CHAPTER NO.3
LIVER – AN INTRODUCTION

3.1 ANATOMY

The liver is the largest gland of the body enclosed within the right lower rib cage beneath the diaphragm. It is almost completely covered by visceral peritoneum as well as completely covered by a dense irregular connective tissue layer that lies deep to the peritoneum. Liver is divided into two principal lobes, a large right lobe, and a smaller left lobe separated by falciform ligament. The right lobe is considered by many anatomists to include an inferior quadrate lobe and a posterior quadrate lobe. Liver has five surfaces as Anterior, posterior, superior, inferior, and right.

3.2 STRUCTURE (HISTOLOGY) 32-33

The lobes of liver are made up of many functional units called lobules. A lobule consists of specialized epithelial cells called hepatic (liver) cells or hepatocytes arranged in irregular, branching, interconnected plates around the central vein. Rather than capillaries liver has larger spaces lined by endothelium called sinusoids through which blood passes. The sinusoids are also partly lined with stellate reticuloendothelial (Kuffer’s) cells. These
phagocytes destroy worn out white and red blood cells, bacteria, and toxic substances. Bile secreted by

Fig 1. External Anatomy of liver
hepatic cells enters bile capillaries or canaliculi that empty into small bile ducts. These ducts eventually merge to form the larger right and left hepatic ducts, which unites and exit the liver as the common hepatic duct. Further this common hepatic duct joins the cystic duct from the gallbladder form the common hepatic duct. The common hepatic duct and pancreatic duct enter the duodenum in a common duct called the hepatopancreatic ampulla.

Fig No.2 Histology of Liver
3.2.1 Blood supply

The liver receives blood from two sources, from hepatic artery it obtains oxygenated blood, and from hepatic portal vein it receives deoxygenated blood containing newly absorbed nutrients. Branches of both the hepatic artery and the hepatic portal vein carry blood into liver sinusoids, where oxygen, most if the nutrients, and certain poisons are excreted by hepatic cells. The reticuloendothelial (Kuffer’s) cells lining the sinusoids phagocytes microbes and bits of foreign matter from the blood.

Branches of hepatic portal vein, hepatic artery, and bile duct typically accompany each other in their distribution through the liver, collectively; these structures are called a “Portal triad”.

3.3 FUNCTIONS OF LIVER

1. Secretion and excretion of bile

Bile is partially an excretory product and partially a digestive secretion. Each day the hepatic cells secrete 800-1000 ml of bile, a yellow, brownish or olive green liquid. It has pH of 7.6-8.6. Bile mainly consists of water, bile salts, cholesterol, a phospholipid called lecithin, bile pigments, and several ions. The principal bile pigment is bilirubin. When worn-out red blood cells (RBCs) break down, iron, globins, and bilirubin (derived from haem) are released.

2. Metabolic functions

A) Carbohydrate metabolism

Liver maintains the normal blood glucose level. e.g. It can convert glucose to glycogen (Glycogenesis) when blood sugar level is high and breakdown of glycogen to glucose (Glycogenolysis) when blood sugar level is
low. Also liver can convert amino acid and lactic acid to glucose (Gluconeogenesis) when sugar level is low.

B) Lipid metabolism

Liver stores some triglycerides (neutral fats) break down fatty acids into acetyl coenzyme-A, this process is called as β-oxidation, and converts excess acetyl coenzyme-A into ketone bodies (Ketogenesis). It synthesizes lipoproteins. Hepatic cells synthesize cholesterol and use cholesterol to make bile salts.

C) Protein metabolism

Liver deaminates (removes the amino group, NH$_2$ from) amino acids so that they can be used for ATP production. It converts the resulting toxic ammonia (NH$_3$) in to the much less toxic urea for excretion in urine.

Hepatic cells synthesize plasma proteins such as alpha and beta globulins, albumin, prothrombin and fibrinogen.

3. **Haematological functions**

Blood formation in the embryo and in some abnormal states in the adults. Production of fibrinogen, prothrombin, heparin and other clotting factors VII, VIII, IX and X.

Destruction of erythrocytes (At the end of their respective life span)

4. **Circulatory functions**

Transfer of blood from portal to systemic circulation. Activity of its reticulo endothelial system (Kupffer cells) in immune mechanism, Blood storage (Regulation of blood volume)
5. Détoxification & Protective functions

Kupffer cells activity in removing foreign bodies from blood (Phagocytosis), Detoxication by conjugation, methylation, oxidation and reduction. Removal of ammonia from blood particularly that absorbed from the intestine by way of the portal vein.

6. Drug metabolism

Liver plays a vital role in biotransformation of drugs. It converts drug molecule from non-polar to polar. These non-polar drugs can be conjugated with more polar compounds, which make it water soluble for the urinary excretion.

3.4 LIVER DISEASES \textsuperscript{36-37}

3.4.1 Acute liver failure

Acute liver failure most commonly results from acute massive liver cells necrosis caused by viral hepatitis and toxic drugs and chemical also it follows acute fatty change of the liver.

Acute liver failure is characterized by

1) Jaundice
2) Hypoglycemia
3) Electrolyte and acid base disturbances (hypokalemia is most dangerous)
4) Hepatic encephalopathy
5) Hepatorenal syndrome
6) Elevation of serum enzymes (LDH, AST, ALT)

There are three types of acute liver failure

a) Fulminant hepatic failure (FHF) – It is a syndrome and abrupt onset, characterized by a progressively severe encephalopathy consequent on massive hepatocellular necrosis.
b) Acute or Chronic Hepatocellular Failure – This may result from protein overload sepsis, or intervention with drugs or surgery.

c) Sub-acute Hepatic Failure – It is defined as acute failure occurring in patients without pre-existing liver disease, in whom the signs of encephalopathy develops more than eight weeks after the onset of illness.

3.4.1.1 Jaundice (Icterus)

The commonest system of liver disease is a yellow coloration of the skin and sclera of the eyes, mucous membrane owing to hyper bilirubinemia.

Jaundice is the sign of abnormal bilirubin metabolism and excretion. Jaundice is visible when serum bilirubin exceeds 2-4 mg/dl.

Classification

1. Pre-hepatic (haemolytic) jaundice

This is due to increased breakdown of Hb, so that the liver cells are unable to conjugate all the increased bilirubin formed.

Since the liver of a newborn functions poorly for the 1st week and hence many babies experience a mild form of jaundice, called neonatal (physiological) jaundice that disappears as the liver matures.

2. Hepatic (Hepatocellular) jaundice

This is the disease of parenchymal cells of liver. This jaundice occurs due to Conditions in which there is a defective conjugation- There may be reduction in no of functioning liver cells eg. Chronic hepatitis (all liver functions impaired)

Conditions such as viral hepatitis and toxic jaundice – In this extensive damage to liver cells associated with intra hepatic obstruction resulting in appreciable observation of conjugated bilirubin.

3. Cholestatic jaundice

This is due to drug induced jaundice eg. Chlorpromazine and steroids cause intrahepatic obstruction, liver function being essentially normal.
4. Obstructive (Posthepatic) jaundice

In this jaundice there is obstruction of bile flow in the extrahepatic ducts, eg. carcinoma of head of pancreas, enlarged lymph glands pressing on bile duct etc.

3.4.1.2 Ascites

Ascites is due to increased transudation of fluid across the peritoneal membrane over the surface of liver. The major factor leading to severe ascites in chronic liver disease is a decrease in serum albumin level, with portal hypertension playing only a contributing role.

3.4.1.3 Hepatic encephalopathy

Hepatic encephalopathy is characterized by cerebral dysfunction (hypersomnia, delirium, flapping tremors of hands) leading it convulsions, coma and death.

The pathogenesis of hepatic encephalopathy is unclear but it believed that nitrogenous products of intestinal bacteria accumulates in the systemic blood, having bypassed the liver through postsystemic anastomoses or having undergone deficient detoxification by failing liver cells.

The substances involved in the pathogenesis of hepatic encephalopathy are ammonia present high in plasma and cerebrospinal fluid in placenta with liver failure. The amides like octopamine act as a false neurotransmitter.
3.4.2 Chronic liver failure

It results from cirrhosis, which associates of liver cells, fibrosis, noduler regeneration.

The effects of chronic liver failure are
- Portal hypertension
- Hepatic encephalopathy
- Hepatorenal syndrome
- Fetor hepaticus – A breath like that of ‘A freshly opened corpse’ believed to be due to deficient methionine metabolism.

3.4.2.1 Cirrhosis

Cirrhosis is premalignant lesion. It is an irreversible and progressive disease that ultimately causes death. Cirrhosis of liver is a pathologic entity characterized by:

1) Necrosis of liver cells, causing liver failure and death.
2) Fibrosis, which involve both central vein and portal areas.
3) Regenerative nodules, a result of hyperplasia of surviving liver cells.
4) Distortion of normal hepatic lobular architecture.
5) Diffuse involvement of the whole liver.

Cirrhosis is classified according to its causes

1. Cryptogenic cirrhosis

Hepatic cirrhosis is said to be cryptogenic when complete evaluation of the patient has failed to identify the cause. It may include cirrhosis following immune mediated chronic active hepatitis or following injury due to drugs or chemicals because there is no way to identify these causes.
2. **Alcoholic Cirrhosis**

   It is frequently associated with evidence of fatty change or acute alcoholic’s hepatitis. It is typically fatty micro nodular cirrhosis. The disease is irreversible and causes death.

3. **Virus Induced Cirrhosis**

   Cirrhosis may follow chronic active hepatitis resulting from infection with hepatitis B and C viruses.

   Typically virus induced cirrhosis is macro nodular. Virus induced cirrhosis may tends to progress rapidly with death due to chronic liver failure, portal hypertension, or hepatocellular carcinoma. Cirrhosis caused by hepatitis B virus may be identified by the presence of HBs Ag in serum and liver cells.

4. **Biliary cirrhosis**

   Two types of Biliary cirrhosis are

   Primary Biliary cirrhosis – It causes portal fibrosis. It can occur mostly in middle aged female with long history of obstructive jaundice.

   Secondary Biliary cirrhosis – It occurs in patients with prolonged large bile duct obstruction (gallstones, stricture, tumor, cholangitis). Biliary cirrhosis causes fine nodularity (micro nodules).

5. **Hemo cirrhosis**

   It results from iron over load in the body by increased serum iron, ferritin and sachration of iron –binding protein, increase iron stores in bone marrow and presence of iron in liver cells.

### 3.4.2.2 Wilson disease

   Wilson disease is an autosomal recessive disorder characterized by

   1) Defective excretion of copper into bile.

   2) Increase in total body copper.
3) Accumulation of copper in cytoplasm of liver cells, complex to an abnormal protein.

4) Increase “free” copper in plasma.

The primary defect is in the liver cell and is corrected by liver transplantation.

Severe Alpha\textsubscript{1} – antitrypsin deficiency (alpha – antiprotease) occurs in homozygous individuals and is a rare cause of cirrhosis, usually with onset during childhood.

1. Neoplasm of liver
   
   Benign-
   
   Hemangiomas
   Adenomas (bile duct and hepatic cells)
   Focal nodular hyperplasia
   
   Malignant-
   
   Hepatocellular carcinoma (Hepatomas)
   Cholangiocarcinoma
   Malignant vascular neoplasm

2. Metastatic neoplasm
   
   Liver neoplasm in infancy
   Infantile hemangioendothelioma
   Mesenchymal hamartoma
   Hepatoblastoma

3.4.2.3 Congenital liver disease

   Cystic liver disease – It is due to mal development of bile duct, it is associated with the polycystic kidney.

   Dubin – Johnson syndrome and rotors syndrome, Genetic defect in excretion of the conjugated bilirubin.
Crigler – Najjar syndrome – It is very rare autosomal recessive disease characterized by complete absence of the enzyme in the homologous patient (Type A disease).

A less caviar form of Crigler- Najjar syndrome (Type B disease) in which enzyme deficiency is partial and compatible with more prolonged survival.

3.4.2.4 Circulatory disorders

Impaired blood flow into the liver-

Banti syndrome – In this syndrome extra hepatic portal vein obstruction is there and also sub clinical occlusion of the portal vein presents as variceal bleeding and ascites years later.

Impaired blood flow through liver-

Passive congestion and centrallobuler necrosis.

Hepatic venous outflow obstruction

Budd – chiari syndrome – In this syndrome the obstruction of two or more hepatic veins produced liver enlargement, pain, and ascites.

Veno – occlusive disease (sinusoidal obstruction syndrome) – It is characterized by obstruction of hepatic vein radicals by varying amounts of sub endothelial swelling and fine reticulated collagen.

3.4.2.5 Viral and other infective hepatitis

Hepatitis means inflammation of liver. The causes of hepatitis are varied and include viruses, bacteria, protozoa as well as drugs and toxins.

1. Viral hepatitis

The viruses mostly infect the liver includes hepatitis A, hepatitis B, hepatitis C and hepatitis E. Although other viral infection may present with symptoms of liver disease these are not classified as viral hepatitis These agents includes Epsein-Barr virus, Cytomegalo virus, Vericella-Zoster virus, Herpes virus, Yellow fever virus.
2. Bacterial hepatitis

Pyogenic liver abscess – Many bacteria as Escherichia coli, other gram negative bacilli, an aerobic bacilli, staphylococcus aureus and streptococci are the causative agents of bacterial hepatitis.

Bacteria may reach the liver in the course of a systemic bacteremia in the hepatic artery or from the intestine along the bile duct or portal vein.

3.5 MECHANISMS OF HEPATOTOXICANT ACTION

As the drug metabolizing and detoxifying organ in the body, the liver is subject to potential damage from an enormous array of Pharmaceutical and Environmental chemicals.

3.5.1 Direct hepatotoxicity

These are the agents that damage the membrane of hepatocytes directly resulting in interference of cell metabolism. The most common chemotoxicants and drugs that impair the function of liver are CCl₄, thioacetamide, paracetamol, galactosamine, fulvine, phalloidin, ethyl alcohol, aflatoxin, lanthanium chloride and pyrazolidine alkaloids.

3.5.2 Indirect hepatotoxicity

These are the agents that produce hepatic injury as a result of selective interference with metabolic pathways or selective binding to or alteration of a specific component. The occurrence of hepatitis by indirect hepatotoxic drug reaction is infrequent and unpredictable. Short exposure of the liver to such drugs results in hepatic disorder.

Following drugs that affect normal liver and brings about certain morphological alterations as valproic acid, phenytoin, methyl-Dopa, chlorpromazine, phenylbutazone, allopurinol, etc.
Table 1. DRUGS AND TOXINS INDUCED HEPATITIS

<table>
<thead>
<tr>
<th>Hepatocellular damage</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-vesicular fatty change</td>
<td>Tetracycline, salicylates, yellow phosphorous, ethanol</td>
</tr>
<tr>
<td>Macro-vesicular fatty change</td>
<td>Ethanol, Meyhotrexate, Amiodarone</td>
</tr>
<tr>
<td>Centrilobular necrosis</td>
<td>Bromo-benzene, CCl4, acetaminophen, Halothane, Rifampicin</td>
</tr>
<tr>
<td>Diffuse or massive necrosis</td>
<td>Halothane, Isoniazid, Rifampicin, acetaminophen, methyldopa, trinitrotoluene, Amanita phalloides (mushroom) toxin</td>
</tr>
<tr>
<td>Hapatitis, acute and chronic</td>
<td>Methyldopa, Isoniazid, nitrofurantoin, phenytoin, oxyphenisatin</td>
</tr>
<tr>
<td>Fibrosis-Cirrhosis</td>
<td>Ethanol, Methotrexate, amiodarone, most drugs that cause chronic hepatitis</td>
</tr>
<tr>
<td>Granuloma formation</td>
<td>Sulphamides, Methyldopa, quinidine, phénylbutazone, hydralazine, allopurinol</td>
</tr>
<tr>
<td>Cholestasis (with or without injury)</td>
<td>Chlorpromazine, anabolic steroids, erythromycin estolate, oral contraceptives, organic arsenicals.</td>
</tr>
</tbody>
</table>
3.6 SIGNS AND SYMPTOMS OF LIVER DISEASES

They are categorized into
1. Jaundice
   Pre-hepatic jaundice.
   Hepatic jaundice.
   Post-hepatic jaundice.
2. Pruritis & other skin signs-
   Spider naevi.
   Palmer erythema.
3. Ascites
4. Encephalopathy (Neurological syndrome)
5. General signs & symptoms

3.7 LIVER FUNCTION TESTS\textsuperscript{45-47}

When the liver is diseased, one or more but not necessarily all of the functions are impaired. There can be no test for liver functions as a whole. The various “Liver Function Tests” (LFTs) are tests of derangements of individual functions of the liver. Since many tests give many similar abnormal results in a particular liver disease, it may be possible to extend a conclusion drawn from single test.

The liver biopsy results may not be comparable with the LFTs since many functional changes are not mirrored by obvious structural changes in the liver cells. For understanding various liver functions of the liver, following tests are performed.

1. Tests for bile pigments and bile salts excretion-
   Serum total, direct and indirect bilirubin.
   Urine bile salts, bile pigments and urobilinogen.
2. Tests for plasma proteins-
   Thymol turbidity test
   Determination of total proteins, albumin, globulin, and A/G ratio
   Determination of plasma fibrinogen
   Various flocculation tests
   Amino acids in urine

3. Tests for carbohydrate metabolism-
   Galactose tolerance test
   Glucose tolerance test

4. Tests for lipid metabolism-
   Serum cholesterol and ester cholesterol and their ratio
   Faecal fats

5. Tests for excretion of injected substances by the liver-
   Bromsulphthalein test (BSP retention test)
   $^{131}$- Rose Bengal test

6. Tests based on detoxicating function of liver-
   Hippuric acid synthesis test

7. Formation of prothrombin by liver-
   Determination of prothrombin time and index

8. Tests based on Amino acid catabolism-
   Determination of ammonia
   Determination of glutamine in CS fluid (indirect liver function test)

3.7.1 Investigative method

Ultrasonography, Computerized Tomography and Magnetic Resonance- Imaging discloses mass lesions in the liver or dilation of the biliary system.

Arteriography and Isotope scans- Hepatic blood flow can be detected by this method.
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Gallium Scanning- Useful in detecting neoplasms and abscesses in the liver.

Liver Biopsy- It is the safe method of obtaining histological examinations. Blind biopsy using a cutting needle indicated for diffuse lesions of the liver. Radiologically dissected fine needle and Aspiration biopsy is indicated when it is necessary to examine a localized lesion.

3.8 PARAMETERS REFLECTING LIVER CONDITION AND THEIR INTERPRETATION

3.8.1 TRANSAMINASES

The transaminase enzymes are involved in nitrogen transfer reactions from amino acids to other substrate for eventual disposal in the urea cycle.

3.8.2 SERUM GLUTAMATE OXALOACETATE TRANSAMINASE (SGOT)

It is also known, as Aspartate Transferase (AST). It is an enzyme present in the cytoplasm and mitochondria of most cells, because SGPT is found in many tissues, abnormalities are not specific for liver injury. SGOT is elevated in conditions as liver cell injury, myocardial infarction, muscle trauma, acute pancreatitis, intestinal injury, pulmonary infarction, cerebral infarctions, and renal infarctions. Levels may be falsely decreased during diabetic ketoacidosis, beriberi, severe liver disease and chronic liver failure. SGOT catalyzes the reaction

\[
\text{Aspartic acid} + \text{SGOT} \rightarrow \text{Oxaloacetic acid} + \text{Alpha-Keto-Glutaric Acid} + \text{Glutamic acid}
\]

The amount of oxaloacetic acid are determined after incubation colorimetrically by the formation of hydrazone with dinitrophenyl hydrazine reagent (DNPH) which is highly coloured in alkaline medium and thus serum level of SGOT is determined by Reitman and Frankel method.
Levels of SGOT and SGPT normally parallel to each other.
Levels very high = acute viral hepatitis
High = Myocardial infarction or shock
If AST high, ALT normal = Alcoholic liver disease.

3.8.3 SERUM GLUTAMATE PYRUVATE TRANSAMINASE (SGPT)

It is also known as Alanine aminotransferase (ALT). It is an enzyme found in mitochondria of many cells but most abundant in liver. Though it may increase in many conditions, an elevation of SGPT is more specific in liver injury, including hepatic necrosis and acute hepatitis. SGPT catalyzes the reaction

\[
\text{Alanine} + \text{SGPT} \rightarrow \text{Pyruvic acid} + \text{Alpha-Keto-Glutaric Acid} + \text{Glutamic acid}
\]

The amount of pyruvic acid can be determined after incubation colorimetrically by the formation of hydrazone with dinitrophenyl hydrazone reagent (DNPH) which is highly colored in alkaline medium and the serum level of SGPT was determined by Reitman and Frankel method. In case of post hepatic condition (Biliary obstruction) SGPT level show a steady elevation of 3-4 times if the upper normal limits and decline shortly after relief of obstruction.

3.8.4 ALKALINE PHOSPHATASE

This enzyme is present in variety of tissues including bone, liver, intestine and placenta. Liver fraction of alkaline phosphatase is predominantly elevated by biliary system obstruction wheather in intrahepatic or extrahepatic. In viral hepatitis moderate
rise in alkaline phosphatase was observed. Higher values are observed in toxic hepatitis.

3.8.5 ACID PHOSPHATASE

Acid phosphatase is frequently employed as a marker enzyme to assess the lysosomal changes in vivo because it is localized almost exclusively in the particles and its release parallels that of lysosomal hydrolases.

3.8.6 TOTAL PROTEINS

Serum total protein level decreases below normal ranges in different clinical conditions such as Cirrhosis of liver and other liver diseases in which liver cells were severely damaged.

3.8.7 TOTAL BILIRUBIN

Disordered bilirubin metabolism could be considered under
1) Increased formation of bilirubin.
2) Abnormal uptake of bilirubin in the liver cells.
3) Defective conjugation.
4) Failure of normal amounts of bile to reach the duodenum i.e. development of condition called cholestasis.

3.8.8 LIVER WEIGHT AND VOLUME

The weight and volume of liver increases due to accumulation of fats in liver disorder.

3.9 SOME ANCIENT AYURVEDIC FORMULATIONS IN THE TREATMENT OF LIVER DISORDER

Dantyadyarishtra, Rohitakarishtra, Kalyanka guda, Danti haritak, Dashmoolaharishtra, Drakshavaleha, Manibhdra yog. Shiva ghutica, Patoladi Kawatch choorna, Triphala ghrita, Shatpaladi ghrita, Sukumara ghrita, Navays choorna, Sudarshan choorna, Chandraprabha vati, Suran vatica, Kasisa bhasma,
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loha bhasma, Mandura bhasma, Shankha bhasma, Pnarnavadi mandura, Kumar Kalyan ras, Lokhantha ras, Dhatri loha, Vidangadi loha, Rohitaka loha, etc.

3.10 DRUGS USED IN THE TREATMENT OF LIVER DISEASES

Table No.2 ALLOPATHIC TREATMENT FOR LIVER DISORDER

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Constituents</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delphicol</td>
<td>Tricholine Citrate, Acetyl dimethionine</td>
<td>Wyeth Pharma</td>
</tr>
<tr>
<td>Mecolin</td>
<td>Tricholine Citrate, Sorbitol</td>
<td>Stadmed</td>
</tr>
<tr>
<td>Silybon-70</td>
<td>Silymarin</td>
<td>Microlabs</td>
</tr>
<tr>
<td>Hepatoglobine</td>
<td>Proteolysed liver, Peptone, Iron, Ammonium citrate &amp; Nicotinic acid</td>
<td>Raptakos</td>
</tr>
<tr>
<td>Livage</td>
<td>Lecithin, Phospholipid.</td>
<td>Aristo Pharma</td>
</tr>
<tr>
<td>Hepacor</td>
<td>L-ornithin, L-Aspartate</td>
<td>Intas</td>
</tr>
<tr>
<td>Ornipan</td>
<td>L-ornithin, L-Aspartate, pancretin.</td>
<td>Moraceae</td>
</tr>
<tr>
<td>Tricodol</td>
<td>Sorbotol, Tricholine</td>
<td>Dr.Reddy’s Lab</td>
</tr>
<tr>
<td>Livercool</td>
<td>Sorbotol, Tricholine</td>
<td>Sanjeevani Bio-Tech</td>
</tr>
<tr>
<td>Sorbitin</td>
<td>Tricholine Citrate, Sorbitol</td>
<td>Franco-India</td>
</tr>
</tbody>
</table>
Table No.3

PLANTS INVESTIGATED FOR THEIR HEPATOPROTECTIVE ACTIVITY

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Part used</th>
<th>Extract /Constituents</th>
<th>Experimental model</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abutilon indicum</em></td>
<td>-</td>
<td>Aqueous</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Adhatoda Vasica</em></td>
<td>Leaves</td>
<td>-</td>
<td>D-galactosamine</td>
</tr>
<tr>
<td><em>Andrographis paniculata</em></td>
<td>Leaves</td>
<td>Aqueous</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Anisotes trisulcus.</em></td>
<td>-</td>
<td>Ethanolic</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Apium graveolens Linn.</em></td>
<td>Seeds</td>
<td>Methanolic</td>
<td>Paracetamol and thioacetamide</td>
</tr>
<tr>
<td><em>Apium graveolens Linn.</em></td>
<td>-</td>
<td>Methanolic</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Aronia melanocarpa</em></td>
<td>Fruit</td>
<td>Juice</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Artemisia absinthium</em></td>
<td>-</td>
<td>Aqueous – methanol</td>
<td>Acetaminophen and CCl₄</td>
</tr>
<tr>
<td>Plant</td>
<td>Part</td>
<td>Extract Type</td>
<td>Compostion</td>
</tr>
<tr>
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<tr>
<td><em>Artemisia vulgaris</em></td>
<td>Aerial parts</td>
<td>Aqueous and Methanolic</td>
<td>D-Galactosamine(D-GalIN) and Lipopolysaccharide (LPS)</td>
</tr>
<tr>
<td><em>Asteracantha longifolia</em></td>
<td>Seed</td>
<td>Methanolic</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Azadirachta indica</em></td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Paracetamol</td>
</tr>
<tr>
<td><em>Ballota glandulosissima</em></td>
<td>-</td>
<td>Aqueous</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Barleria prionitis Linn.</em></td>
<td>Aerial</td>
<td>Methanol-Water</td>
<td>CCl₄ galactosamine and paracetamol</td>
</tr>
<tr>
<td><em>Belamcanda chinensis</em></td>
<td>Rhizomes</td>
<td>-</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Beta vulgaris</em></td>
<td>Root</td>
<td>Ethanolic</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Camellia sinensis</em></td>
<td>Leaves</td>
<td>Decoction</td>
<td>Tamoxifen citrate</td>
</tr>
<tr>
<td><em>Cassia occidentalis L.</em></td>
<td>Leaves</td>
<td>Aqueous and Ethanolic</td>
<td>Paracetamol &amp; ethyl alcohol</td>
</tr>
</tbody>
</table>
**Introduction**

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Part Used</th>
<th>Solvent</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Centaurium erythraea L.</em></td>
<td>Leaves</td>
<td>Methanolic</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Coronopus didymus L.</em></td>
<td>Whole plant</td>
<td>Aqueous extract</td>
<td></td>
</tr>
<tr>
<td><em>Crepis rueppellii</em></td>
<td>-</td>
<td>Ethanol</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Croton oblongifolius Roxb.</em></td>
<td>-</td>
<td>Methanol</td>
<td>CCl₄</td>
</tr>
<tr>
<td><em>Cudrania tricuspidata Breau</em></td>
<td>Root Barks</td>
<td>Methanol</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td><em>Emblica officinalis</em></td>
<td>Fruit</td>
<td>Hydroalcohol</td>
<td>Rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) (in combination)</td>
</tr>
<tr>
<td><em>Erycibe expansa</em></td>
<td>Stem</td>
<td>Methanol</td>
<td>D-galactosamine</td>
</tr>
<tr>
<td><em>Eucalyptus maculata</em></td>
<td>Stem</td>
<td>Chloroform</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Helminthostachys zeylanica</em></td>
<td>Rhizomes</td>
<td>Methanol</td>
<td>CCl₄</td>
</tr>
<tr>
<td>Species</td>
<td>Part</td>
<td>Extraction</td>
<td>Compound</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><em>Nymphaea stellata willd</em></td>
<td>Flower</td>
<td>-</td>
<td>CCl$_4$</td>
</tr>
<tr>
<td><em>Osbeckia octandra</em></td>
<td>Mature leaves</td>
<td>Aqueous</td>
<td>Galactosamine and tert-butyl hydroperoxide</td>
</tr>
<tr>
<td><em>Permna tomentosa Linn.</em></td>
<td>Leaves</td>
<td>-</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Phyllanthus maderaspatensis</em></td>
<td>whole plant</td>
<td>n-hexane, ethyl alcohol</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Premna tomentosa Linn.</em></td>
<td>-</td>
<td>-</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td><em>Psidium guajava Linn.</em></td>
<td>Leaves</td>
<td>-</td>
<td>CCl$_4$</td>
</tr>
<tr>
<td><em>Quercus aliena acorn</em></td>
<td>-</td>
<td>Aqueous</td>
<td>CCl$_4$</td>
</tr>
<tr>
<td><em>Rosmarinus officinalis</em></td>
<td>whole plant</td>
<td>Aqueous and ethanolic extract</td>
<td>CCl$_4$</td>
</tr>
<tr>
<td><em>Sesbania grandiflora</em></td>
<td>Leaves</td>
<td>Ethanol</td>
<td>Erythromycin estolate</td>
</tr>
<tr>
<td><em>Swertia longifolia Boiss.</em></td>
<td>Aerial parts</td>
<td>-</td>
<td>Paracetamol</td>
</tr>
<tr>
<td><em>Telfairia occidentalis</em></td>
<td>Leaves</td>
<td>Aqueous and</td>
<td>Garlic</td>
</tr>
</tbody>
</table>
Cells in human body use oxygen to break down carbohydrates, protein and fats that give them energy. Metabolically active cells produce by products called free radicals. These are atoms or group of atoms that have at least one unpaired electron, which make them highly reactive. They promote beneficial oxidation that produces energy and kill bacterial invaders. If

\[ \text{3.11 ANTIOXIDANTS}^{51-53} \]

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Part</th>
<th>Solvent</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Terminalia catappa</em></td>
<td>Leaves</td>
<td>Chloroform</td>
<td><em>CCl\textsubscript{4}</em></td>
</tr>
<tr>
<td><em>Terminalia chebula Gertn.</em></td>
<td>Fruit</td>
<td>Ethanol</td>
<td>Rifampicin (RIF), isoniazid (INH) and pyrazinamide (in combination)</td>
</tr>
<tr>
<td><em>Teucrium stocksianum</em></td>
<td>-</td>
<td>Ethanol</td>
<td>Paracetamol</td>
</tr>
<tr>
<td><em>Thunbergia laurifolia</em></td>
<td>-</td>
<td>Aqueous</td>
<td>Ethanol</td>
</tr>
<tr>
<td><em>Trianthema portulacastrum</em></td>
<td>-</td>
<td>Ethanol</td>
<td>Paracetamol and thioacetamide</td>
</tr>
<tr>
<td><em>Trichilia emetica</em></td>
<td>Root</td>
<td>Aqueous</td>
<td><em>CCl\textsubscript{4}</em></td>
</tr>
</tbody>
</table>
free radicals are at reasonable level, the human body produces enzymes to combat them and useful immune system and antibacterial cell activity.

Excess of free radicals attack DNA cell’s genetic material (Cancer), blood vessels (cardiovascular diseases). They are also implicated in arthritis, strokes, cataracts and degenerative health problem such as diabetes, ischemia, dementia and aging. Fried food, cigarette smoke, air and water pollution as well as toxins also create free radicals. When this free radical are added to metabolic free radical, they may lead to over exposure, which causes oxidative stress, a condition in which the body’s natural defenses over run.

3.11.1 Mechanism of Antioxidants

The living cell during several metabolic pathways generates reactive oxygen species (ROS) and reactive nitrogen species (RNS). Pathophysiological conditions enhance the generation of ROS and RNS and lead to oxidative stress. The generation of ROS begins with the rapid uptake of oxygen and activation of NADPH oxidase and the production of the super oxide free radical (O$_2^-$)

\[
2O_2 + NADPH \rightarrow 2O_2^- + NADP + H^+ \\
\text{OXIDASE}
\]

ROS can also be generated through the Fenton (I) reaction (II) and Haber-Weiss reaction (I)

I. $H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH + H^+$

II. $H_2O_2 + O_2 \rightarrow O_2 + OH + OH$

The free radical nitric oxide (NO), which is known as endothelium-derived relaxation factor (EDRF), is formed from arginine by nitric oxide synthetase (NOS).
L-arg + O₂ + NADPH $\xrightarrow{\text{NOS}}$ NO + Citrulline

\[
\text{NO} + \text{O}_2 \xrightarrow{\text{NOS}} \text{ONOO}^+ \text{ (Peroxynitrite)}
\]

Peroxynitrite is a very strong oxidant, which reacts with aromatic amino acid residues to form nitrotyrosine. This can lead to enzyme inactivation. To dependence injury, biological structures have protective machinery in the form of endogenous antioxidant. Among different endogenous antioxidants, Super oxide dismutase (SOD), reduced glutathione (GPX) Catalase and Glutathione Peroxidase (GPX) are important for counteracting oxidative stress.

3.11.2 Lipid peroxidation

Lipid peroxidation is a complex process that occurs in aerobic cells and reflects the interaction between molecular oxygen and unsaturated fatty acids. This produces and propagates the Lipid radical (L), uptake of O₂ generation of alkoxy (LO), lipid peroxyl radicals (LOD), rearrangement of double bonds, lipid hydroperoxide (LOOH) as well as a number of degradation products. Two paths are known for the generation of lipid peroxide in vivo. One occurs through auto-oxidation of compound such as catecholamines, quinines, thiols and redox reactions of myoglobin and oxyhaemoglobin, and the other from active oxygen by the action of NADPH oxidase, xanthine oxidase, catalase, superoxide dismutase and glutathion peroxide. The disturbance of balance between the formation of free radicals (lipid radicals) and antioxidants leads to oxidative stress.
Antioxidants act as radical scavengers, hydrogen donors, peroxide decomposers, electron donor, enzyme inhibitors, singlet oxygen quenchers, synergist and metal chelating agents.

3.11.3 Antioxidants Defense System (ADS)

Broad group of compounds that destroy single oxygen molecule (free radicals) in the body, thereby protecting against oxidative damage of cells. They are essential for good health and are found naturally in wide variety of foods and plants including many vegetable and fruits. These include grapes, lemon, melon, blue cherry, strawberries, pineapple, tomatoes, garlic, green tea, maize, wheat, corn.

Antioxidant defense system (ADS) against oxidative stress is composed of several lines, and antioxidants are classified in four categories based on their function.

The first line of defense is preventive antioxidants, which suppress the formation of free radical. The second line of defense is radicals scavenging antioxidants, which suppress the chain initiation and/or breaking chain propagation reaction. These are referred to radical scavenging antioxidants. The third line of defense is repair and de novo antioxidants and last one is adaption where the signal for the production and actions of free radicals induces the formation and transport of the appropriate antioxidant to right side.
PLANT PHOTO