrachloride	173
Andrographis paniculata	Leaves	Alcohol	Carbon tetrachloride	174
Anisotes trisulcus	-	Ethanol	Carbon tetrachloride	175
Annona squamosa	Whole plant	Alcohol	Diethylnitrosamine	176
Apium graveolens	Seeds	Methanol	Paracetomol + Thioacetamide	177
Acanthopanax senticosus	-	-	Carbon tetrachloride & Paracetomol	178
Artemisia vulgaris	Aerial	Aqueous / Methanol	D-galactosamine + Lipopolysaccharide	179
Artemisia iwayomogi	-	Ethyl acetate	Carbon tetrachloride	5
Artemisia capillaris	-	Ethyl acetate	Carbon tetrachloride	180
Anoectochilus formosanus Hayata	Whole plant	Aqueous	Carbon tetrachloride	181
Asteracantha longifolia	Whole plant	Aqueous	Carbon tetrachloride and Paracetomol	182
Achyrocline satureioides	Aerial	Aqueous	Bromobenzene	183
Alchornea cordifolia	Leaves	Ethanol	Paracetomol	184
Acacia catechu	Bark	Ethyl acetate	Carbon tetrachloride	185
Beta vulgaris	Root	Ethanol	Carbon tetrachloride	186
Bauhinia racemosa	Bark	Methanol	Paracetomol + Carbon tetrachloride	187
Bauhinia variegate	Bark	Alcohol	Carbon tetrachloride	188
Borreria hispida		Methanol	Paracetomol	187
Bixa orellana	Seeds	Methanol	Carbon tetrachloride	188
Coronopus didymus	Whole plant	Aqueous	Carbon tetrachloride	189
Commiphora opobalsamum	Aerial	Ethanol	Carbon tetrachloride	190
Caesalpinia sappan	Heartwood	Methanol /Aqueous	Carbon tetrachloride	191
Cajanus cajan	Leaves	Methanol	Alcohol	192
Carum copticum	Seeds	Aqueous / Methanol	Carbon tetrachloride & d-galactosamine	193
Cassia roxburghii	-	Methanol	Ethanol + Carbon tetrachloride	192
Cleome viscose	Leaves	Ethanol	Carbon tetrachloride	194
Casuarina equisetifolia	Leaves, Bark	Methanol	Carbon tetrachloride	195
Chamomile recutita	-	Ethanol	Paracetomol	196
Careya arborea Roxb.	Bark	Methanol	Carbon tetrachloride	197
Cyperus articulates	Whole parts	Methanol	Paracetomol	192
Cichorium endivia L.	Leaves	-	Tertiary Butyl Hydroperoxide	198
Cichorium intybus L.	Seeds	Alcohol	Carbon tetrachloride	190
Cichorium intybus	-	Polyphenolic extracts	Thioacetamide	191
Cissampelos pareira	Root	Hydro-alcoholic	Carbon tetrachloride	192
Cleome viscosa -	Seeds	-	Carbon tetrachloride	193
Clitoria ternatea	Leaves	Methanol	Paracetomol	194
Coccinia grandis Linn	-	Alcohol	Carbon tetrachloride	195
Combretum quadrangulare	Leaves	Methanol	D-galactosamine	196
Cuscutae semen	Seeds	Aqueous	Dimethynitrosamine	197
Crassocephalum crepidioides	Whole plant	Aqueous	D-galactosamine + Lipopolysaccharide + Carbon tetrachloride	198
Desmodium triquetrum	Leaves	Ethanol	Carbon tetrachloride	199
Diospyros malabarica	Bark	Methanol	Carbon tetrachloride	200
Emblica officinalis	Fruits	Hydro-Alcoholic	Anti- Tuberculosis drug	201
Enicostemma axillare	-	Ethyl actetate	Carbon tetrachloride	202
Erycibe expansa	Stem	Methanol	D-galactosamine	203
Feronia limonia	Root	Methanol	Carbon tetrachloride	204
Ficus carica	Leaves	Methanol	Carbon tetrachloride	205
Ficus chlamydocarpa	-	Methanol	Carbon tetrachloride	206
Flacourtia indica	Aerial parts	Petroleum ether and Ethyl acetate	Paracetomol	207
Flaveria trinervia	Leaves	Methanol	Carbon tetrachloride	208
Enicostemma littorale	Whole plant	Alcohol	Carbon tetrachloride	209
Gentiana scabra	-	Aqueous	Carbon tetrachloride	210
Gundelia tourenfortii	Stalk	Hydro-alcoholic	Carbon tetrachloride	211
Hygrophila auriculata	Seeds	Methanol	Paracetomol + Thioacetamide	212
Hypoestes triflora	Leaves	Aqueous	Carbon tetrachloride	213
Indian Phyllanthus	Leaves, Stem	Methanol	tert-Butyl Hydroperoxide	214
Kalanchoe pinnata	Leaves	Ethanol	Carbon tetrachloride	215
Luffa echinata	Fruit	Petroleum ether, Acetone, Methanol	Carbon tetrachloride	216
Ocimum basilicum	Leaves	Ethanol	Carbon tetrachloride + Hydrogen peroxide	217
Lagenaria breviflora	Fruit	Ethanol	Carbon tetrachloride	218
Lepidium sativum	-	Methanol	Carbon tetrachloride	219
Luffa acutangula	-	Hydro-alcoholic	Carbon tetrachloride + Rifampicin	220

Meconopsis integrifolia	Whole part	Ethanol	Carbon tetrachloride	221
Melochia corchorifolia	Aerial parts	Ethanol/ethyl acetate /hexane	Carbon tetrachloride	222
Monochoria vaginalis	Whole parts	Methanol	Carbon tetrachloride	223
Moraceae Ficus carica	Leaves	Methanol	Carbon tetrachloride	224
Morinda citrifolia	-	-	Carbon tetrachloride	225
Moringa oleifera	Leaves	Hydro-ethanolic	Paracetomol	226
Nymphaea stellata	Flowers	Alcohol	Carbon tetrachloride	227
Orthosiphon stamineus	Leaves	Methanol	Paracetomol	228
Phyllanthus atropurpureus	Aerial parts	Alcoholic	Carbon tetrachloride	229
Phyllanthus maderaspatensis	Whole plant	n-Hexane	Carbon tetrachloride + Thioacetamide	230
Phyllanthus niruri	Leaves	Aqueous	Paracetomol	231
Prostechea michuacana	-	Methanol	Carbon tetrachloride & Paracetomol	232
Pterocarpus marsupium	Bark	Methanol	Carbon tetrachloride	233
Rhinacanthus nasuta	Root	Methanol	Carbon tetrachloride	234
Sargassum polycystum	-	Ethanol	D-galactosamine	235
Silybum marianum	-	Polyphenolic extracts	Thioacetamide	236
smilax perfoliata	Aerial parts	Ethanol	Carbon tetrachloride	237
Solanum elaeagnifolium		Aqueous-methanolic	Acetaminophen	238
Solanum nigrum	-	Aqueous	Carbon tetrachloride	239
Solanum xanthocarpum	Fruits	Ethanol	Carbon tetrachloride	240
Sarcostemma brevistigma	Bark	Ethyl acetate	Carbon tetrachloride	241
Roots, Leaves	Aqueous		Carbon tetrachloride & d- galactosamine	242
Trianthema portulacastrum	Leaves	Ethanol	Paracetomol + Thioacetamide	243
Terminalia belerica	Fruits	Ethanol	Carbon tetrachloride	244
Terminalia arjuna	Leaves	Aqueous	Tertiary Butyl Hydroperoxide	245
Trigonella foenum-graecum	Leaves	Ethanol	Carbon tetrachloride + Hydrogen peroxide	246
Vitis thunbergii	Leaves	Ethanol	Carbon tetrachloride	247
Wedelia calendulacea	Leaves	Ethanol	Carbon tetrachloride	248

Screening Models for Hepatotoxic Studies:

Various models needed for the screening of hepatoprotectives can be classified as follows:

i. *In vivo* models
ii. *In vitro* studies

These are briefly described as:

i. *In Vivo* Models:

a. Carbon Tetrachloride (CCl_4) induced hepatotoxicity:

Liver injury due to carbontetrachloride in rats was first reported in 1936 and has been widely and successfully used by many investigators. Carbontetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl_3O^-, a reactive oxidative free radical, which initiate lipid peroxidation. Administration of a single dose of CCl_4 to a rat produces a centrilobular necrosis and fatty changes within 24 hrs. 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. The development of necrosis is associated with leakage of hepatic enzymes into serum.[249-254]

b. Galactosamine induced hepatotoxicity:

D-Galactosamine induced liver damage has been extensively used as an experimental model. 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 decreases 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.[255]

c. Thioacetamide induced hepatotoxicity:

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide 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.[255]

d. Alcohol induced hepatotoxicity:

Among the organs liver is 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. This result in elevated levels of ¡-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.[256,257]

e. Paracetamol induced hepatotoxicity:

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.[249, 257]

f. Nonsteroidal antiinflammatory drugs:

Although individual analgesics rarely induce liver damage due to their widespread use, NSAIDS have emerged as a major group of drugs exhibiting hepatotoxicity. Both dose dependent and idiosyncratic reactions have been documented. Aspirin and phenylbutazone are associated with intrinsic hepatotoxicity and idiosyncratic reaction has been associated with ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac and indomethacin.[258]

g. Glucocorticoids:

Glucocorticoids are so named due to their effect on carbohydrate mechanism. They promote glycogen storage in liver. Enlarged liver is a rare side effect of long term steroid use in childrens. The classical effect of prolonged use both in adult and paediatric population is steatosis.[259]

ii. *In Vitro* Studies:[21]

Fresh hepatocyte preparations and primary cultured hepatocytes are used to study direct antihepatotoxic activity of drugs. Hepatocytes are treated with hepatotoxic and the effect of the plant drug on the same is evaluated. The activities of the transaminases released into the medium are determined. An increase in the activity in the medium indicates liver damage. Parameters such as hepatocyte multiplication, morphology, macromolecular synthesis and oxygen consumption are determined.

CONCLUSION: Popularity of herbal remedies is increasing globally and at least 25% of patients with liver diseases use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting to vigorous preclinical studies followed by clinical trials to unravel the mysteries hidden in the medicinal herbs and build scientific evidence in their favour. This approach will help exploring the

real therapeutic value of these natural pharmaco-therapeutic agents and standardized the dosage regimen on evidence-based findings to become more than herbal folklore.

Liver diseases have become one of the major causes of mortality all over the world and viral hepatitis, alcohol, malnutrition, autoimmune and drug induced hepatotoxicity appears to be the most common contributing factors. Total deaths worldwide from cirrhosis and liver cancer rose by 50 million per year over 2 decades, according to the first-ever World Health Organization (WHO) study of liver disease mortality; 1.25 to 1.75 million from 1990 to 2010 and an increasing proportion was due to liver cancer. In this review article, an attempt was made to compile the reported hepatoprotective plants from India and abroad that may be useful to the health professionals, scientists and scholars working the field of pharmacology, therapeutics, and pharmacognosy to develop evidence based alternative medicines to cure different kinds of liver diseases in man and animals.

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