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Protective role of herbal plants in hepatotoxicity

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Abstract
The liver is largest metabolic organ involved in detoxification and synthesis of essential biomolecules in the human body. Liver damage occurs due to chronic alcohol abuse, viral infections (Hepatitis A, B, C) medicines, poor hygiene, smoking, dietary substances, chemicals (Carbon tetra chloride, thioacetamide, acetaminophen, D-Galactosamine) or herb induced hepatotoxicity. The liver filters all the blood from the digestive tract, before passing it to the rest of the body to avoid the entry of toxins in the other body system and prevent severe consequences. Hepatic insufficiency may increase plasma total cholesterol and triacylglycerols with high risk of atherosclerosis and cardiovascular disease. Free radical formation in the alcohol use result in development of hepatitis leading to cirrhosis. Plants have been used to protect liver injury by various chemicals. Herbal drugs are safe and have potential to cure hepatotoxicity. In India many plants have been identified as hepatoprotective drugs and used to treat liver disorders. In this study we reviewed some popular herbal plants having hepatoprotective potential.

Keywords: protective role, herbal plants, hepatotoxicity

Introduction
Liver is major metabolic organ in human body and also involved in excretion of many endogenous and exogenous compounds [1]. An injury to liver or impairment of its function may develop many consequences on individual health [2]. Liver damage is associated with increase in tissue lipid peroxidation and depletion of reduced glutathione levels. Serum level of many biochemical markers such as transaminases, alkaline phosphatase, bilirubin, triglycerides and cholesterol are elevated in liver disease. Liver involved in the metabolism of nutrients like carbohydrates, proteins, lipids and excretion of waste metabolites and detoxification of exogenous and endogenous compounds like xenobiotics, drugs, viral infections and chronic alcoholism. A liver disease is a worldwide problem. Conventional drugs used in the treatment of liver diseases are inadequate and have some serious side effects. Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practice as well as traditional system of medicine in India. Many naturally occurring products have been reported to contain large amount of antioxidant other than vitamin C, E and carotenoid.

Liver-Anatomy [3]
Liver is the largest gland in the body weighing about 1-2.3 kg. Located in the upper part of the abdominal cavity occupying right hypochondriac region, part of the epigastric region and extending into the left hypochondriac region. Liver is enclosed in thin inelastic capsule and incompletely covered by peritoneum. Peritoneal folds form supporting ligaments that attach liver to interior surface of the diaphragm. The liver has four lobes; right lobe, left lobe, caudate and quadrate lobes. Through portal fissure various structures enter and leave the gland; the portal vein enters carrying blood from the stomach, spleen, pancreas and small and large intestines. The hepatic artery enters carrying arterial blood. Sympathetic and parasympathetic nerves enter into the liver through this fissure. The right and left hepatic duct leaves carrying bile from the liver to the gallbladder. Lymph vessels leave the liver draining lymph to abdominal and thoracic nodes. The lobes of liver are made up of small functional units called lobules. It is formed by cuboidal cells, the hepatocytes arranged in pairs of columns radiating from a central vein. Between two pairs of column of cells are sinusoids containing mixture of blood from the portal vein and hepatic artery. It allows mixing arterial and portal venous blood and coming into close contact with the liver cells. The cells lining the sinusoids are kupffer cells that ingest and destroy worn out blood cells and foreign particles present in the blood flowing through the liver. Blood drains from the sinusoids into centrilobular veins then merge with veins of other lobules forming larger veins leave the liver and empty into the inferior vena cava.

Functions of the liver
The liver regulates plasma glucose level. After meal blood glucose level increases, while insulin from pancreas convert the glucose into glycogen and stored in liver. When the blood glucose level falls glucagon from pancreas convert the glycogen into glucose and maintain the normal blood glucose level. Liver metabolise fat to a form in which it can be used by the tissues to provide energy. The liver involved in deamination of amino acids- removes the nitrogenous portion from amino acids that are not required for protein

synthesis; urea is formed from the nitrogenous part and is excreted in urine. It remove nitrogenous portion of amino acid and attaches it to other carbohydrate molecules forming new non-essential amino acids. Plasma proteins are formed from amino acids includes albumin, globulins and blood clotting factors by the liver. Kupffer cells in the sinusoids breakdown the red blood cells. Liver produces immune factors that fight against the microbes. Phagocytes in the liver produce acute-phase proteins in response to microbes. These proteins are associated with inflammation process, tissue repair and immune cell activities. Liver also involved in fat metabolism i.e. oxidation of fatty acids, formation of lipoproteins, cholesterol and phospholipids. Fatty acids formed by the digestion of lipids used to synthesize cholesterol. It acts as a storage site for vitamin A, K, B12, and D, iron. The liver also stores fats, copper [4].

Removing and excreting body wastes, hormones and other foreign substances. These substances enter the blood through production by metabolism within the body or from outside in the form of drugs or foreign compounds. Breakdown of red blood cells liberate haemoglobin which lead to formation of bilirubin and is excreted in to bile by hepatocytes. If bilirubin can not be removed from the blood due to gallstones, liver disease or excessive breakdown of red blood cells produce jaundice [5]. Bile formation is helpful in digestion. Bile is secreted by liver and stored in gallbladder and it enters into the duodenum of the small intestine.

Pathophysiology of Hepatotoxicity

Metabolism and close relationship with the gastrointestinal tract, the liver is susceptible to injury from drugs and other substances. Seventy five percent of the blood coming to the liver arrives directly from gastrointestinal organ and then spleen via portal vein that brings drugs and xenobiotics. Many chemicals damage mitochondria, an organelle that produces energy. Mitochondrial impairment releases more amounts of oxidants that injure hepatic cells. Activation of CYP2E1 leads to oxidative stress which plays a crucial role in liver damage. Injury to hepatocyte and bile duct cells leads to accumulation of bile acid inside the liver. This promotes further liver damage.

Patterns of Injury

Chemicals produce a clinical and pathological hepatic injury. Biochemical markers such as alanine transferase, alkaline phosphatase and bilirubin used to indicate liver damage. Liver injury is defined as a rise in either ALT level more than three times of the upper limit of normal (ULN). Alkaline phosphatase (ALP) level more than twice ULN when associated with increased ALT or ALP[6].The liver synthesizes concentrates and secretes bile acid and excretes other toxicants such as bilirubin. Drug induced injury to hepatocytes and bile duct cells can lead to chloestasis. It leads to intrahepatic accumulation of toxic bile acids and excretion products which promote further hepatic injury [7].

Marker enzymes such as ALP, AST, and ALT used to assess the liver damage. Membrane damage or necrosis releases the enzyme in to circulation that can be measured in the serum. High level of AST indicates liver damage caused by viral hepatitis, cardiac infarction and muscle injury. AST catalyses conversion of alanine to pyruvate and glutamate. ALT is better parameter for detecting liver injury. Elevated level of serum enzymes are indicative of cellular leakage and loss of functional integrity of cell membrane in liver[8].

APAP induced Hepatotoxicity

Adverse hepatic events caused by drugs may be either predictable or unpredictable. Paracetamol produce predictable liver injury occur within few days as a result of direct liver toxicity of the parent drug or its metabolites. Unpredictable events occur as overt or symptomatic disease within 1-8 weeks like phenytoin or longer one year period of latency such as isoniazid. Most of adverse drug- induced hepatic events are unpredictable and are either immune mediated hypersensitivity reactions or idiosyncratic. The pathogenesis of drug induced hepatotoxicity occurs by toxic drug or metabolite that either elicits an immune response or directly affects the biochemistry of the cell. In both case the resultant cell death is the event that leads to the clinical manifestation hepatitis. Metabolism of chemicals takes place in liver

Acetaminophen is widely used as analgesic and antipyretic for mild to moderate pain and fever. Harmless at low doses, but has direct hepatotoxic potential when taken as an overdose and cause acute liver injury and cell death. Even in therapeutic doses acetaminophen cause serum aminotransferase elevations. Acetaminophen is converted to nontoxic glucuronate or sulphate conjugates and secreted in the urine. A minor amount of acetaminophen is metabolized by CYP450 to N-acetyl-p-benzoquinoneimine that can be toxic. Normally this intermediate is fastly conjugated to reduce glutathione, detoxified and secreted. If level of glutathione are low or the pathway is overwhelmed by high doses of acetaminophen, the reactive intermediate accumulates and bind to intracellular macromolecules that can lead to cell injury through apoptotic pathway. Factors that increase the metabolism of acetaminophen through CYP450 or that decrease the availability of glutathione can predispose to acetaminophen toxicity. Factors that affect downstream toxicity of acetaminophen metabolic intermediates may also affect toxicity. These factors are important in designing therapies for acetaminophen hepatotoxicity.

Table 1: Ethnomedicinal Plants used in Liver Diseases

Plant name	Family	Chemical constituents	Traditional uses	References
Apium graveolens Linn	Apiaceae	Limonene, p-dimethyl styrene, n-pertyl benene, caryophyllene, a-selinene, n-butyl phthalide, and sedanenolide	Liver and spleen disorders, jaundice, rheumatism, gout and inflammatory diseases	12,13
Allium hirtifolium	Alliaceae	Saponins, sapogenins, thiosulfinate, shallomin, quercetin, Kaempferol(12), Alliin, alliinase, allicin, s-allyl-cysteine, diallyl disuophide, diallyltrisulphide, Methylallyltrisulphide(13)	Fatty acids-9-hexadecenoic acid, 14-eicosadienoic acid, n-hexadecanoic acid, linoolenic acid, linoleic acid	9,10
Cynara scolymus	Astraceae	Cynarin, luteolin, chlorogenic acid, caffeic acid, flavonoids, polyphenol	Used for digestive disorders, hyperlipidemia, liver and bile diseases,	14,15

			hepatoprotective, antioxidant, antimicrobial	
Berberis Vulgaris	Berberidaceae	Berberine, oxyacanthine, berbamine, palmatine, columbamine, malic acid, jatrorrhizine, berberrubine, stigmasterol, terpenoids, lupeol, oleanolic acid, stigmasterol glucoside, polyphenols	Antioxidant, hepatoprotective agents.	16,17
Calandula officinalis	Asteraceae	A-thujene, T-murolol, sesquiterpene, flavonol glycosides, triterpene alcohols, triterpenoid saponins, flavonoids, carotenoids, xanthophylls, phenolic acids, mucilage, bitters, phytosterols, tocopherols, calendulin, resin, and volatile oils.	Antibacterial, anti-inflammatory, antiviral, antioxidant, antipyretics, jaundice, Hepatoprotective activity	18,19,20
Nigella Sativa	Ranunculaceae	Thymoquinone, p-cymene, α-pinene,	Asthma, cough, bronchitis, headache, rheumatism, fever, influenza, eczema, anti-inflammatory	21,22
Taraxacum officinale	Asteraceae	Sesquiterpene, lactones, triterpenes, carbohydrates, fattyacids, carotenoids, flavonoids,minerals, taraxalisin, coumarins and cichoriin, aesculin, Germacrane, caffeic acid, chlorogenic acid, luteolin and luteolin-7-glucoside. α-pinene, β-pinene	Antioxidant, Anti-inflammatory, Hepatoprotective.	23
Allium Sativum	Amaryllidaceae	Sapogenins, saponins, sulphuric compounds and flavonoids, S-alkylcysteine, S-allylmercaptocysteine, (alpha) – fructosyl arginine, allicin	Antidiabetic, anti-inflammatory, antihypertension, antimicrobial, antiatherosclerotic,and hepatoprotective	43,44
Marrubium vulgare	Lamiaceae	Diterpene, sterols, Phenylpropanoids, flavonoids, (E)-caryophyllene, germacrene D, bicyclogermacrene	Antihypertensive, analgesic, anti-inflammatory, hypoglycaemic effect, antidyslipidemic effect and antioxidant	24,25
Ammi majus	Apiaceae	Quercetin, Kaempferol, marmesinin	Psoriasis, vitiligo, Diabetic nephropathy, myocardial injury	59
Citrullus lanatus	Curcubitaceae	Cucurbitain, triterpenes, anthraquinones, sterols, alkaloids, flavonoids, saponins, tannins, flavones aglycone, and phenols.	Cytoprotective, antioxidant, antifibrosis	37
Agrimonia eupatoria	Rosaceae	Phenolic compounds, coumarin, flavonoid, tannins, terpenoids, procatechuic acid, coumaric acid, chlorogenic acid, quercitin, gallic acid	Hepatoprotective activity	27
Prunus armeniaca	Rosaceae	Salicylic acid, tannins, potassium salts, pcoumaric acid, protocatechuic acid, ferulic acid and diferulic acids. 4'.5, 7-trihydroxy flavones-7-O(β-D-mannopyranosyl, β-D-galactopyranoside. B-D-allopyranoside and 3, 4', 5, 7 –tetrahydroxy-3.5'-di-methoxy flavones 3-O-, carotenoids, flavonoids, phenols.	Antitussive, antiasthmatic, hepatoprotective	28
Zingiber officinale	Zingiberaceae	Gingerol, curcumin,	Catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes. Anti-platelets, antioxidant, anti-tumor, anti-rhino viral, anti-hepatotoxicity, anti-arthritic and anti-inflammatory.	29
Cucurbita pepo L. (pumpkin)	Cucurbitaceae	Linoleic acid, oleic acid, Tocopherols, Sterols, proteins, peptides, polysaccharides, para amino benzoic acid and fixed oil. Pumpkin seed oil contains omega-6, omega-9, phytosterols, carotenoids, vitamin A, vitamin E, Palmitic acid	Anti-inflammatory, antiviral, analgesic, urinary disorders, anti-ulcer, antidiabetic and antioxidant.	48
Citrus reticulata	Rutaceae	Vitamin C, flavonoids, acids and volatile oils, hesperidin, rutin, naringin	Anticarcinogenic, anti-inflammatory, antioxidant, antimicrobial, hepatoprotective	30
Petroselinum crispum oil	Apiaceae	Apiin, luteolin,apiol, myristicin	Antibacterial, antioxidant, hepatoprotective	31
Andrographis paniculata	Acanthaceae	Flavonoid, phenol and glycosides	Antibacterial, antimalarial, antiviral, cardioprotective, antioxidant, anti-inflammatory, antidiabetic, antitumor activities.	33,34
Silybum marianum	Asteraceae	Silybin, silydianin, silychristin, betaine,	Anti-inflammatory	11,35,36
Camellia sinensis	Theaceae	Catechin, epicatechin, epigallocatechin, tannins, caffeine	Antioxidant, anticancer, lipid lowering activity, neuromuscular blocking action, Antiviral activity, antibacterial activity, antispasmodic activity, anticataract activity, antigenotoxic effect, anti-inflammatory, chemoprotective	60
Acacia mellifera	Fabaceae	Alkaloids, flavonoids, tannins, sterols, and saponins	Bowel problems, stomach trouble, cold, treatment for malaria and inflammation	38

Adansonia digitata L.,	Malvaceae	Terpenoids, flavonoids, steroids, vitamins, amino acids, carbohydrates and lipids	Immunostimulant, anti-inflammatory, analgesic, pesticide, antipyretic, febrifuge and astringent in the treatment of diarrhea	40
Argemone Mexicana L.,	Papaveraceae	Alkaloids as Berberine, protopine, sarguinarine, optisine, and chelerytherine, the seed oil contains myristic, palmitic, oleic, linoleic acid, flavonoids, glycosides, sterols and phenolic compounds.	Analgesic, antispasmodic, hallucinogenic, sedative, tumors, warts, skin diseases, inflammations, rheumatism, jaundice, leprosy, piles, warm infestations and dysentery	41
Anogeissus leiocarpus	Combretaceae	Ellagic acid, Polyalcohol, sorbitol, terpenoids like α-amyrin, β-sitosterol, and traces of alkaloids	Parasitic diseases and dysentery	43,44
Balanites aegyptiaca L.,	Balanitaceae	Rotenone, yamogenin, steroidal sapogenin	Jaundice, liver disorders, spleen problems, the leaves and branches are used as a fumigant for rheumatism, fruits are used against constipation and antidiabetic	45
Cannabis sativa L.	Cannabaceae	Cannabinoids, Cannabidiol, Cannabinol	Spasmolytic, analgesic, hypnotic and to treat cholera, rabies, epilepsy, tetanus, rheumatism, anti-inflammatory	46
Capparis deciduas	Capparaceae	Alkaloids, saponins, flavonoids, tannins, sterols, cyanogenic, glycosides and cumarins	Jaundice, anti-rheumatic, diuretics, antigout, anti-inflammatory, astringent, laxative, Stomachic, astringent and for skin diseases	42,47
Combretum hartmannianum	Combretaceae	Alkaloids, flavonoids, tannins, saponins, cyanogenic glycosides, sterols and coumarins	Barks and leaves extract are used for jaundice	48
Khaya senegalensis	Meliaceae	Saponins, tannins, alkaloids, glycosides,terpenoids, phenolic compounds and flavonoids, steroids	Diarrhea, dysentery and wound infections, fever and to treat syphilis, the bark used to treat jaundice, scorpion bites, allergies	43,44
Kigelia Africana Lam	Bignoniaceous	Verminosides and iridoids and series of polyphenols such as verbascoside	Bark is used to treat ulcer, pneumonia, malaria	48
Lawsonia inermis L.,	Lythraceae	Phenolic derivatives, xanthones, napthoquinone, coumarins, triterpenes, tannins, flavonoids, aliphatic components, sterols, gallic acid, mannitol, glucose, amino acids, trace elements and minerals.	Astringent, hypotensive, sedative and, headache, jaundice, leprosy and skin disease.	48
Lepidium sativum L.,	Brassicaceae	Triterpenes, alkaloids, tannins, flavonoids, coumarins and saponins	Gastrointestinal disorders, arthritis and inflammatory disorders, dysentery and diarrhea.	37,39
Moringa oleifera Lam	Moringiaceae	Alkaloids, saponins, flavonoids, tannins, sterols, glycosides and coumarins	Liver disease, lipid disorders, arthritis,inflammatory disorders, seeds used to clean water for drinking	49
Nigella sativa L.,	Ranunculaceae	Thymoquinone, thymohydro quinine, dithymoquinone, p-cymene, carvacrol, and 4-terpineol	Liver tonics, digestive, anti-inflammatory, immune-stimulant and remedy for jaundice anti-diabetics	21,22
Occimum basilicum L.,	Lamiaceae	Glycosides, gums, mucilage, proteins, amino acids, tannins, phenolic compounds, triterpenoids, steroids, sterols, saponins, flavones and flavonoids. Linalol methylchavikol, methylcinnamate, linolen, essential oil, rosmarinic acid, citral, eugenol and geraniol.	Jaundice, stomach complaints, fever, cough and gout diuretic, aphrodisiac, and anti-dysentric. Seeds are used as demulcents.	50
Phoenix dactylifera Linn	Palmae	Carbohydrates, alkaloids, steroids, flavonoids, vitamins, tannins and phenolic acids	Sexual incapacity and weakness	52, 53
Raphanus sativus L.,	Cruciferae	Flavonoids, saponins, cumarins, and alkaloids	Hepatoprotective, bacterial and viral infections, inflammation.	54
Solanum nigrum L.	Solanaceae	Gallic acid, catechin, Protocatechuic acid, caffeic acid, epicatechin, rutin and naringenin	Inflammatory disorders, rheumatism, swollen joints, hepatomegaly, splenomegaly, gonorrhoea, edema.	55
Sterculia setigera Del.	Sterculiaceae	Saponins, steroidal, sterols, flavonoids, Tannins, saponins, cardiac glycosides and anthraquinone	Jaundice, bilharzia	56, 57
Tamarindus indica L.	Caesalpinaceae	Tannins, alkaloids, flavonoids, and saponins	To treat fever, postpartum remedy and measles	58

Conclusion

Liver is the largest metabolic organ in the human body. It has the function to detoxify toxic substances and synthesize useful biomolecules. So damage to liver may lead to grave consequences. This damage occurs due to chronic alcoholic abuse, viral hepatitis and inherited metabolic disease. Liver damage is associated with cellular necrosis, fibrosis, and increase in tissue lipid peroxidation and depletion in tissue glutathione level. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages. Polyphenols, flavonoids, terpenoids are natural antioxidants and the consumption of foods that contain these compounds in large quantities seems to play an important role in prophylaxis against many diseases.

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