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A Review on Drug Induced Hepatotoxicity and Alternative Therapies

Tejaswi C Chavan[1*] and Aniket A Kuvalekar[1]

[1]Interactive Research School for Health Affairs (IRSHA), Bharati Vidyapeeth Deemed University, Pune-Satara Road, Pune, 411043, Maharashtra, India

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***Corresponding author:** Tejaswi Chavan, Nutrigenomics and Functional Foods Laboratory IRSHA, Bharati Vidyapeeth Deemed University, Pune-Satara Road, Pune, Maharashtra 411043, India, E-mail: teju.chavan21@gmail.com*

Abstract

In today's world, liver diseases are serious health problem. Liver plays key role in regulating the nutritional state and the energy balance in the body. Nutritional supplements and traditional medicinal plants can provide many invaluable drugs to the modern drug industry. Hepatoprotective agents, nutritional supplements and herbal formulations with scientifically documented hepatocellular proliferation activities can be included in treatment for liver diseases. Due to their efficacy and safety, these therapies are in great demand in the developed world for primary health care. With the availability of modern techniques, it is now possible to standardize, optimize, and test these herbal plants and nutritional supplements clinically, for their effective use. Many medicinal plants and nutritional supplements are being used since ancient time owing to their spectrum of activities like antimicrobial, cytotoxic, anti-diabetic, anti-inflammatory etc. Treatment of liver disorders can be revitalised by developing standardized and clinically tested alternative medicines with high safety and efficacy profile. This review provides up-to-date information about drug-induced hepatotoxicity and hepatoprotective effects of different interventions (Nutritional supplements, Medicinal plants and Herbal formulations) for liver disease or hepatotoxicity.

Keywords: Hepatoprotection; Herbal Drugs; Liver Disorders; Nutritional Supplements

Introduction

Liver is the largest gland in the body weighing about 1500g in an adult and accounts for approximately 2.5% of total body weigh [1]. Liver is called as the metabolic "engine-room of the body" [2]. Liver performs vital role in wide range of functions such as metabolism of nutrients like amino acids, carbohydrates, lipids, minerals, vitamins; it also helps in blood clotting through synthesis and secretion of plasma proteins; eliminates dead red blood cells from blood circulation; eliminates bacteria; detoxifies chemicals, drugs, xenobiotics, helps in digestion and fat metabolism by excretion of bile salts; and excretion of end products of metabolism through urine [3]. Liver plays role in both metabolism as well as biochemical transformation [4]. Therefore, it is vital to maintain a healthy liver for overall health and well-being. But liver is continuously and variedly exposed to exogenous substances like environmental toxins, drugs and alcohol which can ultimately lead to various liver disorders, generally presenting as a distinct pattern of diseases such as hepatocellular, cholestasis (obstructive), or mixed type of liver disorders [5]. Liver injuries may lead to hepatic failure and finally death. Liver diseases today are one of the most fatal diseases globally [6]. Due to high cost and severe adverse effects of modern drugs and surgical procedures, there is no suitable cure for liver disorders [7]. The artificial drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effect [3]. Due to these important issues, it is necessary to search for alternative drugs for treatment of liver diseases [8]. Number of different medicinal plants and herbal formulations are being used for liver disorders in ethno-medical practices and in traditional medicine system [9-14]. Herbs play a major role in the management of various liver disorders as evidenced by several research articles based on experimental and clinical studies [4, 15-17].

Hepatotoxicity

Hepatotoxicity is damage to the liver that is related with compromised liver function due to chemicals (Alcohol, Carbon tetrachloride, Beta galactosamine, Thioacetamide) and drugs (Paracetamol, Nimusalide, Anti tubercular drugs like Isoniazid, Rifampicin etc.)[18,19]. The serious drug-related hepatotoxicity is incapacitating as well as life-threatening [20]. The real rate of drug-related hepatotoxicity is difficult to determine owing to complex market structure of over-the-counter drugs. Several chemicals may enter the body as therapeutic drugs or from the environment [21]. Some may be toxic to the liver whereas others only cause damage when converted into toxic metabolites [22]. Several key issues like, nature of metabolites or metabolic profile of the drug, enzymes involved in the metabolism of drug, drug-drug interactions and indirect enzyme activation etc., need to be addressed to study drug induced liver injury (DILI) [22].

Hepatotoxicity classification

The FDA (Food and Drug Administration) working group for drug-induced hepatotoxicity has defined hepatotoxicity or liver injury where Alanine Amino Transferase (ALT) level in the serum increases threefold, Serum Alkaline Phosphatase (ALP) level increases two-fold and/or Serum Bilirubin (SBLN) level is elevated twofold [20,23]. Hepatotoxicity can be classified as

 ***Corresponding author email:** teju.chavan21@gmail.com*

- Hepatocellular injury: Elevated levels of serum ALT or ALP [23];
- Cholestatic injury: Serum ALP and bilirubin levels increase [23];
- Mixed injury: Both serum ALT and ALP levels increase [23].

Drug Induced Liver Injury

Many drugs have intracellular, organellar targets like mitochondria. Mitochondrial dysfunction causes excessive amount of oxidants which in turn injures hepatic cells [18]. The exact mechanism of drug induced liver injury remains largely unknown, but it appears to involve two pathways – direct hepatotoxicity and adverse immune reaction. Direct hepatotoxicity is also known as intrinsic or predictable drug reaction [19, 22]. Drug or one of its metabolites that fall into this category may either cause reproducible, direct toxicity to liver or lowers the host defense mechanisms e.g. paracetamol, alcohol. The adverse effects in most individuals are seen in a dose-dependent manner. Adverse immune reaction is also known as unpredictable idiosyncratic drug reactions. Such drugs cause immune mediated toxicity, which is independent of drug concentration [19, 22]. The drug or one of its metabolites may induce hypersensitivity in the host. The drugs causing particular type of liver disease are tabulated in Table 1 [19].

Table 1: Drug induced liver diseases (adapted from [19])

Liver disease	Agents
Acute fatty liver infiltration	Adrenocortical steroids, Phenothiazines, Sulfonamides, Antithyroid drugs, Phenytoin, Tetracyclines, Isoniazid, Salicylates, Valproic acid, Methotrexate
Acute viral hepatitis	Acebutolol, Indomethacin, Phenylbutazone, Allopurinol, Isoniazid, Phenytoin, Atenolol, Ketoconazole, Piroxicam, Carbamazepine, Quinine, Diltiazem, Naproxen, Ranitidine, Enflurane, Para-aminosalicylic acid, Sulfonamides, Ethambutol, Penicillins, Sulindac, Labetalol, Probenecid, Cimetidine, Maprotiline, Pyrazinamide, Dantrolene, Metoprolol, Quinidine, Diclofenac, Mianserin, Ethionamide, Phenelzine, Tricyclic antidepressants, Halothane, Phenindione, Valproic acid, Ibuprofen, Phenobarbital, Verapamil
Cholestasis jaundice	Actinomycin D, Chlorpropamide, Erythromycin, Amoxicillin/Clavulanate, Cloxacillin, Flecainide, Azathioprine, Cyclophosphamide, Flurazepam, Captopril, Cyclosporine, Flutamide, Carbamazepine, Danazol, Glyburide, Carbimazole, Diazepam, Gold, Cephalosporins, Disopyramide, Griseofulvin, Chlordiazepoxide, Enalapril, Haloperidol, Ketoconazole, Norethandrolone, Sulfonamides, Mercaptopurine, Oral contraceptives, Tamoxifen, Methyltestosterone, Oxacillin, Thiabendazole, Nifedipine, Penicillamine, Tolbutamide, Nitrofurantoin, Phenothiazines, Tricyclic antidepressants, Nonsteroidal, Phenytoin, Troleandomycin, Anti-inflammatory drugs, Propoxyphene, Verapamil
Chronic active hepatitis	Acetaminophen, Dantrolene, Methyldopa, Isoniazid, Nitrofurantoin
Chronic cholestasis	Chlorpromazine/valproic acid (combination), Imipramine, Thiabendazole, Phenothiazines, Tolbutamide, Chlorpropamide/Erythromycin (combination), Phenytoin
Liver cirrhosis or fibrosis	Methotrexate, Terbinafine HCI, Nicotinic acid
Liver granulomas	Gold, Phenytoin, Aspirin, Hydralazine, Procainamide, Carbamazepine, Isoniazid, Guinidine, Chlorpromazine, Quinidine, Nitrofurantoin, Sulfonamides, Diltiazem, Penicillin, Tolbutamide, Disopyramide, Phenylbutazone
Liver tumors	Anabolic steroids, Oral contraceptives, Thorotrast, Danazol, Testosterone

Alternative Therapies for Hepatotoxicity

There are many therapies available for liver diseases like surgical procedures, hepatoprotective agents, nutritional supplements medicinal plants and herbal formulations.

Surgical procedures

To treat end-stage liver disease, liver transplantation has become an acceptable means with excellent long-term outcomes but it's very costly. Liver failure secondary to viral hepatitis (especially hepatitis B and C) is a common indication for liver transplantation [24].

Hepatoprotective agents

Hepatoprotective agents have been given attention due to their role in treatment of liver disease [25-28]. These products include both prescription drugs and nutraceuticals. A drug is defined as "any substance, food, or non-food, that is used to treat, cure, mitigate, or prevent a disease and any non-food substance that is proposed to affect the structure or function of man or animals" [29]. Apart from modern drugs, there are several hepatoprotective agents like L-carnitine, Vitamin C, N-acetylcysteine and Milk thistle (Silymarin) and anti-oxidants, natural products, minerals etc. are used as hepatoprotective agents [25, 30-33, 35, 41-43]. The details of the hepatoprotective agents are arranged systemically in Table 2.

Table 2: List of hepatoprotective agents

Sr. no	Product	Mechanism of action	References
1	L-carnitine	Essential cofactor for transport of fatty acids into mitochondria for oxidation.	[36]
2	Milk Thistle (Silymarin)	Antioxidant; anti-inflammatory; anti-fibrotic; protects against Amanita mushroom toxicity (experimental) in dogs	[37]
3	N-acetylcysteine	Glutathione precursor	[38]
4	SAMe (S- Adenosylmethionine)	Intermediary metabolite: indirect glutathione precursor (antioxidant); choleretic (cats); detoxification; supports membrane function.	[39]
5	Ursodiol	Hydrophilic bile acid shifts bile acid pool to less toxic hydrophilic bile acids. Choleretic in dogs (cats unknown). Protects hepatocyte membranes, modulates immune response.	[40]
6	Vitamin C	Free radical scavenger; functions in converting Vitamin E back to active form. Acts as prooxidant in the presence of high Fe, Cu levels.	[31, 41]
7	Vitamin E	Membrane associated antioxidant, protects liver against oxidative injury.	[42]
8	Zinc	Induces intestinal metallothionein, which preferentially binds Cu and decreases absorption. Zinc has anti-oxidant and anti-fibrotic effects; supports cell membrane function and immune response.	[43]

Nutritional Supplements

It is very important for patients with liver disease, to have balanced diet with suitable calories, carbohydrates, fats and proteins and with good nutritive value helps in regeneration of liver cells [44, 46]. Dietary supplements contain herbal products, vitamins, minerals, and any product that is not a drug (medication) [45]. Several Asian nations use numerous food and nutrition supplements, in routine diet that possess hepatoprotective activity. Several phytochemicals present in nutritional supplements possess potential ability to prevent or reverse different kinds of liver injuries [46]. Recent reports indicate that nutraceuticals like omega-3 fatty acids have hepatoprotective activity [47]. Omega-3 fatty acids are also known to offer significant benefits as nutritional supplement or dietary supplement for hepatoprotection [47-50]. Through pioneering epidemiological studies in early 1970s, Bang and Dyerberg proposed the hypothesis that long chain highly unsaturated Omega-3 fatty acids occurring in the fish oil and other marine animals which the Eskimos consumed, produced beneficial effect [50]. Marine life is rich source of a special class of polyunsaturated fatty acids known as omega-3 fatty acids. Scientific evidence proved that a diet with rich long chain omega-3 fatty acid content helps in the development of healthy brain, heart and immune system [51]. The list of nutritional supplements used in liver disorders is given in Table 3. In above studies, different vegetables and fruits are used as nutritional supplements.

Table 3: List of nutritional supplements

Sr. No	Name of the Nutritional supplement	Sources	Hepatotoxicity inducing agents	Extracts studied	Mechanism of action	Reference
1	Allium flavum (Amaryllidaceae)	Peels	Carbon tetrachloride	Ethanol	Decreased levels of ALT, ALP and improved blood cholesterol profiles	[52]
2	Camel	Milk	Paracetamol	Milk	SGOT, SGPT, ALP, TC, TG levels decreased and total protein, albumin levels increased	[53]
3	Cocos nucifera (Arecaceae)	coconut	Paracetamol	Dried- and Fermented-Processed Virgin Coconut Oil	ALT, AST, ALP levels decreased	[54]
4	Honey	Honey	Paracetamol	Honey	Prevented the increase in the serum levels of hepatic enzyme markers, and reduced both oxidative stress and inflammatory cytokines	[55]

5	Linum usitatissimum L. (Linaceae)	Seeds	Carbon tetrachloride	Flaxseed chutney	Reduces the elevated levels of SGOT, SGOT, ALP, cholesterol and hepatic lipid peroxidation	[48]
6	Linum usitatissimum Linn (Linaceae)	Flaxseed	Carbon tetrachloride	n-butanol	Effective in restoration of increased activities of liver function enzymes	[56]
7	Malus domestica Borkh (Rosaceae)	Peel	Carbon tetrachloride	Aqueous	Inhibits lipid peroxidation, increases the activities of antioxidant enzyme i.e. SOD, MDA, GSH, Strong free radical scavenging activity	[57]
8	Myristica fragrans (Myristicaceae)	Seeds	Carbon tetrachloride	70% methanol	Reduce the levels of AST, ALT, ALP and TBS. Histology showed degenerative changes, bile duct proliferation, necrosis of hepatocytes.	[58]
9	Nigella sativa Linn (Ranunculaceae)	Seeds	Isoniazid, Rifampicin, Pyrazinamide	Oil	Reverses serum enzyme activity i.e. ALT, AST, ALP, TBS, total protein.	[59]
10	Omega -3 polyunsaturated fatty acids	Fish	Cisplatin	Oil	Intrinsic biochemical antioxidant property	[60]
11	Omega -3 polyunsaturated fatty acids	Fish Sunflower	Galactosamine	Oil	Reduce the levels of SGOT, SGPT, SLP. Preventive agents for Hepatic cirrhosis in Mus musculus	[61]
12	Omega-3fatty acids	Fish	Paracetamol	(Cod) liver oil	Decreased level of MDA	[62]
13	Punica granatum Linn (Lythraceae)	Fruits	Carbon tetrachloride	Peel Powder	Restore the biochemical parameters (ALS, AST TBARS and GSH). Improved histological alteration	[63]
14	Spirulina platensis	Spirulina	Carbon tetrachloride	Powder extract	Antioxidant property, radical scavenging, and metal chelatin activities	[64]
15	Vigna radiata (Fabaceae)	Seed	Ethanol	Aqueous	Improved antioxidant levels (SOD, MDA), serum markers (ALT, AST, TG, cholesterol), NO level and histopathological	[65]
16	Vitis vinifera (Vitaceae) (Grape)	Seed	Carbon tetrachloride	Oil	Reduces the levels of ALT, AST, ALP, liver MDA and hydroperoxides. Improved in glutathione, SOD, CAT, and TP	[66]

Note: S: Serum; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALT Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BIL (TB): Total bilirubin; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde; TBARS; Thiobarbituric acid reactive substances; LPO; Lipid hydroperoxide GSH: Reduced glutathione TC: Total cholesterol; TG: Triglycerides; NO: Nitric oxide

Hepatoprotective Medicinal Plants

Medicinal plants play an important role in human health care [67]. Minimizing side effects and increasing therapeutic efficacy of medicines is the basic need of today. Alternative system specifies a broad range of natural health care practices including folk/tribal practices as well as Ayurveda, Siddha and Unani has been proved to be effective with minimum side effects [68, 69]. Management of liver diseases is still a challenge for modern medicine [67]. As per WHO report, around three quarters of the world's population uses herbs and other traditional medicines to cure various diseases, including liver disorders [68-70]. Even the developed countries are now looking for time-tested traditional and alternative medicines as a remedy for liver diseases [68]. To a large extent these medical practices, originated from time immemorial, have developed gradually based on practical experiences [4, 67]. Many medicinal plants extract exhibit significant hepatoprotective activity as indicated from studies in animal models [47, 71]. The hepatoprotective activity is probably due to the presence of flavonoids in few herbal plants [47, 71-73]. The literature till date indicates that extracts of leaves, stems, fruits, roots or even whole plants have significant potential towards treatment of hepatic diseases. These plants and their parts used for treatment are arranged systemically in Table 4.

Table 4: List of hepatoprotective plants

Sr. No	Name of the plant	Plant parts used	Hepatotoxicity inducing agents	Extracts studied	Mechanism of action	Reference
1	*Acalypha racemose* (Euphorbiaceae)	Leaves	Carbon tetrachloride	Methanol	Reduced the levels of serum ALT, AST, total protein and albumin and MDA	[11]
2	*Achillea millefolium* (Asteraceae) *Cichorium intybus* (Asteraceae) *Capparis spinosa* (Capparaceae)	Aerial, Seeds, Fruit	Carbon tetrachloride, Paracetamol	Aqueous, methanol and chloroform	Antihepatotoxic property	[74]
3	*Actinidia deliciosa* Chev (Actinidiaceae)	Roots	Carbon tetrachloride	Ethanol	ALT, AST serum levels decreased. MDA decreased and GSH increased in liver homogenate	[75]
4	*Adina cordifolia* (Rubiaceae)	Leaves	Ethanol	Acetone and aqueous	SGOT, SGPT, ALP, total bilirubin serum levels decreased and increased the levels of total protein in liver	[76]
5	*Aegle marmelos* Corr (Rutaceae)	Leaves	30%Ethanol	Ethanol	Enhanced level of TBRS, GSH, SOD, CAT and GPx in both plasma and liver sample**S**	[77]
6	*Aerva lanata* Linn (Amaranthaceae)	Fresh bulbs	Paracetamol	Ethanol: Water	Reduces the levels of serum ALT, AST, ALP and bilirubin	[78]
7	*Allium ascalonicum* (Amaryllidaceae)	Whole	Paracetamol	Aqueous	Decreased level of ALT and % of liver lesion (Micro vesicular steatosis, Necrosis area and Lymphocytic infiltration)	[79]
8	*Allium sativum* **(**Amaryllidaceae)	Garlic	N-nitrosodiethylamine	Aqueous	Reduced the liver toxicity (ALT, AST,ALP, LPO, SOD,GSH)	[80]
9	*Alocasia indica* (Araceae)	Tuber vegetable	Carbon tetra chloride	80% Ethanol	Strong antioxidant property	[81]
10	*Aloe barbadensis* Mill (Xanthorrhoeaceae)	Aerial	Carbon tetrachloride	Aqueous	Restore the levels of serum ALT, ALP, TBP, triglycerides, MDA, glutathione, glucose-6-phosphatase, microsomal aniline hydroxylase and amidopyrine N-demethylase and integrity of hepatocytes	[82]
11	*Amaranthus caudatus* Linn (Amaranthaceae)	Whole plant	Carbon tertrachloride	Methanol	Decreased levels of ALT AST, ALB, TP, TB, DB Prevents the elevation of MDA, GSH, CAT and TT	[83]
12	*Andrographis paniculata* (Acanthaceae)		Ethanol	Aqueous	Decreased levels of ALT, AST, ALP and Bilirubin	[84]
13	*Anisochilus carnosus* Linn (Lamiaceae)	Stems	Carbon tertrachloride	Ethanol	Prevents the elevation of all liver marker enzyme	[85]
14	*Annona squamosa* (Annonaceae)	Leaves	Isoniazid, Rifampicin	Ethanol	Significant decrease in ALP, AST, ALT and γ-GT	[86]

15	*Anthrodia comphorata* (Incertae sedis)	Mycelium and Sporocarp	Alcohol	Aqueous	Decreased the activity of SGOT, SGPT, glucose in serum. Increased the activities of hepatic TBARS, SOD and catalase in liver tissue	[87]
16	*Artemisia bsinthium* (Asteraceae)	Whole	Acetaminophen, carbon tetrachloride	Aqueous-methanol	Prevents the elevation of SGOT and SGPT	[88]
17	*Artemisia campestris* (Asteraceae)		Carbon tetrachloride	Aqueous	Strong scavenging action of 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydroxyl and superoxide anion radicals in liver Reduced the SGOT, SGPT levels	[89]
18	*Artemisia maritime* (Asteraceae)	Whole	Acetaminophen, carbon tetrachloride	aqueous-methanolic	Prevents the elevation of SGOT and SGPT	[90]
19	*Aspalathus linearis* (Fabaceae)	Leaves	Carbon tetrachloride	Aqueous	Inhibits MDA triacylglycerols and cholesterol in liver tissue. suppressed mainly the increase in ALT, AST, ALP and bilirubin in plasma	[91]
20	*Asparagus racemosus* Linn (Asparagaceae)	Roots	Paracetamol	Ethanol	Significantly altered serum marker enzymes and antioxidant levels	[92]
21	*Azadirachta indica* (Meliaceae)	Leaves	Acetaminophen	Fresh juice	Decreased levels of SGOT, SGPT, acid phosphatase and ALP	[93]
22	*Azadirachta indica* (Meliaceae)	Leaf	Paracetamol	Aqueous	Reduced elevated levels of AST, ALT and γ-GT	[94]
23	*Azima tetracantha* (Salyadraceae)	Leaves	Paracetamol	Ethanol	Restore the levels of serum SGOT, SGPT, ALP, TBS and TC	[95]
24	*Ballota glandulosissima* (Lamiaceae)	Aerial	Carbon tetrachloride,	Aqueous	Significantly ameliorated the levels of AST, ALT, ALP and bilirubin in serum, decreased the ballooning degeneration in histopathological examination and significant reduction in rat paw oedema	[96]
25	*Bauhinia varlegate* Linn (Fabaceae)	Stem bark	Carbon tetrachloride	Ethanol	Reduces the levels of serum marker enzymes, i.e. AST, ALT, ALP and GGT and liver protein and lipid**S**	[97]
26	*Berberis tinctoria* (Berberidaceae)	Leaves	Acetaminophen	Methanol	Decreased the levels of serum SGOT, SGPT, ALP bilirubin and MDA and significantly increased the levels GSH, CAT and SOD in liver	[98]
28	*Boswellia serrate* Roxb. (Burseraceae)	Oleo gum resin	Carbon tetrachloride	Chloroform	Significantly reduced the elevated levels of serum marker enzymes, prevented the increase in liver weight and supported by changes in histopathology	[99]
29	*Butea superba* Roxb. (Euphorbiaceae)	Stem bark	Carbon tetrachloride	Ethanol	Decrease in the levels of serum markers, indicating the protection of hepatic cells.	[100]

30	*Cajanus cajan* Linn (Fabaceae)	Pigeon pea leaf	D-galactosamine	Ethanol	Significantly reduced in serum enzyme such as ALT, AST and increase in reduced MDA and normalized level of SOD, CAT, GSH, and GPx also histopathological improvement in liver tissue.	[101]
31	*Cajanus cajan Linn* (Fabaceae)	Whole	Carbon tertrachloride	70% ethanol	Significantly reduced in SGOT and SGPT and increased in hepatic total protein.	[102]
32	*Cajanus indicus* Linn (Fabaceae)	Leaves	Acetaminophen	Protein Fraction	Significantly reversed SGPT, ALP, creatinine and blood urea nitrogen and antioxidant enzymes (namely, MDA, SOD, CAT, GSH almost normal in both liver and kidney homogenates and protects hepatic and renal tissues against oxidative damages	[103]
33	*Cajanus scarabaeoides* Linn (Fabaceae)	Whole plant	Paracetamol	n-butanol, ethanol	significantly and dose dependently decreased the liver marker enzyme activity i.e. SGPT, SGPT, TBS, ALP, total protein, total bilirubin and an almost normal architecture of liver	[104]
34	*Calotropis procera* (Asclepiadaceae)	Aerial	Paracetamol	Chloroform	Normalize all biochemical parameter	[105]
35	*Calotropis procera* Ait (Asclepiadaceae)	Latex	Carbon tetrachloride	Dried latex	Significantly and dose-dependent reduction in the serum levels of liver enzymes and inflammatory mediators and attenuated the necro-inflammatory changes in the liver	[106]
36	*Capparis Spinosa* Linn (Capparaceae)	Roots	Carbon tetrachloride	Ethanol	decreased in the levels of serum markers AST, ALT and duration of sleep, indicating the protection of hepatic cells	[107]
37	*Careya arborea* (Lecythidaceae)	Stem bark	Carbon tetrachloride	Methanol	Reduced the activity of serum maker enzymes i.e. SGOT, SGPT, ALP, bilirubin, uric acid, and Liver marker enzymes i.e. decreased lipid peroxidation and significantly increased the levels of SOD, CAT, GSH, vitamin C, vitamin E and protein in a dose dependent manner.	[108]
38	*Carica papaya* (Caricaceae)	Fruits	Carbon tetrachloride	Ethanol and Aqueous	Reduced all liver damage marker enzyme	[109]
39	*Carissa carandas* Linn (Apocynaceae) *Pergularia daemia* (Forsk.) Chiov. (Asclepiadaceae)	Root	Carbon tertrachloride, Paracetamol, Ethanol	Ethanol	Significantly reduced in the levels of SGOT, SGPT, ALP, total bilirubin, and total cholesterol, significantly maintained the levels of GSH, MDA, and a normal architecture of the liver	[110]

40	*Cassia fistula* (Fabaceae)	Leaves	Carbon tetrachloride	n-Heptane	Protects against increased serum markers such SGOT, SGPT, bilirubin and ALP	[111]
41	*Cassia auriculata* (Fabaceae)	Leaves	Alcohol	Aqueous	Significantly reduced in serum enzyme markers	[112]
42	*Cassia occidentalis* (Fabaceae)	Leaves	Paracetamol, ethanol	Aqueous-ethanol	Normalized in the levels of serum SGOT, SGPT, ALP, cholesterol, total lipids and histopathological alterations.	[113]
43	*Cassia occidentalis* Linn (Gentianaceae)	Roots	Carbon tetrachloride	Aqueous	Decreases AST, ALT and gamma glutamyl	[114]
44	*Cassia roxburghii* (Fabaceae)	Seeds	Ethanol, carbon tertrachloride	Methanol	Inhibit the enhanced SGOT, SGPT, ALP, TB, TP albumin and TC	[115]
45	*Casuarina equisetifolia* (Casuarinaceae), *Cajanus cajan* (Fabaceae), *Glycosmis pentaphylla* (Rutaceae), *Bixa orellana* (Bixaceae) *Argemone mexicana* (Papaveraceae) *Physalis minima* (Solanaceae), *Caesalpinia bonduc* (Caesalpiniaceae)	Leaf and bark, Whole, leaf and bark, seeds, Whole, leaf and flower, leaf and bark.	Carbon tertrachloride	Methanol	The four plants extract significantly, and dose dependently decreased in the levels of serum markers, indicating the protection of hepatic	[116]
46	*Chamomile* (Asteraceae)	Capitula flower	Acetaminophen	50% ethanol	Suppresses the elevated levels of Na+ K+- ATPase activity, serum marker enzymes, glycogen and TBARS in blood and liver, normalized impair membrane function activity.	[117]
47	*Chenopodium album* Linn. (Chenopodiaceae)	Aerial	Alcohol	Petroleum ether	Restore physiological integrity of hepatocytes	[118]
48	*Silybam marianum* (Asteraceae) *Cichorium intybus* (Asteraceae)	Seeds	Thioacetamide	Ethanol	Significantly decreased in the activity of ALT, AST, ALP and bilirubin, significantly altered the level of Na+, K+ and liver weight	[119]
49	*Cichorium intybus* (Asteraceae)	Leaves	Carbon tetrachloride	Ethanol	Prevents the elevation levels of serum ALT, AST and ALP, and significant hepatoprotection	[120]
50	*Cichorium intybus* (Asteraceae)	Root and root callus	Carbon tetrachloride	Aqueous	SGOT, SGPT, ALP and bilirubin levels decreased	[121]
51	*Cleome viscosa* Linn (Cleomaceae)	Seeds	Carbon tetrachloride	Aqueous	Prevents the elevation of all liver marker enzyme	[122]
52	*Clerodendrum inerme* Linn (Lamiaceae)	Leaves	Carbon tetrachloride	Ethanol	SGOT, SGPT, ALP, TG, TC serum levels decreased, significantly increased the glutathione level	[123]

53	*Clitoria ternatea* Linn (Fabaceae)	Leaves	Paracetamol	Methanol	Antioxidant property	[124]
54	*Commiphora opobalsamum* (Burseraceae)	Aerial	Carbon tetrachloride	Ethanol	significantly protected SGOT, SGPT, ALP and bilirubin	[125]
55	*Cryptolepis buchanani* (Asclepiadaceae)	Leaves	Acetaminophen	Ethanol	Hepatoprotective and antioxidant property	[126]
56	Cucumis trigonus Roxb (Cucurbitaceae)	Fruit	Carbon tertrachloride	Ether, chloroform, alcohol, aqueous	High significantly decreased in the levels of serum markers, indicating the protection of hepatic cells	[127]
57	*Curculigo orchioides* (Hypoxidaceae)	Rhizomes	Carbon tetrachloride	Methanol	Antioxidant property	[128]
58	*Curcuma longa* (Zingiberaceae.) *Allium sativum* (Amaryllidaceae)	Rhizomes	7-12 Dimethylbemzamthracene	Aqueous	Antioxidant property, reverse ALT, AST, ALP, bilirubin urea and creatinine levels	[129]
59	*Curcuma longa* (Zingiberaceae)	Rhizomes	Acetaminophen, isoniazid, pyrazinamide, rifampicin	Ethanol	Lowered serum liver enzyme activities, normal histology	[130]
60	*Curcuma longa* (Zingiberaceae)	Rhizomes	Carbon tetrachloride	Aqueous	Decreased antioxidant enzyme activities such as SOD, CAT, GPx, GST, GSH, total TSH, protein (PSH), non-protein (NPSH) thiols and ascorbic acid in the liver, decreased ALT, AST, Glucose-6-phosphatase (G6Pase) and the membrane bound ATPase activities	[131]
61	*Cuscuta chinensis* Linn. (Convolvulaceae)	Seeds	Acetaminophen	Ethanol	Reduce SGPT, SGPT, ALP levels, prevent hepatic injuries	[132]
62	*Cyperus articulatus* Linn. (Cyperaceae)	Whole rhizome	Paracetamol	Methanol	SGPT, SGOT, ALP, total protein and total bilirubin levels decreased in serum. Improvement or normalized the level of MDA, SOD, CAT, GSH in liver homogenate	[133]
63	*Diospyros malaborica* (Ebenaceae)	Bark	Carbon tetrachloride	Methanol	Hypoglycemic activity, antioxidant activity, antidiabetic activity	[134]
64	*Eclipta alba* (Asteraceae)	Whole	Acetaminophen,	Ethanol	Significantly reduced in serum marker enzyme	[135]
65	*Eclipta alba* (Asteraceae)		Carbon tetrachloride	Ethanol, water	Hepatoprotective activity, Reduced in serum marker enzymes	[136]
66	*Enicostema axillare* Lam (Gentianaceae)	Leaves	Carbon tetrachloride	Ethanol	Decrease in the levels of serum markers, indicating the protection of hepatic cells.	[137]
67	*Epaltes divaricata Casso* (Asteraceae)	Whole	Carbon tetrachloride	Aqueous	Improved liver marker enzyme	[138]
68	*Ervatamia coronaria* (Apocynaceae)	Leaves	Carbon tetrachloride	Methanol	Hepatoprotective activity	[139]
69	*Euphorbia antiquorum* (Euphorbiaceae)	Aerial	Carbon tetrachloride	Aqueous	Hepatoprotective and antioxidant property	[140]

70	*Euphorbia hirta* Linn (Euphorbiaceae)	Whole	Carbon tetra chloride	Ethanol	Enhanced level of SGPT, SGOT, ALP, bilirubin in the dose dependent manner	[141]
71	*Ficus carica* Linn (Moraceae)	Leaves	Carbon tetrachloride	Methanol	Lowed the serum levels of ALT,AST, ALP, total bilirubin, and malondialdehyde	[142]
72	*Ficus religiosa* Linn (Moraceae)	Stem bark	Paracetamol	Methanol	Significantly reduced serum enzyme levels.	[143]
73	*Foeniculum vulgare* (Apiaceae)	Seeds	Carbon tetrachloride	Essential oil	Decreased levels of serum AST, ALT, ALP and bilirubin.	[144]
74	*Garcinia indica* Linn (Clusiaceae)	Fruit	Carbon tertrachloride	Ethanol	Antioxidant and hepatoprotective activity	[145]
75	*Ginkgo biloba* (Ginkgoaceae)	Leaves	Carbon tetrachloride	Dry extract	AST, ALT, ALP, and TP, albumin levels decreased	[146]
76	*Glycyrrhiza glabra* (Fabaceae)	Roots	Lipopolysaccharide / D-galactosamine		Prevents inflammatory responses and IL-18 production, significantly inhibited IL-18 production in liver injury	[147]
77	*Gmelina asiatica* Linn (Lamiaceae)	Aerial	Carbon tertrachloride	Ethanol chloroform	Antioxidant and hepatoprotective activity	[148]
78	*Hibiscus rosa-sinensis* (Malvaceae)	Petals	Carbon tetrachloride	Ethanol	Antidiabetic and antioxidant property, therapeutic Application	[149]
79	*Hyptis suaveolens* Linn (Lamiaceae)	Leaves	Acetaminophen	Aqueous	Significantly reduced in the levels of albumin, TP, total globulin, ALT, AST and catalase in the blood plasma and liver were	[150]
80	*Ichnocarpus frutescens* Linn (Apocynaceae)	Whole	Acetaminophen	Chloroform Methanol	Decreased the activity of serum enzymes, bilirubin, and lipid peroxidation, significantly increased the levels of GSH, SOD, CAT, in a dose dependent manner.	[151]
81	*Indigofera trita* Linn (Fabaceae)	Whole	Carbon tetrachloride	Ethanol	Significantly and dose dependent decreased in the levels of SGOT, SGPT, ALP and TBARS and significantly increased in the levels of albumin, TP, SOD and CAT	[152]
82	*Kalanchoe pinnata* (Crassulaceae)	Leaves	Carbon tetrachloride	Fresh juice	Hepatoprotective Activity	[153]
83	*Lannea coromandelica* Linn. (Anacardiaceae)	Bark	Thioacetamide	Aqueous and ethanol	Hepatoprotective and antioxidant activity	[154]
84	*Launaea pinnatifida* (Asteraceae)	Leaves and roots	Carbon tetrachloride	Ethanol	Significantly restored all the serum and liver parameters near to the normal levels	[155]

85	*Lawsonia alba* (Lythraceae)	Bark	Carbon tetrachloride	50% Ethanol	Reduced GSH level and inhibits the production of free radicals and peroxidation of microsomal lipids in a dose-dependent manner.	[156]
86	*Lawsonia inermis* (Lythraceae)	Roots	Paracetamol and anti-tubercular drugs	Alcoholic and aqueous	Significantly reversed the levels of cytosolic enzymes, a marker of oxidative damage to hepatocytes and significantly increased the levels SOD, GSH	[157]
87	*Leucas cilita* Linn (Lamiaceae)	Whole	Carbon tertrachloride	Ethanol	Strong free radical scavenging and hepatoprotective activity.	[158]
88	*Leucas lavandulaefolia* Rees (Labiatae)	Aerial	Carbon tetrachloride	Chloroform	Hepatoprotective activity	[159]
89	*Leucophyllum frutescens Berl.* (Scrophulariaceae)	Aerial	Carbon tetrachloride	Methanol	ALT, AST levels decreased	[160]
90	*Luffa echinata* (Cucurbitaceae)	Fruit	Carbon tetrachloride	Petroleum ether, acetone, methanol	Hepatoprotective activity	[161]
91	*Lycium chinense* (Solanaceae)	Fruits	Carbon tetrachloride	Aqueous	AST, ALT and ALP levels decreased, strong free radical scavenging activity in a dose-dependent manner, significantly decreased in the level of cytochrome P450 2E1 (CYP2E1) mRNA and protein in liver	[162]
92	*Lygodium flexuosum* Swartz (Lygodiaceae)	Whole	D-galactosamine	n-Hexane	Prevents the elevation of AST, ALT, LDH, hepatic MDA and GSH levels and normal histological index	[163]
93	*Momordica subangulata* (Cucurbitaceae) *Naragamia alata* (Meliaceae)	Leaves, whole plant	Acetaminophen	Aqueous	Hepatoprotective and choleretic activities	[164]
94	*Melia azadiracta* Linn (Meliaceae) *Piper longum* (Piperaceae)	Leaves	Carbon tetra chloride	Ethanol	Restore the levels of biochemical parameters like total protein, total bilirubin, total cholesterol, triglycerides, and urea	[165]
95	*Melia azedarach* Linn (Meliaceae) *Catharanthus roseus* (Apocynaceae) *Brassica oleracea* (Brassicaceae)	Leaves	Simvastatin	Ethanol	Hepatoprotective activity	[166]
96	*Mentha arvensis* (Lamiaceae)	Whole	Alcohol and carbon tetra chloride	Aqueous	Restored all biochemical parameters in serum and liver	[167]
97	*Momordica dioica* (Cucurbitaceae)	Leaves	Acetaminophen	Aqueous	Hepatoprotective, antioxidant and anti-inflammatory property	[168]
98	*Morinda citrifolia* Linn (Rubiaceae)	Fruit	Streptozotocin	Aqueous	Hypoglycemic and hepatoprotective property	[169]

99	*Mussaenda frondosa* Linn (Rubiaceae)	Leaves	20% alcohol	Petroleum ether, chloroform, alcohol	Decreased the level of AST, ALP, ALT, bilirubin, cholesterol, triglyceride, VLDL, MDA in serum and increased the level of protein, HDL and antioxidants (SOD, GSH and CAT) in liver	[170]
100	*Myrtus communis* (Myrtaceae)	Leaves	Paracetamol	Aqueous	Significant reduction in serum hepatic enzymes	[171]
101	*Nelumbo nucifera Gaerth* (Nymphaeaceae)	Flowers	Carbon tetrachloride	Ethanol	Protects against hepatocytic necrosis, fatty changes and oxidative damage	[172]
102	*Nigella sativa* (Ranunculaceae)	Seeds	Carbon tetrachloride	Ethanol	Prevents MDA, increase anti-oxidant defense system activity and also prevent liver damage	[173]
103	*Ocimum gratissimum* (Lamiaceae), *Vernonia amygdalina* (Asteraceae) *Tridax procumbens* (Asteraceae) *Parkia biglobosa* (Fabaceae) *Bridelia ferruginea,* (Phyllanthaceae)	Leaves	2-Acetylaminoflourene	Aqueous	Hepatoprotective potential	[174]
104	*Ocimum sanctum* (Lamiaceae)	Leaves	Carbon tetrachloride isoniazid, pyrazinamide, rifampicin	Ethanol	Hepatoprotective action, antioxidant activity and revers the biochemical and histological changes	[175]
105	*Parkinsonia aculeata* Linn (Fabaceae)	Leaves	Carbon tetrachloride	Ethanol	Potential therapeutic and preventive, antioxidative property	[176]
106	*Pergularia daemia* Forsk (Apocynaceae)	Aerial	Carbon tetrachloride	Ethanol	Hepatoprotective activity	[177]
107	*Phoenix dactylifera* (Arecaceae)	Pits and flesh	Carbon tetrachloride	Aqueous	Effective prophylactic or treatment against liver cytotoxicity	[178]
108	*Phyllanthus longiflorus* (Phyllanthaceae)	Leaves	Acetaminophen	Ethanol	Reduced the necrosis and swelling of the hepatocytes in liver histology, ALT, AST, ALP, TP, albumin and total bilirubin levels in serum.	[179]
109	*Phyllanthus maderaspatensis* (Phyllanthaceae)	Whole	Acetaminophen	n-Hexane	Antihepatotoxic activity	[180]
110	*Phyllanthus niruri* (Phyllanthaceae)	Leaves	Acetaminophen	Alcohol	Regenerative changes, presence of binucleated cells, anisonucleosis and anisocytosis, reduced SGPT level	[181]
111	*Phyllanthus polyphyllus* Willd (Phyllanthaceae)	Leaves	Acetaminophen	Methanol	Significantly altered serum marker enzymes and antioxidant levels to near normal	[182]
112	*Phyllanthus rheedi* (Phyllanthaceae)	Whole	D-galactosamine	Ethanol	Antioxidant and choleretic activity	[183]

113	*Platycodon grandiflorum* (Campanulaceae)	Roots	Acetaminophen	Aqueous	Inhibits P450 lA2-dependent methoxyresorufin O-deethylase activities and the P450 2E1-dependent p-nitrophenol and aniline hydroxylase, blocked P450-mediated APAP bioactivation.	[184]
114	*Pleurotus ostreatus* (Pleurotaceae)	Whole	Carbon tetrachloride	Ethanol	SGOT, SGPT and ALP levels reverted, GSH, CAT, SOD and Gpx levels increased and MDA significantly lowered	[185]
115	*Polygala arvensis* Wild (Polygalaceae)	Leaves	D-galactosamine	Chloroform	Normalized the levels of SGOT, SGPT,), ALP, lactate dehydrogenase TC, TGL, albumin, TP	[186]
116	*Pterocarpus santalinus* Linn (Fabaceae)	Stem bark	Carbon tetrachloride	Aqueous	Decrease in levels of liver enzyme markers, significantly increased in total protein, indicating the recovery of hepatic cells, revealed normal hepatic cords without any cellular necrosis and fatty infiltration	[187]
117	*Raphanus sativus* Linn (Brassicaceae)	Seeds	Carbon tetrachloride	Aqueous, methanol	Inhibits increased SGOT, SGPT, bilirubin and histopathological changes	[188]
118	*Rhodococcum vitis* (Ericaceae)	Leaves	D-galactosamine	Aqueous	Antioxidant activity	[189]
119	*Rhododendron arboretum* (Ericaceae)	Leaves	Carbon tetrachloride	Ethanol	Hepatoprotective property, anti-oxidant activity	[190]
120	*Ricinus communis* (Euphorbiaceae)	Leaves	Carbon tetrachloride, acetaminophen, thioacetamide	n-Hexane chloroform	Protects against hepatotoxicity	[191]
121	*Rubia cordifolia* (Rubiaceae)	Roots	Thioacetamide	Methanol	Hepatoprotective property	[192]
122	Saccharum officinarum (Poaceae)	Cane	20% Ethanol	Juice	Significantly prevented the physical, biochemical, histological and functional changes	[193]
123	*Saponaria officinalis* Linn (Caryophyllaceae) *Punica granatum* Linn. (Lythraceae) *Syzygium aromaticum* Linn (Myrtaceae)		Carbon tetrachloride	Powdered	Ameliorated the histopathological alteration in liver section	[194]
124	*Sarcostemma brevistigma* (Asclepiadaceae)	Stem	Carbon tetrachloride,	Ethyl acetate	Hepatoprotective property	[195]
125	*Schisandra chinensis* (Schisandraceae)	Seeds	Carbon tetrachloride	Alcoholic	Reduced in the levels of ALT, AST, and GGT, glucose, triglycerides, and cholesterol in serum, found new flavonoids	[196]

126	*Sida cordifolia* (Malvaceae)	Leaves	Ethanol	Petroleum ether, chloroform	Analgesic, anti-inflammatory, hypoglycemic activities	[197]
127	*Sida cordifolia* (Malvaceae)	Whole	Carbon tetrachloride, paracetamol and Rifampicin	Methanol Aqueous	Immunomodulator and pharmacological properties	[197]
128	*Sida veronicaefolia* (Malvaceae)	Leaves	Ethanol	Aqueous and ethanol	SGPT, SGOT, ALP, total bilirubin levels decreased and increased the levels of total protein.	[198]
129	*Smilax chinensis* (Smilaceae)	Roots	Acetaminophen	Ethyl acetate	Hepatoprotective and antioxidant activities	[199]
130	*Solanum nigram* Linn (Solanaceae) *Cichorium intybus* (Asteraceae)	Fruits	Carbon tertrachloride	Ethanol	Reduce the serum biochemical indicators like AST, ALT, TB, TP and oxidative stress like GSH, SOD, LPO levels decreased	[200]
131	*Solanum trilobatum* (Solanaceae)	Whole	Carbon tetrachloride	Ethanol	Antioxidant and hepatoprotective	[201]
132	*Swertia longifolia* Boiss (Gentianaceae)	Aerial	Acetaminophen	Ethanol	Significantly reduced AST, ALT ALP	[202]
133	*Syzgium aromaticum* Linn (Myrtaceae)	Flowers buds	Acetaminophen	Ethanol	Antioxidant activity	[203]
134	*Tecomella undulate* (Bignoniaceae)	Leaves	Alcohol and paracetamol	Methanol	Hepatoprotective potential and presence of flavonoids, quinones and other bioactive constituents	[204]
135	*Tectona grandis* Linn. (Lamiaceae)	Leaves	Carbon tetra chloride	Hydroalcoholic	Significantly and dose dependently decreased the levels SGOT, SGPT and ALP	[205]
136	*Tephrosia purpurea* (Fabaceae)	Aerial	Arsenic	Aqueous	ALT, AST, ALP levels decreased and reduced necrosis and inflammation in liver section	[206]
137	*Terminalia bellerica* Roxb (Combretaceae)	Fruits	Alcohol	Aqueous Ethanol	Prevents the physical and biochemical changes against hepatotoxins	[207]
138	*Terminalia catappa* (Combretaceae)	Leaves	Carbon tetrachloride	Chloroform	Protects against liver mitochondrial damage	[208]
139	*Teucrium polium* (Lamiaceae)	Aerial	Carbon tetrachloride	Ethyl acetate	Restore the normal histomorphology pattern of liver cells	[209]
140	*Thespesia lampas* Dalz and Gibs (Malvaceae)	Roots	Carbon tertrachloride	Methanol	Revealed normal liver section without any hepatic steatosis, centrilobular necrosis, and swelling of the hepatic cytoplasm	[210]
141	*Tinospora cordifolia* (Menispermaceae)	Stem, leaves	Carbon tertrachloride	Aqueous	Antioxidant or free radical scavenger property and hepatic regeneration ability	[211]
142	*Tinospora cordifolia* (Menispermaceae)	Leaf, stem, roots	Carbon tertrachloride	Pet ether, Ethanol, Aqueous	Biologically and hepatoprotective activity	[212]

143	*Tinospora cordifolia* (Menispermaceae)	Stem	Carbon tetrachloride	Aqueous	Liver function and immune functions	[213]
144	*Tinospora cordifolia* (Menispermaceae), *Aloe vera* (Xanthorrhoeaceae), *Mangifera indica* (Anacardiaceae)	Stem and bark leaf pulp	Carbon tertrachloride	Aqueous	Restoration of improved level of SOD, CAT, MDA	[214]
145	*Tinospora sinensis* (Menispermaceae) *Tinospora cordifolia* (Menispermaceae) *Neem guduchi* (Menispermaceae)	Stem	Acetaminophen	Satwa	Improved hepatic function normalized the lipid profile in the serum and liver, and improvements in the levels of antioxidant enzymes and oxidative-stress markers. Restore and strengthen the liver functions	[215]
146	*Tinospora cordifolia* Wild. (Menispermaceae) *Ocimum sanctum* L(Labiatae) *Zizyphus mauritiana* Lam (Rhamnaceae) *Curcuma longa* (Zingiberaceae)	Roots	Isoniazid, rifampicin and pyrazinamide	Ethanol	Hepatoprotective potential and prevents immunosuppression	[216]
147	*Trianthema portulacastrum* (*Aizoaceae*)	Leaves	Acetaminophen,	Ethanol	Significant hepatoprotective activity	[217]
148	*Tridax procumbens* (Asteraceae)	Aerial	D-galactosamine	Ethanol	Alteration in biochemical marker enzymes	[218]
149	*Trigonella foenum-graecum* Linn (Fabaceae)	Seeds	Carbon tetrachloride	Diethyl ether	Anti-inflammatory and hepatoprotective	[219]
150	*Tylophora indica* (Apocynaceae)	Leaves	Ethanol	Aqueous	Significantly prevented the physical (liver weight and volume), biochemical (ALT,AST, ALP, TP,TBP, TC, triglycerides), histological (damage to hepatocytes) and functional changes (thiopentone-induced sleeping time) histological (damage to hepatocytes)	[220]
151	*Uetica parviflora* Roxb. (Urticaceae)	Leaves	Carbon tetrachloride	Ethanol	Restore of the levels of serum bilirubin, proteins and hepato protective enzymes, revealed the centrilobular necrosis in a dose dependent manner	[221]
152	*Veronica ciliata* (Plantaginaceae,)	Herbs	Carbon tetra chloride	Petroleum ether, ethyl acetate	Antioxidant	[222]
153	*Vetiveria zizanioides* (Poaceae)	Root	Paracetamol	Methanolic	Antioxidant	[223]

154	*Vetiveria zizanioides* Linn (Poaceae)	Roots	Alcohol	Methanol	Hepatoprotective property	[224]
155	*Vicia calcarata* Desf (Leguminosae)	Aerial	Carbon tetrachloride	Ethanol	Inhibits lipid peroxidation, revealed the flavanol glycosides of F-2 protect against hepatic damage	[225]
156	*Vitex negundo* Linn (Lamiaceae)	Fresh bark	Paracetamol	Methanol	Significantly altered in all biochemical and histopathological sections	[226]
157	*Xylopia phloiodora* Mildbr. (Annonaceae)	Stem bark	Carbon tetrachloride, acetaminophen	Crude extract Ether extract Essential oil	Antihepatotoxicity activity	[227]
158	*Zizyphus mauritian* Lamk	Seed	Isoniazid, Pyrazinamide	Ethanol	Hepatoprotective, strong antioxidant property and indicated probable presence of flavonoids, phenolic compounds, tannins and saponins	[228]
159	*Zizyphus mauritian* Lamk	Seed	Isoniazid, Pyrazinamide	Ethanol	Hepatoprotective, strong antioxidant property and indicated probable presence of flavonoids, phenolic compounds, tannins and saponins	[228]

Note: S: Serum; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALT Alanine aminotransferase; AST: Aspartate aminotransferase ALP: Alkaline phosphatase; BIL (TB): Total bilirubin; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde; TBARS; Thiobarbituric acid reactive substances; LPO; Lipid hydroperoxide GSH: Reduced glutathione TC: Total cholesterol; TG: Triglycerides; NO: Nitric oxide; TT: Thrombin time: γ-GT: Gamma-Glutamyl Transferase; GPx: Glutathione peroxidase

Herbal formulations used in liver disorder

There are numerous medicinal plants and their formulations used to treat liver disorders in ethno-medicine practice as well as traditional system of medicine in India [229, 230]. There are about 600 commercial herbal formulations available in market all over the world, which are claimed to have hepatoprotective activity [231, 246]. In India, about 40 patented polyherbal formulations representing a variety of combination of 93 medicinal plants from 44 families are available [232].

More than 700 mono and poly-herbal preparations from more than 100 plants are in clinical use as hepatoprotective agents in the form of decoction, tincture, tablets and capsules [232, 233]. In recent years, the use of herbal drugs for the treatment of liver diseases has increased all over the world [233]. The herbal drugs are easily available and believed to be harmless and free from serious adverse reactions [234]. The usage of alternative medicine, including herbal preparations, has increased due to limited therapeutic options and disappointing success of modern medicine in treating liver ailments [235]. Several commercial hepatoprotective herbal formulations are known to be effective in liver diseases and are used to treat different types of liver disorders [236-255].

The synchronous activity of ingredients from polyherbal formulation is believed to be responsible for hepatoprotective activities of these formulations mention in Table 5.

The mechanism of action of promising hepatoprotective therapies (Hepatoprotective agents, nutritional supplement, medicinal plants, herbal formulation) is shown in Figure 1.

Table 5: List of herbal formulations

Sr. No	Name of the formulation	Plants used in the formulation	Hepatotoxicity inducing agents	Mechanism of action	Reference
1	Blood wort (Herb pharma, Nigeria)	*Rumex acetosa* L. (Polygonacease; bark) *Cinchona succirubra* Pav. (Rubiaceae; bark).	Carbon tetrachloride	Hepatoprotective property	[236]
2	BR-16A (Mentat) Himalaya Drug Company	*Bacopa monnieri* (Scrophulariaceae), *Asparagus racemosus* (Asparagaceae), *Acorus calamus* (Acoraceae), *Withania somnifera* (Solanaceae), *Tinospora cordifolia* (Menispermaceae), *Emblica officinalis* (Euphorbiaceae), *Evolvulus alsinoides* (Convolvulaceae), *Saurssurea lappa* (Compositae), *Terminalia chebula* (Combretaceae), and *T.bellirica* (Combretaceae)	Ethanol	Anxiogenic response	[237]
3	Clearliv polyherbal formulation (Apex Laboratories Ltd., Chennai)	*Phyllanthus niruri* (Phyllanthaceae), *Eclipta alba* (Asteraceae), *Boerhaavia diffusa* (Nyctaginaceae) *Tinospora cordifolia* (Menisperemacea), *Tribulus terrestris* (Zygophyllaceae), *Tephrosia purpurea* (Fabaceae), *Indigofera tinctoria* (Fabaceae), *Aconitum heterophyllum* (Ranunculaceae), *Andrographis paniculata* (Acanthaceae), *Rubia cordifolia* (Rubiaceae), *Terminalia chebula* (Combretaceae), *Curcuma longa* (Zingiberaceae), *Ricinus cummunis* (Euphorbiaceae)	Thioacetamide D-Galactosamine and carbon tetrachloride,	Reduces plasma liver markers, and elevated antioxidants levels.	[238]
4	DHC-1 (Himalaya Drug Company)	*Bacopa monnieri* Linn. (Scrophulariaceae; whole), *Emblica officinalis* Gaertn. (Euphorbiaceae; fruit), *Glycyrrhiza glabra* Linn. (Papilionaceae; roots), *Mangifera indica* Linn. (Anacardiaceae; bark), *Syzygium aromaticum* Linn. (Myrtaceae; flower bud)	Carbon tetrachloride	Reduces the levels of serum markers and decreased in tissue MDA levels and increased in SOD, catalase, GSH and membrane bound enzymes indicated the hepatoprotective and antioxidant property	[239]
5	HD-03 (Himalaya Drug company.)	*Solanum nigrum L.* (Solanaceae;whole plant), *Cichorium intybus* L. (Asteraceae; seeds), *Picrorrhiza kurroa Benth*. (Plantaginaceae; roots), *Tephrosia purpurea L*. (Fabaceae; whole plant) *Andographis paniculata Nees* (Acanthaceae;leaves)	D-Galactosamine	Hepatoprotective property	[240]
6	Hepax, a polyherbal formulation, (Anglo-French drug industries, Bangalore)	*Plumbago zeylanica* (Chitraka, Plumbaginaceae), *Picrorrhiza kurroa* (Katuka, Plantaginaceae), *Piper nigrum* (Maricha, Piperaceae), *Zingiber officinale* (Ardraka, Zingiberaceae), *Sodii carbonas impure* (Sajikakshara), *Phyllanthus embilica* (Amalaki, Euphorbiaceae), *Terminalia chebula* (Haritaki, Combretaceae), *Calcii oxidum* (chuna), *Potassii carbonas impure* (Yavakshara)	Carbon tetrachloride, paracetamol and thiocetamide	Decreased the levels SGPT, SGOT, ALP and total bilirubin Strongly hepatoprotective effect	[241]

7	Herbal formulation	*Andrographis paniculata* (Acanthaceae; leaves), *Boerhavia diffusa* (Nyctaginaceae; root), *Eclipta alba* (Asteraceae; whole plant) and *Picrorhiza kurroa* (Plantaginaceae*;* rhizome)	Carbon tetrachloride and ethanol	Restores the cellular integrity of liver architecture, strongly indicated the herbal formulation has potential hepatoprotective action	[242]
8	Herbal Preparation (HP-4)	*Aloe vera* (Xanthorrhoeaceae; leaves), *Bacopa monnieri* (Scrophulariaceae; leaves), *Moringa oleifera* (Moringaceae; *Leaves*) and *Zingiber officinale* (Zingiberaceae; *rhizome*)	D-Galactosamine	Free radical scavenging properties, Antioxidants property, Hepatoprotective activity, Synergistic protection	[243]
9	HPN-12	*Glycyrrhiza glabra* (Papilionace*ae),* *Picrorrhiza kurroa (Plantaginaceae*), *Berberis aristata* (Berberidaceae), *Piper longum* (Piperaceae), *Phy1lanthus niruri* (Phyllanthaceae), *Solanum dulcamara* (Solanaceae), *Zingiber officianale* (Zingiberaceae), *Curculigo orchioides* (Hypoxidaceae), *Elettaria cardamomum* (Zingiberaceae), *Tinospora cordifolia* (Menispermaceae), *Desmodium triflorum* **(**Fabaceae), *Saccharum officinarum*(Poaceae)	Carbon tetrachloride	Improved serum, liver function marker such as AST, ALT, ALP	[244]
10	Jigrine (an Unani polypharmaceutical herbal formulation)	*Cichorium intybus* Linn. (Asteraceae), *Tamarix dioica* Roxb. (Tamaricaceae), *Solanum nigrum* Linn. (Solanaceae), *Rheum emodi* Wall. (Polygonaceae), *Rubia cordifolia* Linn. (Rubiaceae), *Vitex negundo* Linn. (Lamiaceae), *Cassia occidentalis* Linn. (Fabacea), *Foeniculum vulgare* Mill. (Apiaceae), *Cuscuta reflexa* Roxb. (Convolvulaceae), *Careya arborea* Roxb. (Lecythidaceae), *Phy1lanthus niruri* Linn Hook. (Euphorbiaceae), *Plantago major* Linn.(Plantaginaceae), *Rosa damascena* Linn.(Rosaceae), *Solanum xanthocarpum* (Solanaceae),	Alcohol, carbon tetrachloride and paracetamol	Hepatoprotective activity of Jigrine and antioxidant property	[245]

11	Liv 52 (Himalaya Drug Company)	*Achillea millefolium* (Asteraceae), *Capparis spinosa* (Capparaceae), *Cassia occidentalis* (Fabaceae) *Cichorium intybus* (Asteraceae), *Solanum nigrum* (Solanaceae), *Tamarix gallica* (Tamaricaceae), *Terminalia arjuna* (Combretaceae)	Carbon tetrachloride and Paracetamol	all the six herbal formulations (Ayurvedic medicine) showed marked beneficial effects in the studied pharmacological, biochemical and histological parameters. Protects liver against different hepatotoxins, promotes appetite and growth	[246]
12	Livergen (Standard Pharamcuticals Serampore, West Bengal)	*Andrographis paniculata* (Acanthaceae), *Apium graveolens* (Apiaceae), *Asteracantha longifolia* (Acanthaceae), *Cassia angustifolia* (Fabaceae), *Trachyspermum ammi* (Apiaceae), *Trigonella foenum-graecum* (Fabaceae)	Carbon tetrachloride and paracetamol	Gastrointestinal and hepatic regulator	[246]
14	Livokin (Herbo-med, Kolkata)	*Andrographis paniculata* (Acanthaceae), *Apium graveolens* (Apiaceae), *Berberis lyceum* (Berberidaceae), *Carum copticum* (Apiaceae), *Cichorium intybus* (Asteraceae), *Cyperus rotundus* (Cyperaceae), *Eclipta alba* (Asteraceae), *Ipomoea turpethum* (Convolvulaceae), *Oldenlandia corymbosa* (Rubiaceae), *Picrrorhiza kurroa* (Plantaginaceae), *Hygrophila spinosa* (Acanthaceae), *Plumbago zeylanica* (Plumbaginaceae), *Solanum nigrum* (Solanaceae), *Tephrosia purpurea* (Fabaceae), *Terminalia arjuna* (Combretaceae), *Terminalia chebula* (Combretaceae), *Trigonella foenum-graecum* (Fabaceae)	Carbon tetrachloride and paracetamol	Herbal formulation, for hepatic dysfunction	[246]
15	Octogen (Plethico Pharamcuticals Ltd., Indore)	*Arogyavardhini rasa*, *Phyllanthus niruri* (Phyllanthaceae)	Carbon tetrachloride and paracetamol	Highly potent hepatoprotective	[246]
16	Stimuliv (Franco-Indian Pharamcuticals Pvt. Ltd., Mumbai)	*Andrographis paniculata* (Acanthaceae), *Eclipta alba* (Asteraceae), *Phyllanthus niruri* (Phyllanthaceae), *Justicia procumbens* (Acanthaceae)	Carbon tetrachloride and paracetamol	Liver stimulant and tonic	[246]
17	Tefroliv (TTK Pharma Pvt. Ltd., Chennai)	*Andrographis paniculata* (Acanthaceae), *Eclipta alba*(Asteraceae), *Ocimum sanctum* (Lamiaceae), *Phyllanthus niruri* (Phyllanthaceae), *Picrrorhiza kurroa* (Plantaginaceae), *Piper longum* (Piperaceae), *Solanum nigrum*(Solanaceae), *Tephrosia purpurea* (Fabaceae), *Terminalia chebula* (Combretaceae)	Carbon tetrachloride and paracetamol	Standardized liver formulation for effective hepatic regeneration	[246]

18	Liv. 100 (Himalaya Drug company)	*Cichorium intybus* (Asteraceae), *Solanum nigrum* (Solanaceae), *Phyllanthus amarus* (Phyllanthaceae), *Picrorrhiza kurroa* (Plantaginaceae), *Emblica officinalis* (Euphorbiaceae)	Isoniazid, rifampicin, and Pyrazinamide	Decreased in the activity of Na^+K^+ ATPase $Ca2^+$ ATPase and $Mg2^+$ ATPase, restores antioxidant enzymes and scavenge reactive oxygen species	[247]
19	Liv. 52 (Himalaya Drug Company)	*Achillea millefolium* (Asteraceae), *Capparis spinosa* (Capparaceae), *Cassia occidentalis* (Fabaceae), *Cichorium intybus* (Asteraceae), *Solanum nigrum* (Solanaceae), *Tamarix gallica* (Tamaricaceae), *Terminalia arjuna* (Combretaceae)	Carbon tetrachloride	Significantly decreased in MDA	[248]
20	Mandur bhasma (Himalaya's herbs)	Ferric oxide/hematite or red iron oxide	Carbon tetrachloride	Prevents the paraffin mediated and $CC1_4$ mediated changes in the enzyme activities, hepatoprotective role	[249]
21	Panchagavya ghrit. (Go-Vigyan Anusandhan Kendra, Deolapar).	cow milk, ghee, urine, dung and curd in equal proportions	Carbon tetrachloride	Prevents elevated levels of serum GPT, GOT, ACP and ALP, normal architecture and reduced the CCl**4** induced hepatotoxicity	[250]
22	Polyherbal formulation	*Curcuma longa* (Zingiberaceae; rhizomes), *Emblica officinalis* (Phyllanthaceae; fruit), *Terminalia chebula* (Combretaceae; fruit), *Terminalia belirica* (Combretaceae; fruit) and *Myrica nagi* (Myricaceae; fruit) and bees wax.	Paracetamol	Hepatoprotective property	[251]
23	Polyherbal formulation	*Emblica officinalis* (Euphorbiaceae;leaves), *Phyllanthus acidus* (Phyllanthaceae; leaves), *Moringa oleifera* (Moringaceae; leaves)	Paracetamol	Inhibits against various hepatotoxicants, SGPT, SGOT, ALP, DB and LDH levels decreased	[252]
25	Polyherbal formulation tablets (TulsiAmrit Pvt. Ltd., Indore, India)	*Andrographis paniculata* (Acanthaceae), *Phyllanthus niruri* Linn. (Euphorbiaceae), *Phyllanthus emblica* Linn. (Euphorbiaceae)	Alcohol, carbon tetrachloride and paracetamol		[252]
24	Polyherbal formulation	*Acacia catechu* (Fabaceae), *Allium sativum* (Amarylidaceae), *Andrographis paniculata* (Acanthaceae), *Azadirachta indica* (Meliaceae), *Boerhaavia diffusa* (Nyctaginaceae), *Curcuma longa* (Zingiberaceae), *Eclipta alba* (Asteraceae), *Emblica officinalis* (Euphorbiaceae), *Luffa echinata* (Cucurbitaceae), *Picrorrhiza kurroa* (Plantaginaceae), *Phyllanthus amarus* (Phyllanthaceae)	Carbon tetrachloride and paracetamol	Prophylactic and therapeutic efficacy Strong biochemical parameters, morphological, pentobarbitone sleeping time and histopathological	[253]

26	Polyherbal formulation tablets	*Phyllanthus niruri* (Phyllanthaceae), *Eclipta alba* (Asteraceae), *Cichorium intybus* (Asteraceae), *Boerhaavia diffusa* (Nyctaginaceae), *Embelia ribes* (Myrsinaceae), *Berberis aristata* (Berberidaceae), *Picrorhiza kurroa* (Plantaginaceae)	Carbon tetrachloride	Antioxidant activity	[254]
27	Rhinax (Hindustan Antibiotics Limited, Pune)	*Withania somnifera* L. (Solanaceae; root), *Asparagus racemosus* Wild. (Liliaceae; root), *Mucuna pruriens* Baker non-DC (Papilionaceae; root), *Phyllanthus emblica* Gasertn. (Euphorbiaceae; fruit), *Glycyrrhiza glabra* L.(Papilionaceae; root), *Terminalia chebula* Retz.(Combretaceae; fruit), *Myristica fragrans* Houtt. (Myristicaceae; seed)	Carbon tetrachloride	Anti-hepatotoxic activity, increased activity of cytochrome P450,	[255]

Note: S: Serum; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase ALP: Alkaline phosphatase; BIL (TB): Total bilirubin; DB: Direct bilirubin; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde; TBARS; Thiobarbituric acid reactive substances; LPO; Lipid hydroperoxide GSH: Reduced glutathione TC: Total cholesterol; TG: Triglycerides; NO: Nitric oxide; TT: Thrombin time: γ-GT: Gamma-Glutamyl Transferase; GPx: Glutathione peroxidase; ACP: Acid phosphatase; CCl_4: Carbon tetrachloride

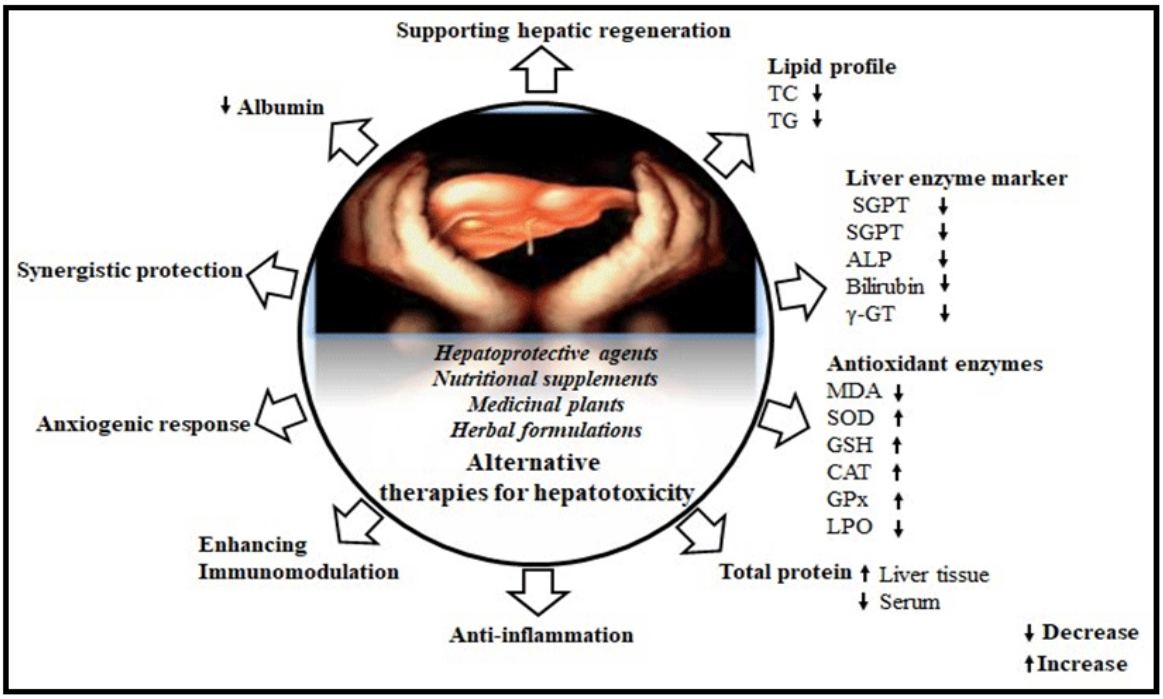

Figure 1: Mechanisms of action of promising hepatoprotective therapies

Note: SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALP: Alkaline phosphatase; γ-GT: Gamma-Glutamyl Transferase; MDA: Malondialdehyde; SOD: Superoxide dismutase; GSH: Reduced glutathione; CAT: Catalase; GPx: Glutathione peroxidase; LPO; Lipid hydroperoxide; TC: Total cholesterol; TG: Triglycerides

Conclusion

Present review concludes the several reports recommended interventions or alternative therapies of nutritional supplements, medicinal plants, and herbal formulations showed hepatoprotective activity against drug induced hepatotoxicity with higher efficacy safety, and long-term benefits without major side effects. Several herbal plants and formulations have been used as medicine in ayurveda from ancient time. Inspite of ample literature, there are very few successfully marketed formulations with excellent hepatoprotective or hepatocorrective activities. There is a need for authentication and scientific investigations of the hepatoprotective claims of ayurvedic or traditional herbal formulations for their wider acceptance. As our review found the alternative therapies having promising effects, either experimentally in animal models or cell cultures or even in clinical trials.

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