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Liver pathophysiology and its herbal treatment alternatives: A review

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Abstract
Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. Quinine, Theophyline, Pencilline G, Morphine, Digitoxine, Vincristine, Doxorubisin, Cyclosporin, and vitamin A, all share two important characteristics- they are the cornerstones of modern pharmaceutical care and they are all natural products. The use of natural substance, particularly plants, to control diseases is centuries-old practice that has lead to the discovery of more than half of all "Modern" pharmaceuticals.
This treatise included description of many medicinal plants that remains important in modern medicine, not because they are continued to be used as crude drug preparations, but because they serve as the important source of pure chemicals that have become mainstays of modern therapy. Hence an attempt has been made to compile a review of these lifesaving plants.

Keywords: Pathophysiology, Liver, Remedies, Serum

Introduction
According to World Health Organization (WHO) - "Any plant and its organs containing any substance which can be used therapeutically, or can be used as raw material for Chemical / Pharmaceutical synthesis is categorized as herbal medicine. Herbal medicine has been described as the oldest form of therapy practiced by humans today, with archaeological evidence of medicinal use of herbs dating back to 60,000 years. Herbal medicine often complement conventional treatments, providing safe, well tolerated remedies for chronic illness.

Why herbal remedies?
The effectiveness, easy availability, low cost and absence of serious toxic effects (time tested) popularizes herbal remedies. Herbal medicine is triumph of popular therapeutics diversity. Nature always stands as a golden mark to exemplify the outstanding phenomenon of symbiosis. Nature has provided the complete storehouse of remedies to cure all ailments of mankind.

Liver - Physiology and pathophysiology of hepatic diseases anatomy and physiology of liver-
Liver is perhaps the most impressive organ in the body in size and in the diversity of its activities. As with several vital organs such as kidney or lungs, the amount of tissue in the liver seems to be super abundant. The liver of a healthy young adult weighs about four times as much as his heart or two kidneys. It is enclosed in a smooth membrane lining a capsule and is flat with a rounded dome, which fits against the curved diaphragm. Since, it stores many substances, and converts them into modified forms as well, its size varies with nutrition and age (Chatterjee T.K., 2000) [1].

Anatomy
The liver is the largest organ in the human body weighing 1400-1600 gm in the male and 1200-1400gm in female. There are two main anatomical lobes-the right and left, the right being about six times the size of the left lobe. The right lobe has quadrate lobe on its inferior surface and a caudate lobe on the posterior surface. The right and left lobes are separated anteriorly by a fold of peritoneum called as falciform ligament, inferiorly by the fissure for the ligamentum teres and posteriorly by the fissure for the ligamentum venosum (Lin H.K., 2000) [2].
The porta hepatis is the region on the inferior surface of the right lobe where blood vessels, lymphatics and common hepatic duct form the hilum of the liver. A firm smooth layer of connective tissue called Glisson's capsule encloses the liver and is continuous with the connective tissue of the porta hepatis forming a sheath around the structures in the porta hepatis. The liver

has a double blood supply, the portal vein brings venous blood from the intestine and spleen and the hepatic artery coming from the coeliac axis supplies arterial blood to the liver. This dual blood supply provides sufficient protection against infarction in the liver. The portal vein and the hepatic artery divide into branches to the right and left lobes in the porta. The right and left hepatic ducts also join in the porta to form the common hepatic duct. The venous drainage from the liver is in to the right and left hepatic veins which enter the inferior vena cava. Lymphatics and the nerve fibres accompany the hepatic artery into their branching and terminate around the porta hepatic (Harsh Mohan, 1998) [3].

Hepatic Drug Reactions

Many drugs are reported to cause severe hepatic drug reactions after periodical use. (Zimmerman J., 1978) [4].

Table 1: Acute liver diseases

S. No	Disease	Agents
1	Zonal necrosis	Acetaminophen, CCl_4, Halothane.
2	Massive necrosis	Halothane, Acetaminophen Methyldopa
3	Fatty Change	Tetracycline, salicylates, Methotrexate, Ethanol.
4	Hepatitis	Methyldopa, INH, Halothane, Ketoconazole.
5	Granuloma formation	Sulfonamides, Methyldopa, Quinidine, Allopurinol.

Table 2: Chronic Liver diseases

S. No	Disease	Agents
1	Fibrosis-cirrhosis	Methotrexate
2	Focal nodular hyperplasia	Vinyl chloride, Vitamin A, Sex hormones.
3	Hepatocellular carcinoma	Sex hormones.

Pathophysiology of Hepatic Disorders

Hepatic disorders are manifested as various conditions e.g., Hepatitis, cholestasis, fibrosis etc. depending on severity of the cell damage. Injury to hepatocytes associated with an influx of acute or chronic inflammatory cells into liver is termed as hepatitis. Following morphological changes are produced for various disorders.

Hepatitis

Inflammation, degeneration with irregular clumped cytoplasm and large clear spaces, followed by steatosis, microvesicular steatosis, macrovesicular steatosis necrosis (coagulative necrosis, apoptosis, hydropic degeneration or lytic necrosis, centrilobular necrosis, focal necrosis, piece metal necrosis, bridging necrosis, or mostly massive necrosis.It then leads to fibrosis (i.e. fibrous tissue is formed in response to inflammation like bridging necrosis) and ultimately leads to cirrhosis. This is particularly evident in yellowing of the sclerae (icterus).

There are following types of hepatitis example-Hepatitis A- Caused by hepatitis A virus (HAV);
Hepatitis B- Caused by hepatitis B virus; (HBV); Hepatitis C- Caused by Hepatitis C virus (HCV); Hepatitis D- Caused by Hepatitis D virus (HDV); Hepatitis E- Caused by Hepatitis E virus (HEV); Hepatitis G- Caused by Hepatitis G virus (HGV).
In Acute hepatitis, hepatocytes undergo diffuse swelling (blooming degeneration) and the fatty change is usual except with HCV. Two types of hepatocyte necrosis are seen. In the first rupture of cell membrane leads to cytolysis and the necrotic cell membrane appear to have "dropped out" with collapse of collagen reticulin frame work where the cells have disappeared; scavenger macrophage aggregates mark the site of drop out. The second pattern of cell death, apoptosis, is more distinctive. Kuffer cells undergo hypertrophy and hyperplasia and are often laden with lipofuscin pigments due to phagocytosis of hepatocellular debris.
The portal tracts are usually infiltrated with a mixture of inflammatory cells. The histological features of chronic hepatitis range from exceedingly mild to severe. The lymphoid aggregates in portal tracts are often seen in HCV infection.

Jaundice and Cholestasis (Sherlock S., 1993)

Jaundice and hepatitis account for high rate of death due to hepatic disorder as only few drugs are available with related therapeutic activity. Actually, unconjugated bilirubin is virtually insoluble in water at physiologic pH and is tightly complexed with serum albumin. This form cannot be excreted in urine even when blood levels are high. Normally, a very less amount of unconjugated bilirubin is present as an albumin free anion in plasma. This fraction of unbound bilirubin is diffused into tissue (particularly brain in infants) and produces toxic injury. In contrast, conjugated bilirubin is water soluble, nontoxic, and only loosely bound to albumin. Because of its solubility and weak association with albumin, excess conjugated bilirubin in plasma can be excreted in urine
The following morphological changes are produced as accumulation of bile pigments within hepatic parenchyma occurs and further leads to foamy degeneration, obstruction to biliary tree, either intrahepatic or extra hepatic, induction of upstream bile, bile duct proliferation, unrelieved obstruction leading to portal tract fibrosis. Because extra hepatic biliary obstruction is frequently amenable to surgical alleviation, correct and prompt diagnosis is imperative. In contrast, cholestasis due to disease of the intra hepatic biliary tree or hepatocellular secretory failure (intrahepatic cholestasis) cannot be benefited by surgery. There should be some urgency in making correct diagnosis of the cause of jaundice and cholestasis.

Cirrhosis

Cirrhosis is characterized by various changes in the normal liver for example interstitial collagen (type I and type III) are concentrated in portal tract and around central veins, with occasional bundles in the parenchyma. A delicate reticulin framework of type IV collagen lies in the space between sinusoidal endothelial cells and hepatocytes. Cirrhosis type I and III collagen are deposited in all portion of lobule, accompanied by alteration in the sinusoidal endothelial cells. The net result is severe disruption of blood flow and impaired fusion of solutes between hepatocytes and plasma particularly in movement of proteins (Tripathi K.D., 2003) [5].
Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrous scar tissue as well as regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated), leading to progressive loss of liver function. Cirrhosis is

most commonly caused by alcoholism and hepatitis C, but has many other possible causes.

Complications

As the disease progresses, complications may develop. In some people, these may be the first signs of the disease.

- Bruising and bleeding, due to decreased production of coagulation factors.
- Jaundice, due to decreased processing of bilirubin.
- Itching (pruritus), due to bile products deposited in the skin.
- Hepatic encephalopathy - the liver does not clear ammonia and related nitrogenous substances from the blood which are carried to the brain, affecting cerebral functioning like neglect of personal appearance, unresponsiveness, forgetfulness, trouble concentrating, or changes in sleep habits.
- Sensitivity to medication due to decreased metabolism of the active compounds.
- Hepatocellular carcinoma is primary liver cancer, a frequent complication of cirrhosis. It has a high mortality rate.

Classification of Liver – Function Tests (Harsh Mohan, 1998) [3]

All liver function tests may be classified according to the type of hepatic function examined. Liver function tests may be classified as follows (Klin Z., 1972) [6]

1. Tests dependent primary on hepatic secretion and excretion.
- Bile pigments.
- Clearance of foreign substances from the serum.
2. Tests dependent upon specific biochemical functions:
- Protein metabolism tests.
- Carbohydrate metabolism tests.
- Lipid metabolism tests.
3. Test dependent upon the measurement of serum enzyme activity:
- SGPT
- SGOT
- SALP
- GGTP
- Other enzymes.

3. Measurement and significance of serum enzyme activity and its level in Hepatic Diseases (Henry R.J, 1960) [7]

Estimation of Serum Glutamate Pyruvate Transaminase (SGPT)

SGPT, also called as Alanine Transminase (ALT), is located in the cytosol of the liver cell. During liver cell inflammation and break down of liver cells, these are released into circulation due to increased permeability of cell membrane. Hence, determination of SGPT is an index of the extent of liver damage. Its normal serum level is 10-35 IU/L.

Alanine amino transferase (ALT) catalyzes the transfer of the amino group from Alanine to α-keto glutarate (α-KG) with the formation of glutamate and Pyruvate. The liberated Pyruvate reduced to lactate-by-lactate dehydrogenase (LDH) and in the same reaction an equivalent amount of NADH is oxidized to NAD. The resulting decrease in absorbance at 340nm is measured spectrophotometrically and is directly proportional to the activity of ALT in serum.

The reaction can thus be written as;

$$\text{L-Alanine} + \alpha\text{- ketoglutarate} \xrightarrow{\text{GPT}} \text{Pyruvate} + \text{L-glutamate}$$

$$\text{Pyruvate} + \text{NADH} \xrightarrow{\text{LDH}} \text{Lactate} + \text{NAD}$$

Estimation of serum Glutamate Oxaloacetate Transaminase (SGOT) (Bergmayer H.V., 1978)

SGOT is located in the cytosol of liver. In addition, it is also found in the mitochondria and in many tissues of heart, liver, skeletal muscle and kidney. Liver being the second richest source of SGOT, the importance of SGOT levels in hepatic cell damage leads to increased levels of SGOT in blood serum.

Serum glutamate Oxaloacetate Transaminase (SGOT) also known as Serum aspartate aminotransferase (AST) is a tissue enzyme that catalyzes the exchange of amino and keto groups between alpha amino acids and alpha keto acids. AST is widely distributed in tissues principally cardiac, hepatic, muscle and kidney; injury to these tissues results in the transfer of SGOT enzyme into general circulation (Scand J., 1974) [9].

Following myocardial infarction, serum levels of SGOT are elevated and reach a peak in 48 to 60 hours after onset. Hepatobiliary diseases, such as cirrhosis, metastatic carcinoma and viral hepatitis also increases serum AST levels.

Estimation of serum Alkaline Phosphatase (ALP) (Karmen. A, 1955) [10].

Many tissues produce serum alkaline phosphatase, especially bone, liver, intestine and placenta which is excreted in the bile. Most of the normal serum alkaline phosphatase (range 25-85 IU/dl) is derived from bone. Elevation in activity of this enzyme can thus be found in diseases of bone, liver and in pregnancy. In the absence of bone disease and pregnancy, an elevated serum alkaline Phosphatase level generally reflects hepatobiliary disease. The greatest elevation (3 to 10 times normal) occurs in biliary tract obstruction. Slight to moderate increase is seen in parenchymal liver diseases such as in hepatitis and cirrhosis and in metastatic liver disease. It is possible to distinguish serum hepatic alkaline Phosphatase by fractionation into isoenzymes but this is not routinely done (Harder M., 1983) [11].

Natural products reported with hepatoprotective activity (Cupp M.J., 1999) [12]

Medicinal herbs are significant source of pharmaceutical drugs. Latest trends have shown increasing demand of phytodrugs and some medicinal herbs have proven hepatoprotective potential. Silymarin, a flavonol lignan mixture) extracted from the *Silybum marianum* (milk thistle) is a popular remedy for hepatic diseases. Today,every herbal company is marketing formulations for liver disorders but the actual scene is that only selected medicinal herbs have been tested for hepatoprotective activity. Some herbal formulations claiming to be hepatoprotective may actually contain chemical constituents having hepatotoxic potential. Andrographolide (*Andrographis paniculata*), Glycyrrhizin (*Glychyrrhiza glabra*), Picrrorihzin (*Picrorrhiza kurroa*) and Hypo-phyllanthin (*Phyllanthus niruri*) are potential candidates with hepatoprotective activity.

Alternative systems of medicine viz. Ayurveda, Siddha, and Traditional Chinese Medicine have become more popular in recent years. 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.

A number of recent reviews have focused on the adverse effects of herbal products. In fact, some herbal products claiming to be hepatoprotective may actually be having some components with hepatotoxic potential.

Silybum marianum, Picrrorhiza kurroa, Andrographis paniculata, Phyllanthus niruri and *Eclipta alba* are proven hepatoprotective medicinal herbs which have shown genuine utility in liver disorders (Bisset N.G, 1994) [13]. These plants are used widely in hepatoprotective preparations and extensive studies have been done on them.

Other plants are namely

Taraxacum officinale (Vogel G., 1997) [14]

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 roots of the plant 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 cholegogue, increasing the flow of bile. Bitter constituents like taraxecerin and taraxcin are active constituents of the medicinal herb. The protective effects of Taraxacum officinale (dandelion) root against alcoholic liver damage were investigated in HepG2/2E1 cells and ICR mice.These results suggest that the aqueous extract of T. officinale root has protective action against alcohol-induced toxicity in the liver by elevating antioxidative potentials and decreasing lipid peroxidation.

Cichorium intybus (Kalantari S., 2001) [16]

Cichorium intybus is a popular Ayurvedic remedy 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 CCl_4 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. A bitter glucoside, Cichorin ($C_{32}H_{34}O_{19}$) has been reported to be the active constituent of the herb. To investigate the hepatoprotective effect of a *Cichorium intybus* L. extract (CIE) on CCl_4-induced hepatic fibrosis in rats. CIE may effectively protect against CCl_4-induced hepatic fibrosis in rats; thus, it is a promising anti-fibrotic therapeutic agent. Li GY

Glychyrrhiza glabra (Numazaki K, 1994) [19]

Glychyrrhiza glabra, commonly known as licorice contains triterpene saponin, known as glycyrrhizin, which has potential hepatotprotective activity. It belongs to a group of compounds known as sulfated polysaccharides. Several studies carried out by Japanese researchers have shown glycyrrhizin to be for anti-viral and 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 has been studied on free radical generation and lipid peroxidation in primary cultured rat hepatocytes.Favourable results have been reported in children suffering from cytomegalovirus after treating with glycyrrhizin. Licorice extract still markedly reverses the increased liver hydroxyproline and serum TNF-α levels induced by CCl_4 intoxication. The data of this study support a chemopreventive potential of licorice extract against liver oxidative injury. Huo H.Z.

Curcuma longa (Sriniwas L., 1991)

Like silymarin, turmeric has been found to protect animal livers from a variety of hepatotoxic substances, including carbon tetrachloride, galactosamine, pentobarbitol,1-chloro-2,4-dinitrobenzene,7-4- hydroxy nonenal,and paracetamol. Diarylhepatonoids including Curcumin is the active constituent of the plant. Curcuma longa L. (CLL) extract has previously been reported to alleviate liver damage. The current study examined the antioxidant activity of CLL by which the extract protects the liver against bleomycin (BLM)-induced hepatotoxicity in mice. The hypothesis was that CLL extract would protect the liver by reducing oxidative stress (induced superoxide dismutase (SOD) and catalase (CAT) activity), inhibiting lipid peroxidation, lowering biochemical parameters, and decreasing ROS production.

Throughout this study, the CLL extract facilitated recovery from BLM-induced hepatic injury by suppressing oxidative stress. Therefore, the CLL extract has the potential to serve as an antioxidant compound to treat chronic hepatotoxicity. Karamalakova YD

Tephrosia purpurea (Sriniwasan. M, 1993)

In Ayurveda, the plant is known as sharpunkha. 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. The roots, leaves and seeds contain tephrosin, deguelin and quercetin. The hepatotprotective constituent of the drug is still to be proved. The present study was conducted to evaluate the hepatoprotective activity of *Tephrosia purpurea* (TP) against sodium arsenite (NaAsO2) induced sub-acute toxicity in rats.

Tephrosia purpurea possess flavonoids having antioxidant and free radical scavenging property, it reduces the oxidative stress caused by arsenic, by reducing the ROS production, maintaining the antioxidant potential and significantly reducing elevated serum bio-marker levels in the body. Our study shows that supplementation of *Tephrosia purpurea* extract (500 mg/kg) could ameliorate the hepatotoxic action of arsenic by reducing oxidative stress.

Nigella sativa (Sriniwasan. M, 1993)

Aqueous extract of the seeds of Nigella sativa were tested for hepatoprotective activity on male Wistar rats against carbon tetrachloride induced hepatotoxicity. Various biochemical parameters were studied to evaluate the hepatoprotective activity. Aqueous extract showed significant hepatoprotective activity against carbon tetrachloride-induced toxicity on the liver indicating promising hepatoprotective activity.

Antioxidant and anti-inflammatory properties of *N. sativa* are the main features of preventing and protecting liver from injury. Several studies have shown the protective effects of *N. sativa* against liver injury produced by ROS with its free radical scavenger properties and enhance antioxidant defenses in body. Thymoquinone is the main active ingredients of *N. sativa* responsible for it. Also, none of the studies reported that the use of thymoquinone in moderate doses had significant toxic effects. The efficacy of *N. sativa* to postpone progression in chronic liver diseases should be considered as preventive medicine in patients with hepatic disorders. Mollazadeh H, 2014

Boerhaavia erecta (Krishna V., 2004) [26]

Administration of alcoholic extracts of roots of *Boerhaavia erecta* L. protect the liver from the toxic effect of CCl_4 under four by restoring the levels of serum bilirubin, serum total protein, albumin and subsequent decrease in the levels of serum globulin in experimental rats. The serum alanine transaminase, aspartate transaminase and alkaline phosphatase activities were also restored as compared to the normal rats. The hepatoprotective activity was evaluated to be more in B. erecta root extract treated groups.

Kalanchoe pinnata

Kalanchoe pinnata Pers. is naturalized throughout the hot and moist parts of India. Juice of the fresh leaves is used very effectively for the treatment of jaundice in folk medicines of Bundelkhand region of India. The juice of the leaves and the ethanolic extract of the marc left after expressing the juice were studied in rats against CCl4-induced hepatotoxicity. The test material was found effective as hepatoprotective as evidenced by in vitro, in vivo and histopathological studies. The juice was found more effective than ethanolic extract.

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