



An Updated Review on Hepatoprotective Potential of Medicinal Plants

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Abstract

The Liver, it is the foremost organ for maintaining the human body's internal surroundings. There is currently no way to reimburse for the absence of liver function. Its major influence is on the flow of nutrients and controls the metabolism of carbohydrate, macromolecule and fats. Liver cell injury caused by varied cyanogenetic chemicals (Paracetamol, Carbon tetrachloride, Alcohol, D-galactosamine, Thioacetamide, etc.), excessive alcohol consumption and microbes square measure well-studied. The offered medical aid medicine to treat liver disorders during this condition conjointly cause more injury within the liver. Hence, Herbal drugs became progressively in style and their use is wide-spread. Herbal medicines are used for the treatment of liver diseases for an extended time. Variety of herbal preparations square measure offered on the Indian market. This general review principally is concentrated on herbal plants as hepatoprotective in varied ancient medicines and explores the herbal plant, isolated active constituent and formulation with hepatoprotective activity.

Keywords: Cirrhosis; Lobules; Silymarin; Rifampicin; Genetic

Abbreviations

PCM: Paracetamol; TAA: Thioacetamide; CCL4: Carbon Tetrachloride; WHO: World Health Organization; ALT: Alanine Aminotransferase; SGOT/AST: Aspartate Aminotransferase; ALP: Alkaline Phosphate; TB: Total Bilirubin; mRNAs: Messenger Ribonucleic Acids; MMP-9: Matrix Peptidase-9; TNF α : Tumour Necrosis Factor Alpha; KLF-6: Kruppel Like Factor-6; TGF- β 1: Transforming Growth Factor Beta-1; LDH: Lactate Dehydrogenase; SGPT: Serum Glutamic Pyruvic Transaminase; TGs: Triglycerides; TP: Total Protein; 5'-NT: 5'-nucleotidase; AcHz: Acetyl Hydrazine

Introduction

The liver is the largest internal organ in the body with 4 lobes of different size and shape and surrounded by a firm layer of connective tissue called Glisson's capsule encloses the whole liver (Figure 1) [1]. It gets the nutrients and element through the most internal organ blood vessels; portal and artery [2]. The lobes of liver are composed of several practical units known as lobules. Lobules are the practical units of the liver; every lobe is formed from either parenchymal cells (hepatocytes), that are the essential metabolic

cells, or non-parenchymal cells [hepatic symmetric cells, kupffer cells epithelium cells] (Figure 2) [3,4]. Liver play a crucial role in regulation of physiological processes. It is due to the defective synthesis of curdling factors, digestive fluid secretion, metabolism of lipid, carbohydrate and proteins, elimination of many substances, blood detoxifications, synthesizes, and regulation of essential hormones. Moreover, detoxification of many drugs and xenobiotics takes place in liver [5]. The principal inductive factors for the liver diseases in developed countries are excessive alcohol consumption, and viral-induced chronic liver diseases whereas within the developing countries the foremost frequent causes are environmental toxins, parasitic malady, viral hepatitis B and C viruses, and toxic drugs (certain antibiotics, chemotherapeutic agents, high doses of paracetamol (PCM), thioacetamide (TAA), carbon tetrachloride (CCl₄), etc) [6]. 90% of cases with carcinoma are related to liver disease. The fatal and irreversible liver disease is the end-stage of most liver pathologies of various aetiologies and results in metabolic alterations and chronic liver disfunction [7,8]. The high prevalence of those liver disorders worldwide places them among the foremost serious diseases. Moreover, the value of liver disease

on economy like hospital prices, lost productivity and human suffering is incredibly high. Chronic liver cirrhosis and drug evoked liver injury accounting the 9th leading explanation for death by disease in western and developing countries [9]. Till date, there is solely few numbers of medication accessible for the treatment of liver diseases. Therefore, completely different medicinal plant extracts are tested for their potential as inhibitor and hepatoprotective liver injury in experimental animal model. A long time ago, man started treatment with herbal plants for varied diseases. Herbal drugs have gained quality and importance in recent years as a result of their effectuality, safety, and price effectiveness. Medicinal herbal plants area widely used everywhere the planet as folk's medication for many functions [10,11]. Estimations created by the world health organization (WHO) disclosed that 80% of people who live in developed countries generally use traditional medicines. One in every of the foremost necessary and well documented use of medicinal herbal plants historically is their use as hepatoprotective medicine. Hence, there is an ever-increasing need for safe hepatoprotective drugs [12]. Within the absence of reliable hepatoprotective drugs in modern medicine, an oversized variety of herbal preparations became progressively fashionable for the treatment of liver disorders. Variety of herbs show promising activity, e.g. silymarin for liver cirrhosis, *Phyllanthus amarus* is effective in chronic hepatitis B, *Glycyrrhizin* is used to treat chronic viral hepatitis, and a few herbal combinations from China and Japan are scientifically tested for treatment of liver diseases [13]. Silymarin, a flavonolignan from "milk thistle" *Silybum marianum*, is widely used for hepatoprotection. Silymarin showed a rational protection in several cyanogenetic models of induced liver cirrhosis of the liver experiments in laboratory animals. These days there is growing focus to evaluate scientific basis for the use of traditional herbal medicines that are claimed to possess hepatoprotective and antioxidant activity [14,15].

Hepatotoxicity inducing agents

Many xenobiotics like chemicals, drugs, house hold things, herbs and environmental factors are well-known to induce hepatotoxicity. Most significant for xenobiotic-induced liver injury, the centrilobular (zone-3) hepatocytes are the 1st sites of haemoprotein P450 accelerator activity, which regularly makes them at maximum risk of xenobiotic-induced liver injury. CCl₄, N-nitrosodiethylamine, Acetylaminofluorene, Galactosamine, d-Galactosamine/Lipopolysaccharide, TAA, Antitubercular drugs, PCM, Arsenic etc. Have been shown to induce experimental hepatotoxicity in laboratory animals [16].

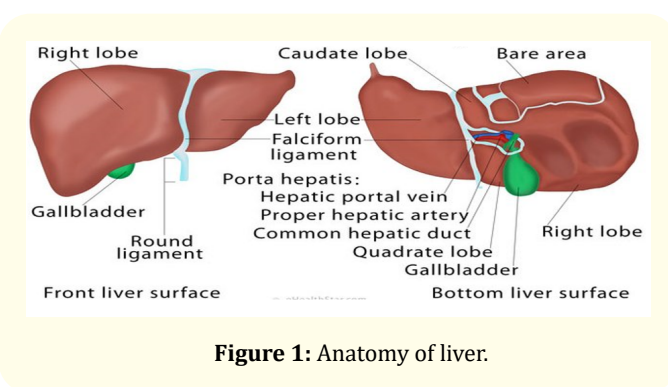


Figure 1: Anatomy of liver.

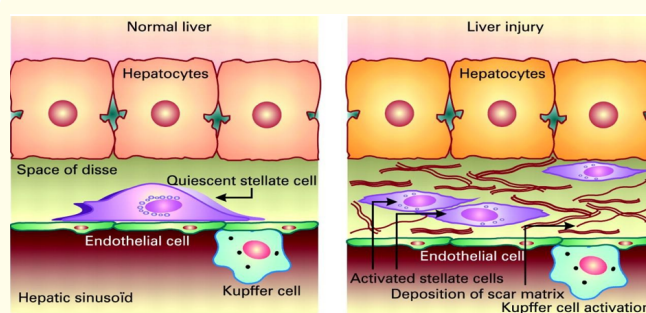


Figure 2: Diagram illustrates the 4 major liver cell types (hepatocytes, Kupffer cells, endothelial cells and stellate cells) in healthy liver and injured liver.

Thioacetamide induced hepatotoxicity model: TAA, originally used as an antimycotic agent, is potent toxin bioactivated by haemoprotein P450 to sulfine (sulfoxide) and sulfene (sulfone) metabolites; it is known to induce liver cirrhosis of the liver in murine models, that is caused by free radical-mediated super-molecule peroxidation. TAA administration results in liver harm in experimental rats by a marked increase alanine aminotransferase (ALT), aspartate aminotransferase (AST) in serum and malondialdehyde in liver; conjointly centrilobular necrosis in internal organ design. TAA interferes with the movement of RNA from the nucleus to protoplasm which can cause membrane injury. A substance of TAA is chargeable for internal organ injury. TAA cut back the number of viable hepatocytes likewise as rate oxygen consumption. Usually TAA dosage is 100 - 300 mg/kg, administrated subcutaneous or intraperitoneal. Future administration and/or high doses of TAA ends up in an organic chemistry modification, microscopic anatomy and characteristic lesion in rat liver, that corresponds to cirrhosis of the liver-like patterns of micro-nodular liver cirrhosis in humans

and associated protein-energy deficiency disease. Investigation on therapeutic principles ought to be done throughout TAA administration (prophylactic agents) or inside 2 months when withdrawal of harmful agents (therapeutics) [17,18].

Carbon tetrachloride induced hepatotoxicity model: CCl₄ is a strong hepatotoxin producing hepatic necrosis. Liver injury due to CCl₄ in experimental rats has been induced experimentally by many investigators. CCl₄ is metabolized by cytochrome P450 in endoplasmic reticulum and mitochondria with the formation of a highly reactive trichloromethyl peroxy free radicals, which initiate lipid peroxidation and finally cell necrosis. Administration of a single dose of CCl₄ to a rat produces, within 24 hrs, a centrilobular necrosis and fatty changes. The development of necrosis is associated with the leakage of hepatic enzymes into serum. Toxic dose of CCl₄ is 0.1 - 3 ml/kg administered intraperitoneally [19].

Paracetamol induced hepatotoxicity model: PCM, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. PCM 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 PCM to sulphhydryl groups of protein, result in degradation and lipid peroxidation of glutathione level and thereby, produces cell necrosis in the liver. Dose of PCM is 1 - 2 gm/kg administered orally [20].

Chloroform: Chloroform has toxic effects similar to those of CCl₄. Metabolism by microsomal cytochrome P450 is obligatory for the chloroform induced hepatic, renal and nasal toxicity. It seems that the cytochrome P450-mediated oxidative metabolism of chloroform results in the formation of inorganic chloride (excreted in the urine), carbon dioxide (exhaled), phosgene, and some hepatic covalently bound carbon (either via free radical or phosgene formation). Extensive covalent binding to the kidney and liver protein has been found in direct relationship with the extent of hepatic centrilobular and renal proximal tubular necrosis [21].

Rifampicin: Patients on coincidental rifampicin medical care have associated accumulated incidence of liver disease. This has been postulated due to rifampicin-induced cytochrome P450 enzyme-induction, inflicting associated accumulated production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin conjointly will increase the metabolism of isoniazid to isonicotinic acid and reducer, each of that are hepatotoxic. The plasma half-life of AcHz (metabolite of isoniazid) is shortened by rifampicin and AcHz is

quickly reborn to its active metabolites by increasing the oxidative elimination rate of AcHz, that is said to the upper incidence of liver necrosis caused by isoniazid and rifampicin together. Rifampicin conjointly interacts with antiretroviral medicine and affects the plasma levels of those drugs also as risk of hepatotoxicity [22].

Isoniazid: Isoniazid hepatotoxicity may be a common complication of antituberculosis medical care that ranges in severity from well elevation of serum transaminases to hepatic failure requiring liver transplantation. This can be not caused by high plasma bactericide levels however seems to represent an individual response. Isoniazid is metabolized to mono-AcHz, that is additionally metabolized to a toxicant product by haemoprotein P450 resulting in hepatotoxicity. Human genetic studies have shown that haemoprotein P4502E1 (CYP2E1) is concerned in antitubercular drug hepatotoxicity. The CYP2E1/c1 genotype is related to a better CYP2E1 activity and will result in a better production of hepatotoxins. Experimental Rodent studies showed that Isoniazid and Hydrazine induce CYP2E1 activity. Isoniazid has an inhibiting result on CYP1A2, 2A6, 2C19 and 3A4 activity. CYP1A2 is usually recommended to be concerned in reductant detoxification. Isoniazid will induce its own toxicity, presumably by the induction or inhibition of those enzymes [23].

Other drugs: Few other drugs reported to cause hepatotoxicity are Glucocorticoids, Antibiotics (Amoxicillin, Ciprofloxacin, Erythromycin), Oral contraceptives and antifungals (Fluconazole, itraconazole) [24].

Hepatoprotective herbal plants

The traditional drugs refer to a broad variety of ancient natural health care practices as well as folk/tribal practices likewise as Ayurveda, Siddha and Unani. WHO calculable that concerning 7500 plants area unit utilized in native health traditions in largely, rural and social group villages of India (Table 1). Out of these, the real medicinal value of over 4000 plants is either very little proverbial to the thought population. The classical systems of medication like Ayurveda, Siddha, Unani and Tibetan use concerning 1200 plants [25].

Conclusion

Hepatotoxicity could be a prime concern for patients furthermore as doctors, scientists and drug development agencies. However, scientist have obtained many mechanisms and conjointly effecting factors which may be utilized in diagnosing and determination of liver disease. From this review, it is clear that the medici-

S. No.	Scientific name	Part used	Extract	Active constituent	Experimental model	Hepatoprotective activity/ study outcomes
1	<i>Allium cepa</i>	Fresh bulbs	Aqueous extract	Proteins, carbohydrates, polyphenolic compounds tannins, saponins and flavonoids	Ethanol induced liver damage in male rats	AST, ALT, ALP and TB, were significantly decreased
2	<i>Alocasia indica</i>	Tuber	Ethanollic 80% and Aqueous extract	Alkaloids, flavonoids, glycosides, saponin and tannins	CCl ₄ induced hepatic injuries in male Albino Wister rats	Recovery percentage of serum ALT by 65.32% and AST by 77.36%
3	<i>Antrodia Cinnamomea</i>	Fruiting bodies and Mycelia	Aqueous extract and Ethanollic extract 90%	Benzenoids, diterpenes, triterpenoids, steroids and maleic/succinic acid derivatives	CCl ₄ induced liver injury and ethanol induced liver injury in rats	Suppression of ethanol and CCl ₄ induced elevation of expression of hepatic mRNAs, i.e. MMP-9, TNF α , KLF-6 and TGF- β 1 levels
4	<i>Bidens pilosa</i>	Dried aerial parts	Ethanollic extracts 90%	Flavonoids and polyacetylenes	CCl ₄ induced liver injury in Male Balb/c mice.	Significant decrease serum enzymatic activities of AST, ALT and LDH
5	<i>Boerhavia diffusa</i>	Roots	Ethanollic extract 95%	Flavonoid glycosides, isoflavonoids, steroids, alkaloids, phenolic and lignan glycosides	Hepatotoxicity induced by country made liquor in rats	Reduced the increment in serum parameters like SGPT, TGs, and total lipid levels
6	<i>Caesalpenia crista</i>	Leaves	Ethanollic extract 90%	Carbohydrate, alkaloids, glycosides and phenolic compounds	PCM induced hepatotoxicity in rats.	Reversed the levels of SGPT, SGOT, ALP, TB and TGs
7	<i>Chelidonium majus</i>	Whole plant	Ethanollic extract	Benzyl isoquinoline alkaloids viz. protoberberine, protopine and benzo-phenanthredine	p-dimethyl amino-azobenzene (p-DAB) induced hepatocarcinogenesis in mice	Biochemical assay of some toxicity marker enzymes and histology of liver sections suggest hepatoprotective effects
8	<i>Cyperus rotundus</i>	Leaves	Methanollic extract	Flavonoids and alkaloids	CCl ₄ induced liver damage in wistar albino rats	Lowering the serum levels of various biochemical parameters such as serum SGOT, SGPT, and ALP
9	<i>Dendrophthoe falcate</i>	Leaves	Aqueous and Ethanollic extracts	Phenol and flavonoids	Liver damage was induced by intraperitoneal administration of 25% CCl ₄ in olive oil in rats	Reduced the increment in serum parameters like AST, ALT, ALP, TP and TB
10	<i>Ficus carica</i>	Leaves, Fruit and Roots	Petroleum ether extract, Aqueous extract and Methanollic extract	Phenolics organic acids and volatile compounds	Rifampicin induced liver damage in male rats	Significant reversal of biochemical, histological, and functional changes induced by rifampicin on rats indicated potential hepatoprotective activity
11	<i>Hibiscus rosa sinensis</i>	Flower	Aqueous extract	Saponins, flavonoids, tannins, phenols, sterols, alkaloids, and anthocyanins	Induced hypercholesterolemia by feeding pure cholesterol and cholic acid orally mixing with coconut oil in rats	Decreased the levels of AST, ALT, ALP enzymes in the serum
12	<i>Hibiscus sabdariffa</i>	Seeds, Leaves and Roots	Aqueous extracts	Phenolic acids, organic acid and anthocyanins	CCl ₄ induced oxidative damage of rat liver	Significantly reduced serum activities of ALT, AST, and ALP

13	<i>Leptadenia pyrotechnica</i>	Whole plant	Methanolic, petroleum ether, chloroform, acetone and aqueous extract	Flavonoids and polyphenolic compounds	PCM induced liver damage in wistar rats	A marked reduction in the elevated activities of the hepatic enzymes i.e. SGOT, SGPT, ALP and TB levels
14	<i>Loranthus parasiticus</i>	Leaves	Ethanol extract	Sesquiterpene lactones (coriamyrtin, tutin, coriandin and coriatin)	D-galactosamine and CCl ₄ damage in rat liver cells	50% inhibition on SGPT
15	<i>Melastoma malabathricum</i>	Leaves	Methanolic extract	Flavonoids	PCM induced liver toxicity in rats	Serum liver enzymes ALT, ALP and AST as well as the microscopic observations and microscopic scoring supported the hepatoprotective potential
16	<i>Oxalis corniculata</i>	Whole plant	Ethanol extract 95%	Flavonoids, phenols and tocopherols	PCM induced hepatotoxicity in Wistar rats	Lowering the serum levels of various biochemical parameters such as SGOT, SGPT and ALP
17	<i>Petroselinum crispum</i>	Leaves	Aqueous extract	Flavonoids, Phenolic compounds and ascorbic acid	Streptozotocin induced diabetic rats	Significant decrease in blood glucose, ALP, sialic acid, uric acid, potassium and sodium levels, liver lipid peroxidation and non-enzymatic glycosylation and increase in liver glutathione
18	<i>Rheum palmatum</i>	Dried root	Ethanol extract 90%	Anthraquinone derivatives and Tannin related compound	CCl ₄ Induced liver injury in rats	Elevation of ALT, AST, and laminin levels were reversed
19	<i>Salvia miltiorrhiza</i>	Dried pulverized roots	Ethanol extract 95.6%	Salvianolic acids, tanshinone, cryptotanshinone	CCl ₄ induced liver injury in rats	Induce apoptosis of hepatic stellate cells
20	<i>Tephrosia purpurea</i>	Root	Ethanol extract	Isolonic acid, purpurin, dehydrosiderin, maackiain, purpurin, semiglabin and pseudosemiglabin	CCl ₄ induced oxidative damage and resultant dysfunction in the liver of rats.	Decreasing the serum levels of AST, ALT, ALP, LDH and 5' NT
21	<i>Terminalia arjuna</i>	Bark	Aqueous extract	Flavonoids, tannins and oligomeric proanthocyanidins	Cadmium induced toxicity in Albino Rats	Significantly reversed the elevated the serum levels of following biomarkers ALT, AST and ALP
22	<i>Trigonella foenum-graecum</i>	Dried seeds	Ethanol extract	β -carotene, saponins, coumarin, nicotinic acid, phytic acid, scopolatin and trigonelline	Thioacetamide induced liver cirrhosis in rats	The elevated levels of alkaline phosphatase, cglutamyl transferase and selected biochemical markers of liver cirrhosis were reversed.
23	<i>Ziziphus mucronata</i>	Leaves	Methanolic extract 70%	Phenols	Dimethoate induced liver damage in rats	A significant decline serum marker enzymes SGOT, SGPT and ALP

Table 1: 23 Traditional herbal plants showing Hepatoprotective activity [26-29].

nal herbal plants play an important role against on numerous liver diseases. Numerous herbal plants and plants extracts have vital hepatoprotective activity in animal models. Herbal medicines have an emerging role in hepatoprotection. They can be used in treatment of alcoholic liver disease and drug induced liver cirrhosis.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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