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HEPATOTOXICITY AND HEPATOPROTECTISM HERBS: HERBAL REMIDIES

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ABSTRACT
Liver disorders are serious health problem most common form occurring in people of all ages. Hepatotoxicity implies chemical-driven liver damage.Liver is the largest organ in the body is being evolved to maintain the body's internal milieu and also protect itself from the challenges it faces during its functioning.The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g. microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins.Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases.
KEYWORDS: Herbal medicines, hepatoprotective activity, traditional system of medicine.

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INTRODUCTION

Liver is the vital organ of metabolism and excretion. About 20,000 deaths found every year due to liver disorders. Hepatocellular carcinoma is one of the ten most common tumors in the world with over 2,50,000 new cases each year[1] .In the absence of reliable liverprotective drugs in allopathic medical practices, herbs play a role in the management of various liver disorders. Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practices and in traditional system of medicine in India. However, we do not have satisfactory remedy for serious liver disease; most of the herbal drugs speed up the natural healing process of liver. So the search for effective hepatoprotective drug continues[2].

Hepatotoxicity (from hepatic toxicity) implies chemical-driven liver damage **.**The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g. microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins.

More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures.

Mechanism of liver damage

Drugs continue to be taken off the market due to late discovery of hepatotoxicity. Due to its unique metabolism and close relationship with the gastrointestinal tract, the liver is susceptible to injury from drugs and other substances. 75% of blood coming to the liver arrives directly from gastrointestinal organs and then spleen via portal veins which bring drugs and xenobiotics in concentrated form. Several mechanisms are responsible for either inducing hepatic injury or worsening the damage process. Many chemicals damage mitochondria, an intracellular organelle that produces energy. Its dysfunction releases excessive amount of oxidants which in turn injures hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress[6]. Injury to

hepatocyte and bile duct cells lead to accumulation of bile acid inside liver. This promotes further liver damage[7]. Non-parenchymal cells such as Kupffer cells, fat storing stellate cells and leukocytes (i.e. neutrophil and monocyte) also have role in the mechanism[3].

Factors influencing drug induced hepatotoxicity

Age, Ethnicity and race, Gender, Nutritional status, underlying liver disease, renal function, Pregnancy, Duration and dosage of drug Enzyme induction, Drug-drug interaction.

Type of liver damage

Zonal Necrosis

This is the most common type of drug induced liver cell necrosis where the injury is largely confined to a particular zone of the liver lobule. It may manifest as very high level of ALT and severe disturbance of liver function leading to acute liver failure.

Hepatitis

In this pattern hepatocellular necrosis is associated with infiltration of inflammatory cells. There can be three types of drug induced hepatitis. (A) Viral hepatitis type picture is the commonest, where histological features are similar to acute viral hepatitis. (B) In the focal or non specific hepatitis scattered foci of cell necrosis may accompany lymphocytic infiltrate. (C) Chronic hepatitis type is very similar to autoimmune hepatitis clinically, serologically as well as histologically.

Cholestasis

Liver injury leads to impairment of bile flow and clinical picture is predominated by itching and jaundice. Histology may show inflammation (cholestatic hepatitis) or it can be bland without any parenchymal inflammation. In rare occasions it can produce features similar to primary biliary cirrhosis due to progressive destruction of small bile ducts (Vanishing duct syndrome).

Steatosis

Hepatotoxicity may manifest as triglyceride accumulation which leads to either small droplet (microvesicular) or large droplet (macrovesicular) fatty liver. There is a separate type of steatosis where phospholipid accumulation leads to a pattern similar to the diseases with inherited phospholipid metabolism defects (e.g. Tay-Sachs disease).

Granuloma

Drug induced hepatic granulomas are usually associated with granulomas in other tissues and patients typically have features of systemic vasculitis and hypersensitivity. More than 50 drugs have been implicated.

Vascular lesions

They result from injury to the vascular endothelium.

Neoplasm

Neoplasms have been described with prolonged exposure to some medications or toxins.Hepatocellular carcinoma, angiosarcoma and liver adenomas are the ones usually reported[4].

HEPATOPROTECTIVE HERBS

Since time immemorial, mankind has made the use of plants in the treatment of various ailments. The Indian Tradi-tional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. Medicinal herbs and extracts prepared from them are widely used in the treatment of liver diseases like hepatitis, cirrhosis, and loss of appetite. Medicinal herb is a biosynthetic laboratory, for chemical compounds like glycosides, alkaloids, resins, oleoresins, etc. These exert physiological and therapeutic effect. The compounds that are responsible for medicinal property of the drug are usually secondary metabolites[5]. Aimed to possess liver protecting activity. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well-documented uses of plant-products is their use as hepatoprotective agents.

Herbal medicines as the major remedy in traditional system of medicine have been used in Medical practices. The practices continue today because of its biomedical benefits as well as place in cultural beliefs in many parts of world.

In India, about 40 polyherbal commercial formulations reputed to have hepatoprotective action are being used. It has been reported that 160 phytoconstituents from 101 plants have hepatoprotective activity. Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthines. Plant extracts of many

Crude drugs are also used for the treatment of liver disorders. Extracts of different plants of about 25 plants have been reported to cure liver disorders[6].

HERBAL TREATMENT

CLASSIFICATION

These are generally classified into 3 categories without any strict delineation amongst them.

1. **Anti hepatotoxic agents:** These generally antagonise the effects of any hepatotoxin causing hepatitis or any liver disorder or disease.

2. **Hepatotropic agents:** These generally support or promote the healing process of the liver. In practice these

two activities can not be easily distinguished from each other

3. **Hepatoprotective agents:** These generally prevent various types of liver affections prophilactically.

In general any hepatoprotective agent can act as an antihepatotoxic or hepatotropic agent but the vice versa is always not true[7].

Plants used in the treatment of liver disease

Hepatoprotective natural plants

Some of the crude drugs with activity against liver diseases are:

- *Silybum marianum*
- *Taraxacum officinale*
- *Cichorium intybus*
- *Solanum nigrum*
- *Glycyrrhiza glabra*
- *Wilkstroemia indica*
- *Curcuma longa*
- *Tephrosia purpurea*
- *Fumaria officinalis*
- *Peumus boldus*

1) *Silybum marianum*

Synonyms: Carduus marianus, mariane thistle.Common name: Milk thistleFamily: Asteraceae ,Origin: indigenous to the Mediterranean region, North Africa & Western Asia Parts used: Aerial parts, Chemical constituents: The active constituents of milk thistle are flavonolignans including silybin, silydianin, and silychristine, collectively known as silymarin.Silybin is the component with the greatest degree of biological activity, and milk thistle extracts are usually standardized to contain 70-80 percent silybin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds. Silybum seeds also contain betaine (a proven hepatoprotector) and essential fatty acids, which may contribute to silymarin's anti-inflammatory effect. Active ingredients: Silymarin – a flavolignin (hepatoprotective), lipids, proteins. Milk seeds seeds also contain other flavonolignans namely dehydrosilybin, desocysilycristin, desoxysilydianin, silyhermin, neosilyhermi, silybinome, and silandrin.

Use: Silybum marianum is currently the most well researched plant in the treatment of liver disease. Also use in the dyspepsia, disorders of biliary system, liver disorder. It is used as hepatoprotective and in chronic inflammatory hepatic disorders including hepatitis, cirrohis and fatty infiltration which occur due to industrial pollutants and alcohol. It has also been found to be effective against liver poisioning due to alpha-galactosamine, carbontetrachloride and tioacetamide.The michanism of hepatoprotective effect of silymarin has been suggested variously like antioxidant activity by trapping superoxide anions, stimulation of RNA synthesis and in case of amanita phalloides poisioning, blocking the receptor sites of outer liver cell membranes Silymarin is preferably given by parantral route, due to low water solubility of flavonoligans if taken orally, only 20-50% is absorbed[8]. The hepato-protective effect of *Silybum marianum* extracts on liver cells due to the presence of flavonoids and their antioxidant effects[9].

2) *Taraxacum officinale*

Synonyms: Dandelion, Family: Asteraceae, Origin: All parts of the northern hemisphere.Parts used: Leaves & roots.Chemical constituents: Bitter constituents like taraxecerin and taraxcin are active constituents of the medicinal herb. Other Active ingredients: sesquiterpene lactones, phenolic acid, inulin, K.

Use: Hepatic & biliary disorders, kidney stones.Traditionally taraxacum officinale has been used as a remedy for jaundice and other disorders of the liver and gallbladder, and as a remedy for counteracting water retention. Generally, the rots of the plants have the most activity regarding the liver and gallbladder. Oral administration of extracts from the roots of taraxacum officinale has been shown to act as a cholagogue, increasing the flow of bile.

3) *Cichorium intybus*

Synonyms: Cichory.Common name: KasniFamily: Compositae (asteraceae) Chemical constituents: A bitter glucoside, Cichorin has been reported to be the active constituent of the herb.

Use: Use for the treatment of liver diseases. It is commonly known as kasni and is part of polyherbal formulations used in the treatment of liver diseases. In mice, liver protection was observed at various doses of Cichorium intybus but optimum protection was seen with a dose of 75 mg/kg given 30 minutes after CCl4 intoxication. In preclinical studies an alcoholic extract of the Cichorium intybus was found to be effective against chlorpromazine-induced hepatic damage in adult albino rats.

4) *Solanum nigrum*

Synonyms: Black nightshade. Ayurvedic name: Kakamachi.Family: Solanaceae. Chemical constituents: Main active constituents are solamargine, andsolasonine.

Use: Aromatic water extracted from the drug is widely prescribed by herbal vendors for liver disorders. Although clinical documentation is scare as far as hepatoprotective activity is concerned, but some traditional practitioners have reported favorable results with powdered extract of the plant. It is in treatment of cirrhosis of the liver. Also used as an emollient, diuretic, antiseptic, and laxative properties.Antimicrobial,

antioxidants, cytotoxic properties.It is also having antiulcerogenic activity and hepatoprotective activity.

5) *Glychyrrhiza glabra*

Synonyms: Liquorice, Family: Leguminosae.Chemical constituents: Licorice contains triterpene saponin, known as glycyrrhizin, which has potential hepatotprotective activity. It belongs to a group of compounds known as sulfated polysaccharides. Glycyrrhizin is potassium and calcium salt of Glycyrrhizinic acid.Glycyrrhizinic acid is a glycoside and on hydrolysis yields glycyrrhetinic acid which has a triterpenoid structure. Other constituents are glucose, sucrose, bitter principle glycyramarin resin, aspargin and fat.Another chemical aspects of liquorice is prencence of flavonoids(liquiritin and isoliquiritin) which cauce antigastric effect and are useful in peptic ulcer treatment.

Use: Glycyrrhizin use for anti-viral. It has potential for therapeutic use in liver disease.

Experimental hepatitis and cirrhosis studies on rats found that it can promote the regeneration of liver cells and at the same time inhibit fibrosis. Glycyrrhizin can alleviate histological disorder due to inflammation and restore the liver structure and function from the damage due to carbon tetrachloride.The effects including: lowering the SGPT, reducing the degeneration and necrosis and recovering the glycogen and RNA of liver cells. Effects of glycyrrhizin have been studied on free radical generation and lipid peroxidation in primary cultured rat hepatocytes. Favorable results have been reported in children suffering from cytomegalovirus after treating with glycyrrhizin.

6) *Wilkstroemia indica*

Synonyms: Aradon indica, wilkstromia.Family: Thymelaeaceae.Chemical constituents: A dicoumarin, daphnoretin is the active const- ituent of the herb.The drug has shown to suppress HbsAG in Hep3B cells.

Use: W. indica is a Chinese herb and has been evaluated in patients suffering from hepatitis B.It is said to activator of protein kinase C.

7*) Curcuma longa*

Synonyms: Curcuma, turmeric, Indian saffron. Family: Zingiberaceae.Chemical constituents: Diarylhepatonoids including Curcumin is the active constituent of the plant. It contains yellow colour substances known as curcuminoids.Curcuminoids is responsible for yellow colour.Curcuma species contain volatile oil, starch etc.

Use: Like silymarin, turmeric has been found to protect animal livers from a variety of hepatotoxic substances, including carbontetrachloride, galactosamine, pentobarbital, 1-chloro-2, 4-dinitrobenzene, 7 4-hydroxy-nonenal paracetamol.Diarylhepatonoids.Curcumin has been proved as anti-inflamatory drug.

8) *Tephrosia purpurea*

Synonyms:

basterdindigo,hoarypea.Ayurvedicname:sharpunkha.Family: Fabaceae.Chemical constituents: The roots, leaves and seeds contain tephrosin, deguelin and quercetin.The hepatotprotective constituent of the drug is still to be proved.

Use: Alkali preparation of the drug is commonly used in treatment of liver and spleen diseases. In animal models, it offered protective action against carbon tetrachloride and D-galalactosamine poisoning[10 11].

9) *Fumaria officinalis*

Synonyms: Fumatory.Family: Papaveraceae. Chemical constituents: Alkaloids, flavonoids.Origin: Europe, Mediterranean, Middle East, but has now become a weed all over the world. Parts used: aerial parts. Actions: Cholagogue, antispasmodic.

Uses: Biliary & dyspeptic disorders, especially spastic discomfort of the GIT, the gallbladder & bile ducts.

10) *Peumus boldus*

Synonyms: Boldo. Family: Monimiacee. Parts used: Leaf

Chemical constituents: Alkaloids, volatile oils, flavonols and their glycosides.

Origin: Chile and other South American regions. Actions: Choleretic, diuretic, stomachic, mild sedative.

Use: Dyspepsia, spastic complaints. It is the traditional anthelmintic in Chiled. It is also used in pharmaceutical slimming mixtures.

SOME OF HERBAL FORMULATIONS USED IN LIVER DISORDER:

1) Liv-52

It is non-toxic hepatoprotective substance from The Himalaya Drug Co. Liv.52 can improve the subjective condition and clinical parameters in patients with liver damage, in particular in alcoholic liver damage.

2) LIMARIN®

Capsules and Suspension: It has a potent hepatoprotective and free radical scavenging (antioxidant) action. LIMARIN® is developed from the active extract of the fruit of silybum marianum, or the milk thistle. Basically a European herbal product.

3) Cirrhitin

Cirrhitin is a natural medicine formulated specifically to treat Cirrhosis of the liver. Marketed by CCNOW. Some other polyhedral preparations such as Livex, HD-03, Hepatomed, Live 100 and Hepatoguard with proven efficacy are also use in different types of liver disorders.

EVALUATION OF HEPATOPROTECTIVE ACTIVITY

►Investigation of Liver Function: The liver function tests are employed for accurate diagnosis, to assess the

severity of the damage, to judge the prognosis and to evaluate the therapy. The routinely performed liver function tests (LFTS) are as follows:

A. **Abnormalities of bile pigments and bile salts excretion tests**

Serum total direct and indirect bilirubin. Urine bile salts, bile pigments and urobilinogen.

B. **Serum enzymes assays**

SGOT (AST), SGPT (AST).Alkaline phos- phatase (ALP) and if necessary.γ – Glutamyl transpeptidase (γ-GT) other enzymes

C. **Changes in plasma protein tests**

Thymol turbidity test Determ- ination of total proteins, albumin globulins.

►Hepatoprotective activity can be most easily evaluated / screened with the aid of several model systems of liver damage in experimental animals. In all test model systems conditions for liver damage are implemented and an attempt is made to counteract this toxicosis with the substance / preparation under test. The magnitude of the protective effect can be measured by estimating the enzymes and the rate of survival and can be verified histologically. The available methods are invivo, exvivo & invitro methods.

A. ***In vitro* method**

Hepatocytes are isolated by using in-situ under aseptic condition and placed in chilled HEPES (N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid).These isolated hepatocytes than exposed to test samples and toxins like CCl4, thioacetamide, ethanol and paracetamol etc. After a specified time period the degree of toxicity or protection is assessed by viability tests (Trypan blue dye exclusion method) and enzyme levels such as SGOT and SGPT.

Advantages of *in vitro* models: More rapid and requires small quantities of test substances and fewer animals, where as in vivo studies require a large number of animals (six per group), *In Vivo* study need up to 3-7 days of drug administration for a significant effect to produced and thus requires large quantities of drugs but In vitro method require 3 days study and less quantities of drugs. Ability to dispose numerous samples at a time. Low cost with a small size little variation and reproducibility of results. The major disadvantage is that sometimes it may not reflect the events which occur in animals.

B. ***Ex vivo* method**

In this method after completion of preselected *in vivo* test protocol hepatocytes are isolated and the percentage of viable cells and biochemical parameters are determined as liver function tests. These methods are somewhat better correlated to clinical models than in vitro or in vivo methods.

C. ***In vivo* method**

These are of two types. 1) Based on bile parameters: The compounds having hepatoprotective claims are evaluated in general for their choleretic or anticholeretic activity in order to know whether the liver disorder is due to an abnormality of bilirubin metabolism or not. 2) Based on serum para- meters: Hepatotoxicity is produced in experimental animals by the administration of known dose of hepatotoxin like carbon tetrachloride, paracetamol, D-galacto- samine, thioacetamide, ethyl alcohol etc., which produce marked measurable effects, the magnitude of which can be measured by carrying out various liver function tests. It is very convenient laboratory method; reproducibility of results is rather poor.

Experimental models for Hepatoprotective screening

Several chemical reagents and drugs which induce liposis, necrosis, cirrhosis, carcinogenesis and hepatobiliary dysfunctions in experimental animals are classified as hepatotoxins. The most important ones used are carbon tetrachloride (CCl4), thioacetamide (TAA). D-galactosamine, Paracetamol, chloroform, ethyl alcohol and Pyridine. The following are some of the experimental rat models employing these hepatotoxins:

1. CCl4 model: A number of CCl4 models are devised depending upon its dosage through different routes of administration.

A. **Acute Hepatic Damage**

Acute liver damage, characterized by ischemia, hydropic degeneration and central necrosis is caused by oral or subcutaneous administration of CCl4 (1.25ml / kg). The biochemical parameters elevated are found to be maximum after 24 hours of CCl4 administration. Normally administered as 50 % V/V solution in liquid paraffin or olive oil.

B. **Chronic Reversible Hepatic Damage**

Administration of CCl4 (1ml/kg s.c) twice weekly for 8 weeks produces chronic, reversible liver damage.

C. **Chronic, Irreversible Hepatic Damage**

Administration of CCl4 (1ml/kg s.c) twice weekly for 12 weeks simulates chronic, irreversible liver damage.

1. Thioacetamide model: Thioacetamide (100 mg / kg s.c) induces acute hepatic damage after 48 hrs of administration by causing sinusoidal congestion and hydropic swelling with increased mitosis.

2. D-Galactosamine model :D-galactosamine 800 mg /kg i.p induces acute hepatotoxicity after 48 hrs of administration with diffused necrosis and steatosis.

3. Paracetamol model: Paracetamol induces acute hepatotoxicity depending upon its dosage through

different routes of administration, such as-A. Paracetamol 800 mg/kg i.p. induces centrilobular necrosis without steatosis.B. Paracetamol at a dose of 3 g/kg p.o stimulates acute hepatic damage.

4. Chloroform model: It produces hepatotoxicity with extensive central necrosis, fatty metamorphosis, hepatic cell degeneration and necrosis either by inhalation (for 1hrin atmosphere) or by subcutaneous administration. (0.4-0.5 ml/kg).

5. Ethanol model: Ethanol induces liposis to a different degree depending upon its dose, route and period of administration as follows-A. A single dose of ethanol 1 ml/kg induces fatty degeneration.B. Administration of 40 % (v/v) ethanol 2 ml/100g/day p.o for 21 days produces fatty liver.C. Administration of country made liquor 3ml/100g/day p.o for 21 days produces liposis[7].

CONCLUSION

Chronic hepatic diseases stand as one of the foremost health troubles worldwide. Therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the de-veloping world. Therefore, treating liver diseases with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, an attempt has been made to compile the reported hepatoprotective plants from India and abroad and may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of liver diseases in man and animals.

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