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STUDY AND ANALYZING THE HEPATIC ACTIVITY OF SOME ENDEMIC PLANTS PRODUCING HEPATOPROTECTIVE ACTIVITY

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ABSTRACT

Liver being an important organ is often exposed to array of threats. Injury to the liver can lead to deterioration of its functions and may culminate in organ failure. Te likely risk factors for the development of the liver diseases have been suggested to include pathogenic microorganisms and viruses, hepatotoxins, overdose and duration of drugs, obesity and malnutrition, alcohol, autoimmune disorders, type-2 diabetes, and genetic factors. Te diseases of the liver are of public health concern because orthodox remedies for liver diseases produce limited results with attendant side efects. As such, utilization of complementary and alternative herbal medicine has attracted research interest for novel plausible hepatoprotective agents capable of ameliorating or reversing liver injury with little side efects]. Over the years, this search has gained impetus with many studies focusing on hepatoprotective potentials of plant drugs. Carbon tetrachloride (CCl4) is a known hepatotoxicant in humans and animal models. It has been successfully used in hepatotoxicity research as a model and to appraise hepatoprotective agents. With reports on the rise of liver diseases and numerous literature reports on plants with potential hepatoprotective activity, this review highlighted the mechanism of CCl4

toxicity, the signifcance, efectiveness, and underlying mechanisms of herbal plant extracts on CCl4-induced toxicity in experimental animal models.

INTRODUCTION

A liver disease is always associated with cellular necrosis, increases in tissue lipid peroxidation and depletion in the tissue GSH levels. In addition, serum levels of many biochemical markers like SGOT, SGPT, triglycerides, cholesterol, bilirubin, alkaline phosphatase are elevated. Inspite of phenomenal growth of modern medicine, there are few synthetic drugs available for the treatment of hepatic disorders. However there are several herbsor herbal formulations claimed to have possess beneficial activity in treating hepatic disorders (Austin, 2004).

Inspite of tremendous strides in modern medicine, there are hardly many drugs that stimulate liver function, offer protection to the liver from damage (or) help regeneration of hepatic cells. However, there are number of drugs employed in traditional system of medicine for liver infections (Austin, 2004). In the present investigation methanolic leaf extract of *Evolvulus nummularins* is selected to study its hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in rats because it induces both liver dysfunction and liver cirrhosis.

About 600 commercial preparations with claimed liver protecting activity are available all over the world. About 100 Indian medicinal plants belonging to 40 families are used for herbal formulation. A few reports on the hepatoprotective activity are cited here, e.g. *Apium graveolens* Linn. (Umbelliferae), *Boerhaavia diffusa* Linn.(Nyctagina ceae), *Euphorbia antisyphilitica* (Euphorbiaceae), *Rubia cordifolia* (Rubiaceae), *Solanum lyratum* (Solanaceae),*Tylophora indica* (asclepiadaceae) (William M Lee, 1995).

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 (William M Lee, 1995). Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignins, essential oil, monoterpenes, carotenoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes. 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 (Kulkarni, 2001). Several Indian medicinal plants have been extensively used in the Indian traditional system of

medicine for the management of liver disorder. Some of these plants have already been reported to posses strong antioxidant activity (Achuthan, 2003).

Table 1: Plants reported as hepatoprotective agents.

Sl. No.	Name of plant	Part of plant	Family	*Reference*
1.	*Cistus laurifolius*	Leaf	Cistaceae	Agarwal, 2006
2.	*Beta vulgaris*	Root	Chenopodiaceae	Mehta, 2006
3.	*Chelidonium majus and Myrica cerifera*	Whole plant	Papaveraceae	Manjunatha, 2006
4.	*Pterocarpus santalinus*	Stem	Fabaceae	Chanchal K Roy, 2006
5.	*Psidium guajava*	Leaf	Myrtaceae	Chattopadhyay, 2003
6.	*Azardirachta indica*	Leaf	Meliaceae	Jayaprakash, 2003
7.	*Balanites aegyptiaca*	Bark	Simaroubaceae	Mankani, 2006
8.	*Diospyros cordifolia*	Bark	Ebenaceae	Vishwakarma, 2006
9.	*Lactuca scariola*	Leaf	Asteraceae	Absar, 2007
10.	*Calotropis procera*	Flower	Asclepiadaceae	Baheti, 2006

Liver disease is still a worldwide health problem and unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are few and sometimes can have serious side effects. This is one of the reasons for many people in the world over including those in developed countries turning to words complementary and alternative medicine (Harsh Mohan, 2000).

In absence of reliable liver-protective drugs in modern medicine, a large number of medicinal preparations are recommended for the treatment of liver disorders and quite often claimed to offer significant relief. Attempts are being made globally to get scientific evidences for these traditionally reported herbal drugs (Damjanov, 1996).

Oxidative stress has been identified to be the major cause of hepatotoxicity which provides that plants with anti-oxidant chemical constituents would be useful in this regard. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them (Grover, 2002). Thus we have focused our

attention on plants containing flavonoids and tannins as major chemical constituents since they have been proved of their anti-oxidant potential.

In our review of literature, we found that a plant "*Evolvulus nummularius* L." contains flavonoids (Pavithra, 2011) as one of the major chemical constituent and thus has the antioxidant potential.

It is also well documented that carbon tetrachloride (Ccl_4) triggers hepatic and renal changes in animals and man. Its mechanism of action is also very well illustrated by several authors and hence we have opted for this animal model (Boll, 2001) in our study of hepatotoxicity.

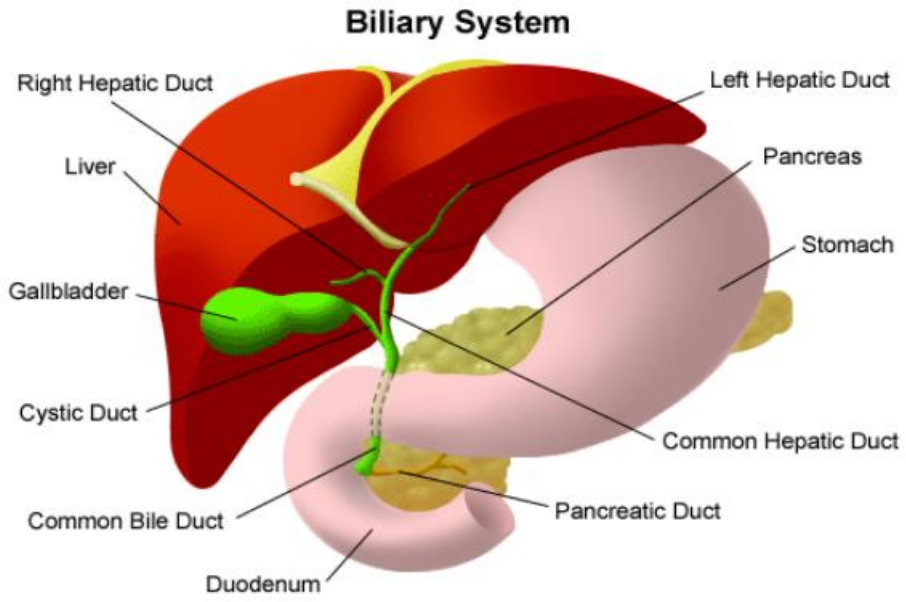
Anatomy and Physiology of liver

Liver is a largest gland in the body, weighing between 1 to 2.5 kg situated in the right upper quadrant of the abdomen, just below the diaphragm. Its upper and anterior surface are sooth and curved to fit the under surface of the diaphragm; and posterior surface is irregular in outline (Ross and Wilson, 2001).

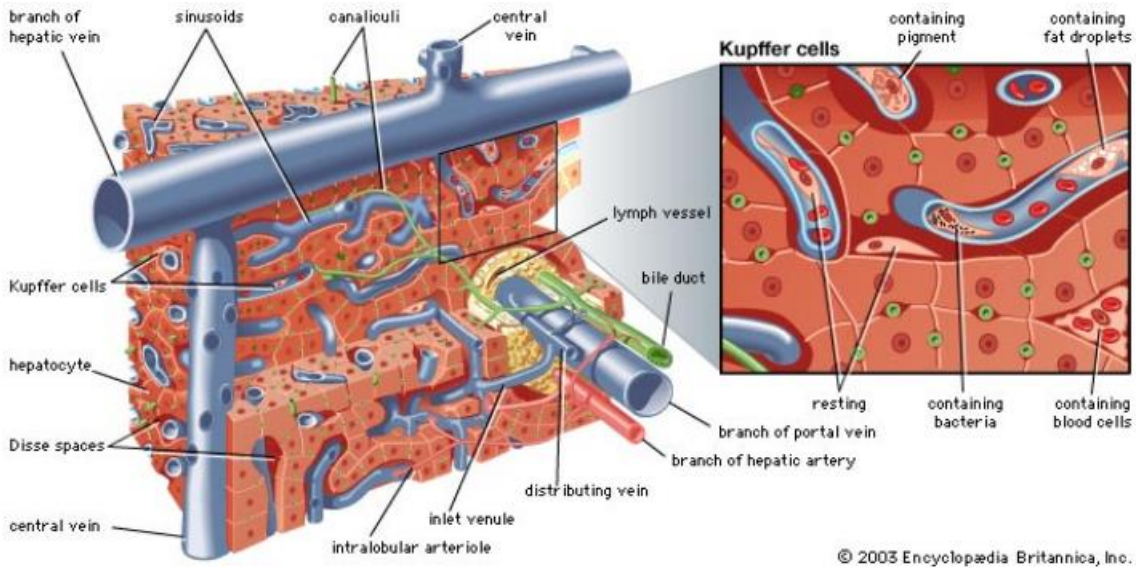
A thick capsule of connective tissue called Glisson's capsule covers the entire surface of the liver. The liver is multi-lobed organ i.e., it has 4 distinct lobes, divided into a large right lobe and a smaller, wedge-shaped, left lobe, the other two, the caudate and quadrate lobes. The falciform ligament divides the two lobes of the liver. Each lobe is further divided into lobules that are approximately 2mm high and 1mm in circumference. These hepatic lobules are the functioning units of the liver, each of them approximately 1 million lobules consists of a hexagonal row of hepatic cells called "hepatocytes", secrete bile into the bile channels and also perform a variety of metabolic functions. Between each row of hepatocytes there are small cavities called "sinusoids", and each sinusoid is lined with kupffer cells, phagocytic cells that remove amino acids, nutrients, sugar, old red blood cells, bacteria and debris from the blood that flows through the sinusoids. The main functions of the sinusoids are to destroy old or defective red blood cells, to remove bacteria and foreign particles from the blood and to detoxify toxins and other harmful substances (Ross and Wilson, 2001).

Almost all blood that enters the liver via the portal tract originates from the gastrointestinal tract as well as from the spleen, pancreas and gallbladder. Total human liver blood flow represents approximately 25% of the cardiac output up to 1500 ml/min. Hepatic flow is subdivided into 25-30% for the hepatic artery (500 ml/min) and the major part for the portal

vein (1000 ml/min). A second blood supply to the liver comes from the hepatic artery, branching directly from the coeliac trunk and descending aorta. The portal vein supplies venous blood under low pressure conditions to the liver, while the hepatic artery supplies high-pressured arterial blood. Since the capillary bed of the gastrointestinal tract already extracts most O2, portal venous blood has a low O2 content. Blood from the hepatic artery on the other hand, originates directly from the aorta and is, therefore, saturated with O2. Blood from both vessels joins in the capillary bed of the liver and leaves via central veins to the inferior caval vein (Guyton Hall, 2000).



The liver



Microscopic structure of the liver

The porta hepatis is the region on the inferior surface of the right lobe where blood vessels, lymphatic and common hepatic duct forms 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 the 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 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 into 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 portal hepatis (Karan, 1999).

Histology

The hepatic parenchyma is composed of numerous hexagonal or pyramidal classical lobules each with a diameter of 0.5 to 2 nm. Each classical lobule has a central tributary from the hepatic vein and at the periphery are 4 to 5 portal tracts or triads containing branches of bile duct, portal vein and hepatic artery. Cords of hepatocytes and blood-containing sinusoids radiate from the central vein to the peripheral portal triads. The functioning lobule or liver acinus as described by Rappaport has a portal triad in the centre and is surrounded at the periphery by portions of several classical lobules. However in most descriptions on pathology of the liver, the term lobule is used in its classical form (Karan, 1999).

The blood supply to the liver parenchyma flows to the portal triads and to the central veins. Accordingly, the hepatic parenchyma of liver lobule is divided into 3 zones:

- Zone 1 or the periportal (peripheral) area is closed to the arterial and portal blood supply and hence bears the brunt of all forms of toxic injury.
- Zone 2 is the intermediate midzonal area.
- Zone 3 or the centrilobular area surrounds the central vein and is most remote from the blood supply and thus suffers from the effects of hypoxic injury.

The hepatocytes are polygonal cells with a round single nucleus and a prominent nucleolus. The liver cells have a remarkable capability to undergo mitosis and regeneration. Thus it is not uncommon to find liver cells containing more than one nuclei and having polyploidy up

to octoploidy. A hepatocyte has 3 surfaces; one facing the sinusoid and space of disse, the second facing the canaliculus and the third facing neighbouring hepatocytes (Karan, 1999).

The blood-containing sinusoids between cords of hepatocytes are lined by discontinuous endothelial cells and scattered flat Kupffer cells belonging to the reticuloendothelial system (Harsh Mohan, 2000). The space of disease is the space between hepatocytes and sinusoidal lining endothelial cells. A few scattered fat storing cells lie within the space of disease.

The portal triad or tract besides containing portal vein radical, the hepatic arteriole and bile duct has a few mononuclear cells and a little connective tissue considered to be extension of Glisson's capsule. A limiting plate of hepatocytes surrounds the portal triads. The intrahepatic biliary system begins with the bile canaliculi interposed between the adjacent hepatocytes. The bile canaliculi are simply grooves between the contact surfaces of the liver cells and are convered by microvilli. These canaliculi join at the periphery of the lobule to drain eventually into terminal bile ducts or ductules (canal of hering) which are lined by cuboidal epithelium (Harsh Mohan, 2000).

Functions of the liver

The liver is responsible for important functions, which includes (Guyton, 2000).

- Secretion and excretion of bile
- Excretion of bilirubin, cholesterol, hormones and drugs
- Metabolism of carbohydrates, fats, proteins and various chemicals including drug.
- Fibrinogens, prothrombin and heparin production
- Enzyme activation
- Storage of glycogen, vitamins and minerals (Iron and Copper)
- Synthesis of plasma proteins, such as albumin, globulin and clotting factors.
- Blood detoxification and purification.

The liver synthesizes and transport bile pigments and bile salts that are needed for fat digestion. Bile is a complex mixture of bile salts, bile pigments, alkaline phosphatase, water and various lipids, include cholesterol, lecithin, bilirubin, potassium, sodium and chloride. Bile salts are produced by the metabolism of cholesterol, are involved in the absorption and metabolism ofa fat (Hyman J. Zimmerman, 1978).

Bilirubin is the main bile pigment that is formed from the breakdown of hemoglobin liberated when red blood cells are broken down in the reticuloendothelial system. The break down haem travels to the liver, where it is secreted into the bile by the liver. Bilirubin production and excretion follow a specific pathway. When the reticuloendothelial system breaks down old red blood cells, bilirubin is one of the waste products. This "free bilirubin" is a lipid soluble form that must be made water soluble to be excreted.

The conjugation process in the liver converts the bilirubin from the fat soluble to a water soluble form. The liver also plays a major role in excreting cholesterol, hormones, and drugs from the body. The liver plays an important role in metabolizing nutrients such as carbohydrates, proteins and fats. Thus liver helps in metabolizing carbohydrates in three ways (Hyman J. Zimmerman, 1978).

- Through the process of glycogenesis i.e., glucose, fructose, and galactose are converted to glycogen and stored in the liver.
- Through the process of glycogenolysis, the liver breaks down stored glycogen to maintain blood glucose levels when there is decrease in carbohydrate intake.
- Through the process of gluconeogenesis, the liver synthesizes glucose from Proteins or fats to maintain blood glucose levels.

- **Metabolism**

Liver is an organ that orchestrates the metabolism of fats, carbohydrates and protein. It does this in conjunction with the circulatory system, the lymphatic system and the endocrine (hormone) system. A healthy liver is critical to proper protein, carbohydrate and fat metabolism (Hyman J. Zimmerman, 1978).

- **Protein metabolism**

The liver produces all of the proteins except for the proteins synthesized by the immune system (Called gammaglobulins or immunoglobulins). It does this by reassembling amino acids into protein. The main protein produced by the liver is called albumin. Normal albumin in the bloodstream is important for many physiologic functions. One of these functions involves the normal maintenance of fluid pressure in the arteries and veins. When the protein level falls below a certain point the fluid in these vessels can leak out and pool in the abdominal or thoracic cavities. This fluid is called ascites when it occurs in the abdominal cavity, pleural effusion when it occurs in the thoracic cavity. Albumin also functions to

"carry" other compounds through the bloodstream. These compounds include calcium, vitamins, hormones, fatty acids, many drugs and bilirubin.

- **Carbohydrate metabolism**

Glucose that is stored in hepatocytes is called glycogen. It is used as a reservoir during times when carbohydrate intake is low (Fasting or starvation). The liver can also manufacture glucose from proteins or fats.

In liver disease the body can have a difficult time regulating the blood glucose level, usually leading to hypoglycemia (Low blood glucose). This is one of the reasons why caloric intake is an important aspect of treatment.

- **Lipid metabolism**

The liver regulates fats (called fatty acids) in the bloodstream. It does this by converting excess amounts of carbohydrates and proteins into fatty acids. The liver also manufactures cholesterol from this fat. Cholesterol is necessary for many functions, particularly the sex hormones and steroids like cortisone. Excess fatty acid accumulation in the hepatocytes is called lipidosis.

- **Detoxification**

Drug metabolism is an important liver function. It is a complex process that occurs in the endoplasmic reticulum of the hepatocyte. Several phases are involved with this detoxification:

(i) Phase - I reation

In the phase 1 reaction, oxidation or demethylation occurs, mediated by cytochrome P450. A variety of oxidative phase 1 reactions are performed by the enzymes that make up the P450 system found primarily in the liver but also in the gastrointestinal tract, kidneys, brain and other tissues. P450 enzymes are composed of a unique apoprotein and a heme prosthetic group, which binds oxygen after electron-transfer reactions from NADPH, resulting in aliphatic and aromatic hydroxylation, O, N, or S dealkylation or dehalogenation. A typical reaction of this type generates a hydroxyl group, which can then participate in the phase 2 reactions. Each group of genes with 40 percent amino acid homology composes a family w hose gene products (isozymes) may function in a similar fashion. For example, CYP3 is a family that contains an A subfamily and several genes, numbered 1, 2, and so forth. The

primary enzyme for the metabolism of erythromycin in humans is P450 3A4 (Ross and Wilson, 2001).

(ii) Phase II reaction

After a phase 1 reaction, most compounds are still not very water-soluble and require further metabolism. In a typical phase 2 reaction, a large water-soluble polar group is attached to a hydroxyl oxygen by glucuronidation or sulfation, forming ether or ester linkages. These are the sole steps required for the hepatic metabolism of some compounds. But for most, the phase 2 reaction is preceded or follo wed by phase 1 oxidation. Compounds requiring glucuronidation include acetaminophen, morphine, and furosemide, as well as bilirubin. Sulfation is as important as glucuronidation, particularly for the metabolism of steroid compounds and bile acids. There are several species of sulfotransferases with overlapping specificities, each employing 3-phosphoadenosine- 5-phosphosulfate synthesized from ATP and sulfate ions. Although phase 2 reactions are usually accomplished without a detrimental effect, they can occasionally lead to toxic or carcinogenic byproducts.

- **Bile metabolism**

Bile is secreted by liver and drugs are eliminated in the bile, red blood cells are recirculated through the bile system and fats are absorbed from the intestines into the bloodstream only in the presence of bile. When red blood cells break down and are recycled they release bilirubin fromtheir hemoglobin. The liver, along with spleen and bone marrow, recycle this bilirubin, salvaging some of the compounds (iron) and excreting the rest in the bile. Bilirubin, which is toxic, binds to albumin and is detoxified and excreted. This is eventually excreted into the intestines and broken down by intestinal bacteria into urobilinogen, where it imparts the dark color to stool. If this bilirubin cannot be excreted from the gallbladder, there will be very light colored (acholic) stool. The excess amounts of bilirubin that build up in the bloodstream will cause jaundice (the yellow discoloration of the skin) and mucous membranes that can occur with liver disease.

The fat soluble vitamins A, D, E, and K require bile for proper absorption form the intestines. These vitamins are stored in the liver, and are converted to active compounds as the liver maintains normal physiology (Homeostasis).

- **Red blood cell system**

The liver removes old or damaged red blood cells from the circulation and is involved with the storage of iron and the breakdown of hemoglobin. Because of this, chronic liver disease could cause anemia. The liver (along with the spleen) is a storage organ for blood. If there was a severe blood loss the liver expels this blood into the bloodstream to help make up for the loss.

(i) Reticuloendothelial system

Kupffer cells eliminate and degrade the substances that are brought into the liver by the portal vein. Some of these substances are bacteria, toxins, nutrients and chemicals. A diseased liver will not filter these compounds normally, resulting in toxic accumulations of drugs, chemicals, or bacteria. Excess accumulation of bacteria in the bloodstream cause septicemia liver.

(ii) Vitamins

Many vitamins are stored in the liver and perform their functions only when activated by the liver, and are degraded by the liver. These include some of the B vitamins and Vitamin C along with A, D, E and K.

Diseases of liver

The liver may take several forms and involve the hepatocytes, vascular cells or bile ducts. The most important diseases are

1. Biliary obstruction.
2. Metabolic lesions caused by genetic disease or exogenous substance, such as alcohol.
3. Inflammation especially caused by hepatitis viruses.
4. Cirrhosis.

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