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A brief review on hepatoprotective herbs

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Abstract
Liver is one of the most complex and essential organs of the human body and it is involved in numerous metabolic processes. Hepatic diseases can be caused by various causes which includes- alcoholism, viral infection, malnutrition and due to some drugs. There are number of treatments available for the liver diseases but they are not adequate and also shows severe adverse effects. So, there is need of alternatives to these treatments. In recent decades there is increased interest of researchers in the field of herbal medicines. The beneficiary effects are known from centuries. In this review we focus on the herbs with hepatoprotective activity and on the types of studies conducted and their results, the part/extract and its dose used, phytoconstituent responsible for the hepatoprotective activity of herb. The main mechanism of hepatoprotection is observed to be by combating the free radical species, by decreasing serum levels of increased liver enzymes and by improving the activity of antioxidant system.

Keywords: hepatoprotection, hepatoprotective herbs

Introduction

Liver is the largest gland in the body. It plays important role in bodies vital functions such as; metabolism, storage of nutrients, glucose, provide defense against infection, formation of blood clotting factors, secretion of digestive enzyme (bile), etc [1].

Now a days due to work pressure, malnutrition, lack of exercise, excessive alcohol consumption and viral infections have increased liver load in people which makes them susceptible to series of liver diseases [2, 3]. Liver diseases are the conditions in which liver fails to do its functions at its full capacity. According to etiologies they can be classified as viral hepatitis, alcoholic or non-alcoholic liver diseases, autoimmune live diseases, cholestatic liver diseases further leads to advanced stage liver diseases like cirrhosis, hepatic malignancies including hepatocellular carcinoma. Certain medications and herbal compounds, fat deposition in liver cause the liver diseased condition [4, 5, 6, 7]. Obesity, type 2 Diabetes Mellitus, family history of liver disease are the risk factors.

According to available data approximately 2 million deaths per year worldwide are caused due to liver diseases. From which 1 million deaths are due to cirrhosis complications and another 1 million due to viral hepatitis and hepatocellular carcinoma. Cirrhosis is the 11th and liver cancer are the 16th leading cause of death globally **[8]**. According to World Health Organization approximately 500 million people of world are suffering from severe form of liver diseases that is chronic hepatitis [9].

There are many approaches available for the treatment of these liver diseases but they are too costly and not affordable especially for the developing world, limited in efficacy also there is risk of adverse effects. On the other hand, herbal medicines are gentle and due their easier availability, safety, cost effectiveness makes them favorable option in comparison to modern drug therapies [10].

Pathophysiology of various liver diseases

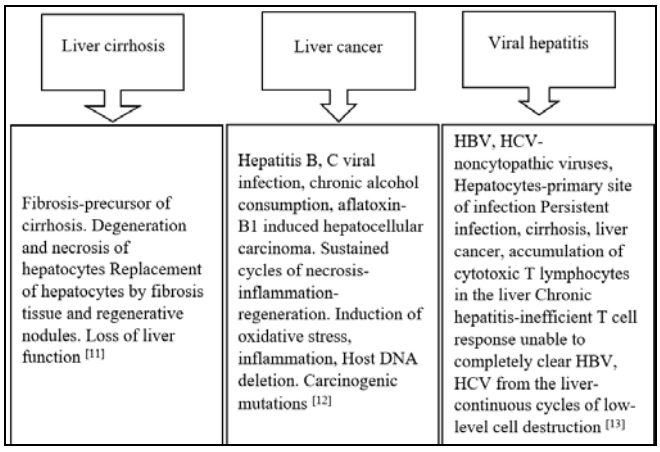
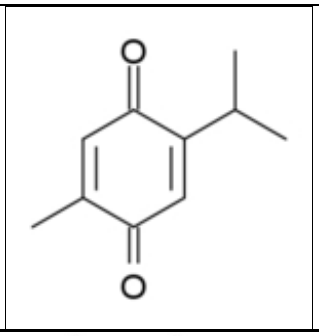
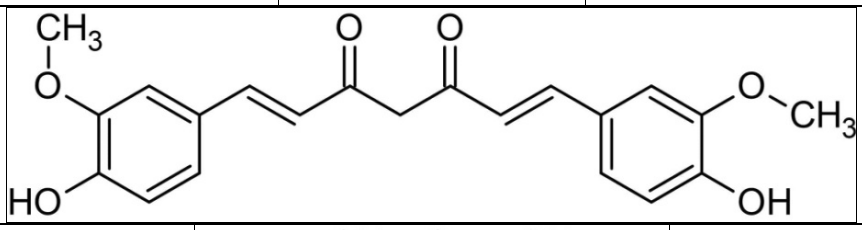
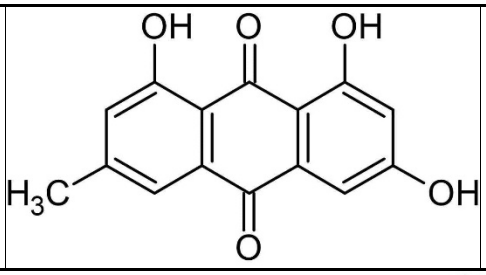
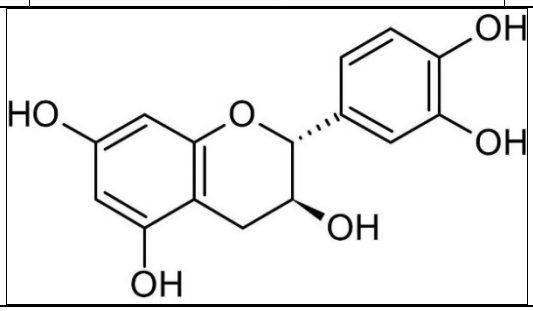
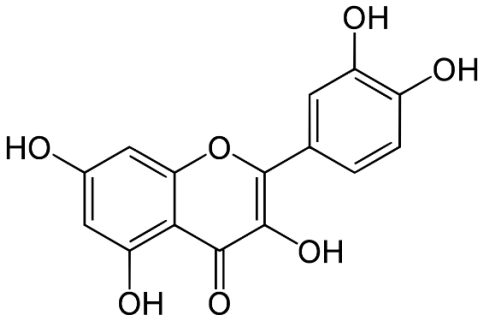


Fig 1: Pathology of various liver diseases

Table 1: Chemical Structure of hepatoprotective phytoconstituent present in herbs

Name	Chemical Structure
Thymoquinone	
Curcumin	
Emodin	
Catechin	
Quercetin	

General mechanism of hepatoprotection

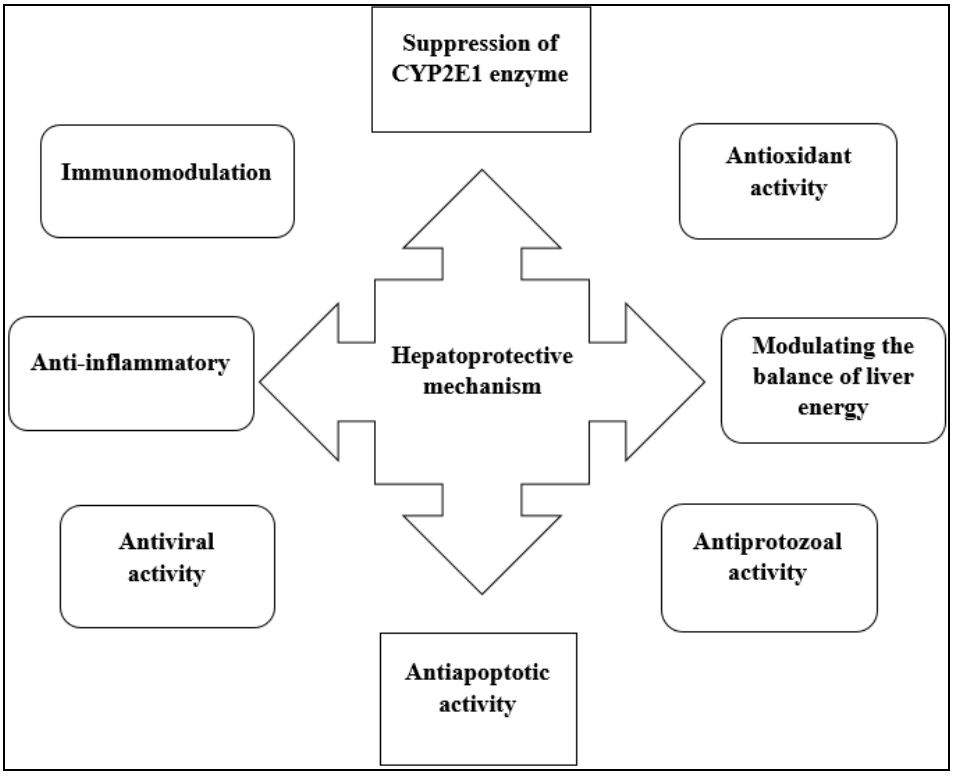


Fig 2: General mechanism

Table 2: List of Hepatoprotective herbs

Sr. No.	Name of Plant Family	Extract	Dose	Phytoconstituent	Pharmacological Model	Reported Mechanism of action	Reference
1	Melaleuca styphelloids Myrtaceae	Methanol extract of air-dried powdered leaves	25, 50, 100 microM	Ellagitannin named Stypheliodin	HepG2 cell	Reduce ALT&AST levels in CCl4 treated group & increase GSH level by antioxidant effect, increases SOD activity.	[14]
2	Ephedra pachyclada Ephedraceae	E. pachyclata extract	140, 1400 mg/kg bw	Phenolic compounds	*In vivo* mouse model	Anti-inflammatory & antioxidant effect reduces AST, ALT in CCl4 induced chronic and acute liver failure.	[15]
3	Astragalus membranaceus Fabaceae	Dried roots extract	1.5, 3 g/kg for 60 days before CCl4 intoxication	Polysaccharides	*In vivo* Common carp model	Against CCl4 induced hepatotoxicity – Reduced the increased levels of GPT, GOT, LDH, elevated levels of total protein and albumin, SOD, glutathione.	[16]
4	Nigella sativa Ranunculaceae	Volatile oil of seeds	100 mg/kg oral	Thymoquinone (TQ)	*In vivo* Male Swiss albino mice model	Against CCl4 induced toxicity through antioxidant properties.	[17]
5	Gardenia jasminoides Ellis Rubiaceae	Dried ripe fruit powder extract	20, 40, 80 mg/kg	Geniposide	*In vivo* Male mice model	Alcohol induced damage in liver – upregulated the expression of main antioxidant enzymes GSH, GST, GPx, GuZnSOD, CAT.	[18]
6	Lycium barbarum L. Solanaceae	Lycium barbarum polysaccharides extract	0.1, 0.3, 0.6 mg/ml	Polysaccharides	*In vitro*	CCl4 induced liver injury-pretreatment and pre & post treatment showed decreased levels of all marker enzymes like GOT, GPT, LDH at all concentration, inhibited formation of MDA after pretreatment and pre and post treatment at 0.3& 0.6 mg/ml, pretreatment showed significant elevation in antioxidant enzymes activities.	[19]
			0.1, 0.5, 1 %	Polysaccharides	*In vivo*	Against CCl4 induced liver injury – pretreatment showed decreased serum levels of GOT, GPT, LDH enzymes, inhibited decrease in antioxidant enzymes	[19]

						and increase in MDA level.	
7	Syzygium cumini (syn. Eugenia jambolana) Jamun Myrtaceae	Ethanolic extract of pulp of E. jambolana (EPEJ)	100, 200 mg/kg orally	Flavonoids, garlic acid, anthocyanins	Paracetamol induced hepatotoxicity in Wistar albino rats.	Against paracetamol induced hepatotoxicity – antioxidant activity showed decrease in serum levels of AST, ALT, ALP. Increase total protein & albumin. Increased glutathione contents & activity of antioxidant enzymes like SOD.	[20]
8	Phyllanthus emblica Phyllanthaceae	50 % alcoholic extract of P. emblica	100 mg/100 g	Flavonoid (Quercetin)	Paracetamol induced liver damage in Albino mice.	Against paracetamol induced liver damage – pretreatment shows reduction in GSH, GST. Reduces alkaline phosphate activity in thioacetamide induced liver damage in animal model.	[21]
9	Phyllanthus urinaria L. Phyllantaceae	Methanolic extract of whole plant	2 ml/kg	Corilagin	*In vivo*	Inhibit CCl4 induced liver damage by modulating serum glutamate-pyruvate-transaminase and glutathione peroxidase.	[22]
10	Rhubarb Polygonaceae	Dried roots and rhizomes	20-80 mg/kg/day	Emodin	*In vivo*	Decrease serum ALT, ALP, Globulin and improve liver fibrosis in rats.	[23]
11	Byrsocarpus coccineus Connaraceae	Aqueous Leaf extract	200, 400, 1000 mg/kg	Flavonols, glycosides	*In vivo* Albino rat model	In CCl4-induced liver damage – shows antioxidant effect by increasing antioxidant enzymes activity with peak effect at 1000 mg/kg. Lowers the elevated levels of ALT, AST, ALP.	[24]
12	Trichosanthes cucumerina Cucurbitaceae	Methanolic extract of whole plant	Pretreatment 250, 500 mg/kg	CucurbitacinB, cucurbitacinE	*In vivo* Wistar albino rats and Swiss albino rats	In CCl4 induced hepatotoxicity – controlled the raise of AST, ALT, ALP, total bilirubin (TB), MDA.	[25]
13	Eruca sativa Brassicaceae	Leaves ethanolic extract	Pretreatment 250, 500 mg/kg orally	Fatty acids, glucoerucin, isothiocyanates	*In vivo* Wistar albino rat model	Antioxidant effect in CCl4 induced hepatic injury. Prevented the elevation of GOT, GPT, ALP, GGT, bilirubin and decrease the concentration of MDA.	[26]
14	Alocasia indica Araceae	Hydroalcoholic extract of leaves	Pretreatment 250, 500 mg/kg	Cynogenetic glycosides, Alocasin, β-lectins	*In vivo* Wistar albino rats' model	In CCl4 and paracetamol induced hepatotoxicity – reduction in serum marker enzymes AST, ALT, ALP, SB, CHL and increase in levels of TP, SA.	[27]
15	Forsythiae fructus Oleaceae	Dried Forsythiae fructus extract	20, 50, 100, 200 mg/kg 30 min before and 2h after CCl4 injection.	Pinoresinol, saponins, flavonoids	*In vivo* Male mice model	In CCl4-induced liver toxicity shows antioxidative activity & inhibition of NF-κB. Attenuates increase in the serum AST, ALT levels also decrease MDA levels.	[28]
16	Polygala arvensis Polygalaceae	Chloroform extract of leaves	200, 400 mg/kg	Flavonoids, saponins	*In vivo* Male Wistar rats' model	In d-galactosamine induced liver damage – showed significant decrease in the levels of ASAT, ALAT, ALP, LDH, TB, total cholesterol and increase in TP, TGL, albumin in serum.	[29]
17	Cassia fistula Leguminosae	n-heptane extract of leave	400 mg/kg	Anthraquinone, polyphenols	*In vivo* White albino rats' model	Protective action against Paracetamol induced liver toxicity, decreases the elevated serum levels of transaminases, bilirubin, ALP.	[30]
18	Clerodendrum inerme Verbenaceae	Ethanolic extract of leaves	200 mg/kg bw	Iridoid glycosides, verbascoside	*In vivo* Swiss albino mice model	Against CCl4-induced hepatotoxicity– showed decrease in serum enzymes AST, ALT, ALP also significantly improved TGL and Cholesterol levels.	[31]
19	Adhatoda vasica Acanthaceae	Aqueous extract of leaves	50, 100 mg/kg p.o.	Quinazoline alkaloids, vasicine	*In vivo* Wistar rat model	In d-galactosamine induced liver injury – significantly decreased levels of SGPT, SGOT, MDA.	[32]
20	Momordica dioica Cucurbitaceae	Ethanolic and aqueous extract of leaves	200 mg/kg	Flavonoids, saponins, momordicin	*In vivo* Wistar albino rat model	CCl4 induced hepatotoxicity – lowered elevated levels of serum enzymes AST, ALT, ALP, TB. Ethanolic extract more potent hepatoprotective.	[33]

						Free Radical scavenging and antioxidant activity.	
21	Amaranthus spinosus Amaranthaceae	50% ethanolic extract of whole plant	100, 200, 400 mg/kg	Flavonoids, phenolic glycosides	*In vivo* Sprague Dawley rat model	In CCl4-induced hepatotoxicity – normalized the elevated serum enzymes AST, ALT, ALP, total bilirubin, Antioxidant effects.	[34]
22	Tinospora cordifolia Menispermaceae	Polysaccharide preparation (satwa) obtained from stem.	100 mg/kg	Tinosporone, tinosporic acid, cordifolisides A to E	*In vivo* adult male albino rat model	In CCl4-induced– reduction in serum level of SGOT, SGPT, ALP, bilirubin.	[35]
23	Nymphaea stellate Nymphaeaceae	Flower extract	250, 500, 750 mg/kg	Flavonoids, astragalin	*In vivo* Male albino rat model	Shows antioxidant effects against CCl4-induced hepatotoxicity and reduced the enhanced levels of serum AST, ALT, ALP and bilirubin.	[36]
24	Phellinus rimosus Hymenochaetaceae	Ethyl acetate extract	25, 50 mg/kg	Polyphenols, flavonoids	*In vivo* Female Sprague Dawley rat model	Inhibition of activities of serum transaminases (SGPT, SGOT) & ALP also reduced serum level of MDA and increased antioxidant enzymes activity in CCl4 induced hepatotoxicity.	[37]
25	Cytisus scoparius L. Leguminosae	Aerial parts plant extract	250, 500 mg/kg per day for 7 days	Flavonoids, sparteine, scoparin	*In vivo* Wistar albino rat model	Antioxidant effects– GSH & hepatic enzymes like SOD, CAT, GPx, GST were increased significantly and lowered SGOT, SGPT, LDH levels against CCl4-induced liver damage.	[38]
26	Helminthostachys zeylanica (Hz) Botrychiaceae	Methanolic extract of rhizomes of HZ	100, 200 mg/kg	Flavonoids, quercetin, ugonin, carotene, ascorbic acid	*In vivo* Male Wistar albino rat model	In CCl4-induced liver damage– decreased levels of serum enzymes AST, ALT, Serum bilirubin.	[39]
27	Strychnos potatorum Loganiaceae	Aqueous extract of seeds. Seed powder	100, 200 mg/kg	Triterpenes, sterols, diaboline	*In vivo* Wistar albino rat model	Significant rise in antioxidant levels with reduction in lipid peroxidation and attenuated the increased levels of serum enzymes SGOT, SGPT, ALP, serum bilirubin against CCl4-induced hepatotoxicity.	[40]
28	Premna tomentosa Verbanaceae	Leaves extract	Pretreatment 750 mg/kg orally	Limonene, premnones A–C	*In vivo* Adult male albino rat model	Attenuates the levels of membrane bound enzymes & protected animals against acetaminophen induced membrane damage.	[41]
29	Vitis vinifera Vitaceae	Ethanolic extract of leaves	62.5, 125, 250 mg/kg	Resins	*In vivo* Male Wistar-albino rat model	In CCl4-induced hepatotoxicity – MDA levels reduced at 125 mg/kg, GSH levels increased at 250 mg/kg and at 62.5 mg/kg showed toxic effects on AST, ALT, MDA.	[42]
30	Boerhaavia diffusa Nyctaginaceae	Aqueous extract of roots Powder form	2 ml/kg 150 mg/kg	Punarnavine, punarnavoside, liirodendrin	*In vivo* Adult male albino rat model	Hepatoprotection against thioacetamide induced liver damage – increased levels of serum GOT, GPT, ALP was markedly reduced.	[43]
31	Acacia catechu (L.f.) Willd. Fabaceae	Seed extract	400 mg/kg	Catechin	Wistar female rat model of acetaminophen induced liver injury.	Pretreatment in acetaminophen associated liver injury (ALI) decrease LPO accumulation, reduced liver function enzymes – AST, ALT, ALP and increased antioxidant enzymes activity.	[44]
32	Adansonia digitata L. Malvaceae	Methanol extract Of fruit pulp	200 mg/kg	Vitamin C, flavonoids, steroids,	Acetaminophen-induced hepatotoxicity in adult Wistar rats	Reduced ALP, ALT, AST, MDA, SOD by taking pretreatment in Acetaminophen-Induced hepatotoxicity also showed antioxidant effects.	[45]
33	Alnus japonica (Thunb.) Steud Betulaceae	Methanol extract Stem bark	50, 100, 150, 200 micro g/ml pretreatment	Phenolic compounds	*In vitro* Male SD rat model	Act as antioxidant in Acetaminophen-Induced Hepatotoxicity.	[46]
34	Arctium lappa L. Asteraceae	Root extract	300 mg/kg pretreatment	Arctiin, arctigenin	Acetaminophen-induced hepatotoxicity in SD rats	Reduced ALP, ALT, AST, DNA fragmentation in acetaminophen-induced hepatotoxicity.	[47]
35	Artemisia absinthium L Asteraceae	Aerial parts Aqueous – methanolic extract	500 mg/kg pretreatment	Flavonoids, ascorbic acid, carotenoids,	Acetaminophen-induced hepatotoxicity in	Hepatoprotective effect in Acetaminophen-Induced hepatotoxicity reducing AST,	[48]

					Male albino Wistar rats	ALT levels and inhibiting microsomal drug metabolizing enzymes (MDME).	
36	Artemisia scoparia Waldst. & Kitam. Asteraceae	Hydromethanolic extract	150 mg/kg pretreatmet	Flavonoids, carotenoids, phenolic compounds, l-ascorbic acid	Acetaminophen-induced hepatotoxicity in – Swiss male mice, Male albino Wistar rats	Reduced serum GOT, GPT in acetaminophen induced hepatotoxicity.	[49]
37	Cuscuta chinensis Lam Convolvulaceae	Ethanolic extract	125, 250 mg/kg pretreatment	Flavonol, flavonoid	Acetaminophen-induced hepatotoxicity in Male Wistar albino rats	Against Acetaminophen-Induced hepatotoxicity – Decreased levels of GOT, AGP, ALP, antioxidant effects by increasing levels of SOD, CAT, GPxand by decreasing MDA.	[50]
38	Centaurium erythraea Rafn Gentianaceae	Methanolic extract of leaves	300 mg/kg/day or 900 mg/kg pretreatmet	Phenolic acids, sterols, secoiridoid, glycosides	Acetaminophen-induced hepatotoxicity in Male white Wistar rats	Reduced serum conc. of AST, ALT, lactate dehydrogenase (LDH) in acetaminophen induced hepatotoxicity.	[51]
39	Cuscuta arvensis Beyr. Convolvulaceae	Methanolic and aqueous extract	125, 250g/kg pretreatment	Kaempferol-3-O-rhamnoside, Kaempferol 3-O-rutinoside, kaempferol 3-O-glucoside	*In vivo* SD female rat model	In acetaminophen induced hepatotoxicity significantly decreased liver enzyme levels AST, ALT, ALP, increased antioxidant enzyme levels (SOD, CAT, GSH) and decreased MDA levels.	[52]
40	Genista quadriflora Munby Fabaceae	Aerial parts Polyphenolic extract	300 mg/kg pretreatment	Polyphenols	*In vivo* Male Wistar Rat model	Prevented the elevation of marker liver enzymes AST, ALT. Showed antioxidant properties by restoration of GSH levels and antioxidant enzymes activity Suppression of miRNA expression of CYP2E1, GSTpi, TNF-alpha in Acetaminophen-induced hepatotoxicity.	[53]
41	Glossogyne tenuifolia Composite	Hot water extract	300 mg/kg pretreatment	Chlorogenic acid, luteolin-7-glucoside	*In vitro* Male BALB/c mice model	Possesses strong antioxidant activity. Increases GSH, inhibit peroxidation, decrease AST, ALT in Acetaminophen-induced hepatotoxicity.	[54]
42	Hydrastis canadensis L. (goldenseal) Ranunculaceae	Goldenseal roots extract	300 or 1000 mg/kg pretreatment	Alkaloids	*In vitro* Male Wistar Rat model	Inhibit CYP2E1, CYP450, at 300 mg/kg dose decreases serum levels of AST, ALT in acetaminophen-induced hepatotoxicity.	[55]
43	Musanga cecropioides R.Br. ex Tedlie Urticaceae	Aqueous extract of stem bark	500 mg/kg pretreatment	Flavonoids, alkaloids	Acetaminophen-induced acute hepatotoxicity in Inbred male Wistar rats	Decreases AST, ALT in CCl4 and acetaminophen-induced hepatotoxicity.	[56]
44	Eclipta alba Asteraceae	Alcoholic extract of fresh leaves	62.5, 125, 250, 500 mg/kg	Wedelolactone, deAsmethyl wedelolactone	*In vivo* Rat, mice model	Shows hepatoprotective effect against CCl4 induced hepatotoxicity	[57]
45	Curcuma longa Zingiberaceae	Curcumin powder	50, 100 mg/kg	Curcumin	Paracetamol induced liver toxicity in Swiss albino Mice	In paracetamol induced hepatotoxicity- Decreases marker enzymes in serum, and MDA level in liver. Increases GSH activity and catalase level.	[58]
46	Ocimum sanctum Lamiaceae	Alcoholic leaf extract	100 mg/kg BW & 200 mg/kg BW	Ursolic acid, eugenol, apigenin and luteolin	Paracetamol induced liver damage Albino rats	Hepatoprotective effects due to antioxidant properties in paracetamol induced liver damage.	[59]
47	Magnifiers indica L. Anacardiaceae	Stem bark extract (vimang)	50, 100, 250 mg/kg vimang or 40mg /kg magniferin	Magniferin	*In vivo* Female Wistar rat model	Acts as an antioxidant in iron induced oxidative damage to liver – prevent iron overload, liver oxidative stress, decreases serum and liver lipid peroxidation, increases antioxidant condition.	[60]

[AST-Aspartate aminotransferase, ALT-Alanine aminotransferase, ALP-Alkaline phosphatase, SGOT-Glutamic-oxalacetic transaminase, SGPT-Glutamic-pyruvic transaminase, GSH-Glutathione, GST-Glutathione s-transferase, SOD-Superoxide dismutase, CAT-Catalase, GPx-Glutathione peroxidase, CuZnSOD-Copper and zinc containing superoxide dismutase, MDA-Malondialdehyde, LDH-Lactate dehydrogenase, LPO-Lipid peroxides, TB-Total bilirubin, TP-Total protein, SB-Serum bilirubin, SA-Serum albumin, TGL-Triglycerides]

Conclusion

Herbs/Plants have been used for the treatment of many diseased conditions since ancient time. Many Traditional Medicinal systems like Ayurveda, Chinese system of medicine etc. have summarized herbs/plants having hepatoprotective activity. In this article we reviewed herbs with hepatoprotective activity. We summarized the active phytochemical constituent present in that herb and collected the data of studies conducted to evaluate hepatoprotective potential. The major hepatoprotective mechanism observed by many studies is through antioxidant activity. We mentioned the different extracts used and their effect on biomarkers of liver diseases. We concluded that the herbs are one of the most prominent remedies for hepatoprotection. However, there is need to focus on research and clinical trials to identify the exact phytoconstituent, their efficacy to relieve the diseased condition of liver.

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