INTRODUCTION

The liver is a vital organ present in vertebrates and other animals. The liver is both the largest gland and largest internal organ in the human body, plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, and detoxification. It lies below the diaphragm in the thoracic region of the abdomen. It produces bile, an alkaline compound which aids in digestion, via the emulsification of lipids. It also performs and regulates a wide variety of high-volume biochemical reactions requiring very specialized tissues.

The liver is enclosed in a thin capsule and incompletely covered by a peritoneum. The liver is described having four lobes. The two most obvious are the right lobe and the smaller wedge shaped left lobe. The other two, the caudate and quadrate lobes, are the areas on the posterior surface.

ANATOMY

The adult human liver normally weighs between 1.4 - 1.6 kilograms and is a soft, pinkish-brown, triangular organ. Averaging about the size of an American football in adults, it is both the largest internal organ and the largest gland in the human body. It is located on the right side of the upper abdomen below the diaphragm anatomy. The liver lies to the right of the stomach and overlies the gallbladder.
The lobes of liver are made-up of tiny lobules just visible to naked eyes. These lobules are hexagonal in shape and formed by cubical shaped cells. The hepatocytes, arranged in pairs of column radiating from the central vein. Between two pairs column of cells there are sinusoids (blood vessels with incomplete walls) containing mixture of blood from the tiny branches of portal vein and hepatic artery. Some cells lining the sinusoids are hepatic macrophages (kupffer cells).

**BLOOD SUPPLY**

The hepatic artery and the portal vein supply blood to the liver. Hepatic veins varying in the number, leave the posterior surface, and immediately enter the inferior venacava, just below the diaphragm. Blood drains from the sinusoids into central vein, these then join with vein from other lobules,
forming larger vein eventually they become the hepatic vein which leaves the liver and empty blood into inferior vena cava, just below the diaphragm. Bile canaliculi run between the columns of liver cells.

**PHYSIOLOGY**

The various functions of the liver are carried out by the liver cells or hepatocytes.

1. The liver produces and excretes bile (a greenish liquid) required for emulsifying fats. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.

2. The liver performs several roles in carbohydrate metabolism: Gluconeogenesis (the synthesis of glucose from certain amino acids, lactate or glycerol). Glycogenolysis (the breakdown of glycogen into glucose). Glycogenesis (the formation of glycogen from glucose). The breakdown of insulin and other hormones.

3. The liver is responsible for the protein metabolism. For instance, the liver can convert lactic acid to alanine.

4. The liver also performs several roles in lipid metabolism such as Cholesterol synthesis, Lipogenesis, the production of triglycerides (fats).
5. The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X and XI, as well as protein C, protein S and antithrombin.

6. The liver breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin).

7. The liver breaks down toxic substances and most medicinal products in a process called drug metabolism. This sometimes results in toxication, when the metabolite is more toxic than its precursor.

8. The liver converts ammonia to urea.

9. The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1-2 years' supply), vitamin D (1-4 months' supply), vitamin B₁₂, iron, and copper.

10. In the first trimester fetus, the liver is the main site of red blood cell production.

11. The liver is responsible for immunological effects- the reticuloendothelial system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.

12. The liver produces albumin, the the major osmolar component of blood serum.
LIVER DISEASES

Liver diseases is a broad term describing any number of diseases affecting the liver. Many are accompanied by jaundice caused by increased levels of bilirubin in the system. Liver disease may be classified as:-

1. **Hepatitis**, inflammation of the liver, caused mainly by various viruses but also by some poisons, autoimmunity or hereditary conditions.

2. **Cirrhosis** is the formation of fibrous tissue in the liver, replacing dead liver cells. The death of the liver cells can be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals.

3. **Haemochromatosis**, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage.

4. **Cancer of the liver** (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract).

5. **Wilson's disease**, a hereditary disease which causes the body to retain copper.

6. **Primary sclerosing cholangitis**, an inflammatory disease of the bile duct, likely autoimmune in nature.
7. Primary biliary cirrhosis, autoimmune disease of small bile ducts.

8. Budd-Chiari syndrome, obstruction of the hepatic vein.

9. Gilbert's syndrome, a genetic disorder of bilirubin metabolism, found in about 5% of the population.

10. Glycogen storage disease type II, the build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly the heart, skeletal muscles, liver and nervous system.

Liver diseases are mainly caused by

1. Infections
2. Autoimmune disorder
3. Chemical agents (certain antibiotics, peroxidised oil, aflatoxin, carbon tetra chloride, chlorinated hydrocarbon, paracetamol etc)
4. Excess consumption of alcohol.

**FATTY LIVER**

Fatty liver, also known as fatty liver disease (FLD), steatorrhoeic hepatosis, or steatosis hepatitis, is a reversible condition where large vacuoles of triglyceride accumulate in liver cells via the process of steatosis. Normal liver may contain as much as 5% of its weight as fat. Lipiotic liver may contain as much as 50% of its weight as fat, most of being triglycerides.
Severe fatty liver is sometimes accompanied by inflammation, a situation that is referred to as steatohepatitis. The progression to cirrhosis may be influenced by the amount of fat and degree of steatohepatitis and by a variety of other sensitizing factors.

CIRRHOSIS

Cirrhosis can be defined as a chronic disease condition presenting morphological alteration of the lobular structure characterized by destruction and regeneration of the parenchyma cells and increased connective tissue. Major morphological changes induce granular or nodular appearance and are characterized by the presence of septate or collagen throughout the liver.

HEPATITIS

Hepatitis implies injury to the liver characterized by the presence of inflammatory cells in the tissue of the organ. The condition can be self-limiting, healing on its own, or can progress to scarring of the liver. A group of viruses known as the hepatitis viruses cause most cases of liver damage worldwide. Hepatitis can also be due to toxins (notably alcohol), other infections or from autoimmune process.

Viral hepatitis

Viral hepatitis is the cause of most cases of acute hepatitis. Types include Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis B with D, Hepatitis E, Hepatitis F virus (existence unknown), and Hepatitis G or GBV-C. Hepatitis
A or infectious jaundice is caused by a picornavirus transmitted by the fecal-oral route. It causes an acute form of hepatitis and does not have a chronic stage. Hepatitis B is caused by a hepadnavirus, which can cause 500,000 to 1,200,000 deaths per year worldwide due to the complications of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis C (originally "non-A non-B hepatitis") is caused by a virus with an RNA genome that is a member of the Flaviviridae family. Hepatitis C may lead to a chronic form of hepatitis, culminating in cirrhosis. Hepatitis D is caused by hepatitis delta agent, which is similar to a viroid as it can only propagate in the presence of the Hepatitis B virus. Hepatitis E produces symptoms similar to hepatitis A. Hepatitis F virus is a hypothetical virus linked to hepatitis. Several hepatitis F virus candidates emerged in the 1990s; none of these reports have been substantiated. Another potential viral cause of hepatitis, initially identified as hepatitis G virus by (Linnen et al., 1996), is probably spread by blood and sexual contact (Stark et al., 1996). There is very little evidence that this virus causes hepatitis, as it does not appear to replicate primarily in the liver (Pessoa et al., 1998). It is now classified as GB virus C. In addition to the hepatitis viruses, other viruses can also cause hepatitis, including cytomegalovirus, Epstein-Barr virus, yellow fever, etc. Non viral infection like Toxoplasma, Leptospira and Q fever also causes hepatitis.

**LIVER CANCER**

The liver is susceptible to cancer induction by a variety of human made and naturally occurring chemicals. Chemical substance include, aflatoxin B, cycasin, and saffrole etc. among human made substance are DDT,
carbon tetrachloride, chloroform, thioacetamide. Studies in experimental animals indicate quite clearly that development of cancer of the liver is associated with the number of obvious non-malignant lesions appearing prior to the occurrence of neoplastic malignancy.

HEPATOTOXICITY

Hepatotoxicity 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, and natural chemicals (e.g. microcystins) can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins.

The human body identifies almost all drugs as foreign substances (i.e. xenobiotics) and subjects them to various chemical processes, (i.e. metabolism) to make them suitable for elimination. This involves chemical transformations like reduction in fat solubility and change in biological activity. Although almost all tissue in the body have some ability to metabolize chemicals, smooth endoplasmic reticulum in liver is the principal "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins), and exogenous substances (e.g. drugs). The central role played by liver in the clearance and transformation of chemicals also makes it susceptible to drug induced injury.
The mechanism of hepatotoxicity in liver can be described by two methods.

1) **Direct:** This group includes the products (or their metabolic products) that produce direct injury to the plasma membrane, endoplasmic reticulum and other organelles of the hepatocytes. Direct hepatotoxicity may be epitomized as non-selective destruction of the structural basis of hepatocyte metabolism. Some of the direct hepatotoxins include carbon tetra chloride, chloroform, tetrachloroethane, iodoform and elemental phosphorus.

2) **Indirect:** These are more selective, and are anti metabolic and related compounds that produce hepatic injury by interference with specific metabolic pathway or process. The hepatic damage produced by indirect hepatotoxins may be mainly cytotoxicity expressed as necrosis or mainly cholestatic expressed as arrested bile flow with or without bile duct injury.

A group of enzymes located in the endoplasmic reticulum, known as cytochrome P-450, is the most important family of metabolizing enzymes in the liver. Cytochrome P-450 is the terminal oxidase component of an electron transport chain. It is not a single enzyme, but rather consists of a family of closely related 50 isoforms, six of them metabolize 90% of drugs (Lynch and Price, 2007). There is a tremendous diversity of individual P-450 gene products and this heterogeneity allows the liver to perform oxidation on a vast array of chemicals (including almost all drugs).
Due to its unique metabolism and close relationship with the gastrointestinal tract, the liver is susceptible to injury from drugs and other substances. About 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 produce 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 lead to oxidative stress injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside liver (Jaeschke et al., 2002). This promotes further liver damage. Non-parenchymal cells such as Kupffer cells, fat storing stellate cells and leukocytes (i.e. neutrophil and monocyte) also have role in the mechanism (Patel, 1998).

More than 900 drugs have been implicated in causing liver injury (Friedman et al., 2003), and it is the most common reason for a drug to be withdrawn from the market. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures (Ostapowicz et al., 2002).

The liver produces large amounts of oxygen free radicals in the course of detoxifying xenobiotic and toxic substances. Reactive oxygen species (ROS) has been shown to be linked to liver diseases, such as hepatitis, cirrhosis, portal hypertension, viral infections and other liver pathological conditions (Mehendale et al., 1995). They play an important role in the inflammation process after intoxication by ethanol, carbon tetrachloride or carrageenan. These radicals and the reactive species derived from them react
with cell membrane, induce lipid peroxidation and are responsible for various deleterious effects in cells and tissues where they are generated. ROS induce alterations and loss of structural-functional architecture in the cell, leading directly to cytotoxicity and/or indirectly to genotoxicity, with numerous serious anomalies favouring disharmony and diseases (Sies, 1985). Hepatic injury caused by chemicals, drugs, and virus is a well-known toxicological problem to be taken care of by various therapeutic measures.

IMPORTANCE OF MEDICINAL PLANTS

Liver disease is still a worldwide health problem. Conventional or synthetic drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effects. So there is a worldwide trend to go back to traditional medicinal plants. Many natural products of herbal origin are in use for the treatment of liver ailments (Mitra et al., 2000). The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. In the past, several studies have examined the effects of plants used traditionally by herbalists to support liver function and to treat diseases of the liver. Experimental and clinical research has confirmed the efficacy of few plants like *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea) and *Glycyrrhiza glabra* (licorice) (Luper, 1999).

In spite of significant advances in medicinal plant research and rapid strides in modern medicine, there was increasing problem of liver disorders and demands for more precise, safe and effective treatments of liver disorders.
In recent years, there has been a shift towards therapeutic evaluation of herbal products in liver diseases by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation. Herbs have recently attracted attention as health beneficial foods (physiologically functional foods) and as source materials for drug development. Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases, with relatively little knowledge regarding their mode of action.

Numerous plants and polyherbal formulations are used for the treatment of liver diseases. However, in most of the severe cases, the treatments are not satisfactory. Although experimental evaluations were carried with plenty of plants and formulations, the studies were mostly incomplete and insufficient. The therapeutic values were tested against a few chemicals-induced sub clinical levels of liver damages in rodents. The treatment should include in addition to the therapeutic agents, agents that can stimulate liver cell proliferation. For developing satisfactory herbal combinations to treat severe liver diseases, plants have to be evaluated systematically for properties such as antiviral, antihepatotoxic, antioxidant, and stimulation of liver regeneration and choleretic activity. The plants with remarkable activities for each of the above properties have to be identified. Single plant may not have all the desired activities. A combination of different herbal extracts/fractions is likely to provide desired activities to cure severe liver diseases. Development of such medicines with standards of safety and efficacy can revitalize the treatment of liver disorders.
MELIA AZEDARACH

Figure 1.2 Melia azedarach

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Sapindales
Family : Meliaceae
Genus : Melia
Species : M. azedarach

Vernacular Names

Name : China berry, Persian lilac
Bengali : Bakarjan, Ghora Nim, Mahanim, Mahnim
English : Azedarach, Bead tree, China berry, China tree, Persian lilac, Pride of India

Hindi : Bakain, Bakarja, Betain, Deikna, Dek, Drek, Mallan Nim

Sanskrit : Mahanimba

Tamil : Malaivembu, Mallayvembu, Puvempu

Telugu : Koda-Vepa, Konda-Vepa, Kondavepa

Malayalam : Aryaveppu, Malaveppu, Valiyaveppu

Kannada : Arebevu, Bettada-Bevina, Bettada-Bevu, Bettadabevu

Pharmacognostic characteristics

*Melia azedarach* is a deciduous tree grown up to 45 m tall, bole fluted below when old, up to 30-60 cm in diameter, with a spreading crown and sparsely branched limbs. Smooth bark, greenish-brown in colour when young, turning grey and fissured with age. Leaves alternate, 20-40 cm long, bipinnate or occasionally tripinnate. Leaflets 3-11, serrate and with a pungent odour when crushed. Inflorescence is long, axillary panicle up to 20 cm long, flowers showy, fragrant, numerous on slender stalks, white to lilac, sepals 5-lobed, 1 cm long, petals 5-lobed, 0.9 cm long, pubescent, staminal tube deep purple blue, 0.5 cm long, 1 cm across. Fruit is small, yellow drupe, nearly round, about 15 mm in diameter, smooth and becoming a little shrivelled, slightly fleshy. Seed is oblongoid, 3.5 mm × 1.6 mm, smooth, brown and surrounded by pulp. Because of the divided leaves, the generic name is
derived from the Greek ‘melia’ (the ash); the specific name comes from the Persian ‘azzadirackt’ (noble tree).

**Phytochemical constituents**

Several compounds from Chinaberry have been isolated for medical purposes. *Meliacine*, a peptide isolated from leaves of *M. azedarach*, exhibits potent activity against Herpes simplex type 1 (HSV-1). Plant parts contain a number of compounds, with medical and insecticidal - anti-parasitic properties.

**Medicinal properties and uses**

*M. azedarach* is well known for its medicinal uses. Its various parts have antihelmintic, antimalarial, cathartic, emetic and emmenagogic properties and are also used to treat skin diseases. It has also been used as an abortifacient, an antiseptic, a purgative, a diuretic, an insect repellent. It is used for generally healing arthritis, rheumatism, for Pulmonary, stomach troubles, diarrhoea and dysentery. It is also used as vermifuges, to treat, cutaneous, subcutaneous parasitic infection and for menstrual cycle problems. According to (Perry, 1980) it is being used against intestinal worms, in skin diseases, stomach ache, intestinal disorders, uterine illnesses, cystitis, diuretic, and febrifuge It has got antiviral, antimalarial, antihelmintic, and cytotoxic activities (Castilla *et al.*, 1998).
**PIPER LONGUM**

**Figure 3. Piper longum**

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**Vernacular Names**

- Hindi and Punjabi: Pipul, Pipli, Piplamul
- Bengali: Pipli, Piplamore (root)
- Gujarati: Pipli
- Kannada: Hippali, Hippalibali, Kuna
Pharmacognostic characteristics

Pepper long is the dried fruit of *Piper longum*, which is a slender, aromatic plant with creeping jointed stems and perennial woody roots. *Piper longum* fruits are ovoid, yellowish orange, minute, and drupe and are sunk in the fleshy spike. The spikes are red when ripe. Aromatic in odor and the taste is pungent. Leaves numerous, lower one broadly ovate, very cordate with broad rounded lobes at base, upper one oblong – oval, cordate at the base, all subacute, entire glabrous thin, bullate with reticulate venation.

Phytochemical constituents

The fruits contain 1% volatile oil, resin, alkaloids piperine and piperlonguminine, isobutyldeca-trans-2-trans-4-dienamide and a terpenoid substance. Roots contain piperine, piperiongumine. Dihydrostigmasterol has been isolated. It contains aromatic oil an alkaloid and pipalartine. Besides this it contains sesamin and piplasterol. The root contains pipperin, pippalartin, pipperleguminin, sterols and glycosides.
*Piper longum* an important medicinal plant belonging to the family Piperaceae is being used as traditional medicine by many people in Asia and Pacific islands especially in Indian medicine (Guido *et al.*, 1998). *Piper longum* is a component of medicines reported as good remedy for treating gonorrhea, menstrual pain, tuberculosis, sleeping problems, respiratory tract infections, chronic gut related pain, and arthritic conditions (Singh, 1992).