



## DIFFERENT MODELS OF HEPATOTOXICITY AND RELATED LIVER DISEASES: A REVIEW

Singh Robin\*, Kumar Sunil, Rana A.C., Sharma Nidhi

Rayat Institute of Pharmacy, Railmajra, Dist. Nawanshahar, Near Ropar, Punjab, India

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\*Email: robinsinghmaip@yahoo.com

### ABSTRACT

The liver is among the most complex and important organs in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. Hepatotoxicity implies chemical-driven liver damage. Chemicals that cause liver injury are called hepatotoxins. Hepatic injury leads to disturbances in transport function of hepatocytes resulting in leakage of plasma membrane thereby causing an increased enzyme level in serum. There are many diseases that are related with hepatotoxicity caused by certain chemicals or hepatotoxins. Herbal medicines are great demand in various chemicals and drugs disordered hepatic, the developed world for primary health care because of their efficacy, safety, lesser side effects and narrow therapeutic window. This review focus on liver, its function, liver diseases and different models of hepatotoxicity.

**Keywords:** Hepatotoxicity, CCl<sub>4</sub>, mercury, Paracetamol, Hepatitis, Jaundice etc.

### INTRODUCTION:-

Hepatotoxicity implies chemical-driven liver damage. 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 (e.g. ccl<sub>4</sub>, paracetamol) and industries (e.g. lead, arsenic), natural chemicals (e.g. microcystins, aflatoxins) and herbal remedies (*Cascara sagrada*, ephedra) can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. These agents are convert in chemically reactive metabolites in liver, which have the ability to interconnect with cellular macromolecules such as protein, lipids and nucleic acids, leading to protein dysfunction, lipid per oxidation, DNA damage and oxidative stress. This damage of cellular function can dismiss in cell death and likely liver failure. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug-induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. More than 75 percent of cases of idiosyncratic drug reactions result in liver transplantation or death<sup>1</sup>. Liver plays a pivotal role in regulating various physiological processes. It is also involved in several vital function, such as metabolism, secretion and storage. It has great capacity to detoxicate toxic substances and synthesize useful principle. It helps in the maintenance, performance and regulating homeostasis of the body. It involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. It aids metabolism of carbohydrate, protein and fat, detoxification, secretion of bile and storage of vitamins<sup>2</sup>. The role played by this organ in the removal of substances from the portal circulation makes it susceptible to first and persistent attack by offending foreign compounds, culminating in liver dysfunction. These hepatotoxic agents activated some enzymes activity in the cytochrome p-450 system such as CYP2E1 also leads to oxidative stress. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside liver. This promotes further liver damage. Liver is also the major reticulo-

endothelial organ in the body as such has important immune function in maintaining body veracity. Damaging hepatocyte results in the activation of innate immune system like kupffer cells (KC), natural killer (NK) cells, and natural killer T (NKT) cells and result in producing proinflammatory mediators such as tumor necrosis factor- $\alpha$  (TNF), interferon- $\gamma$  (IFN), and interleukin- $\beta$  (IL) produced liver injury. Many agents damage mitochondria, an intracellular organelle that produces energy. In mitochondria hepatocellular death is a direct result of drugs acting on these organelles (e.g., drug accumulation, inhibition of electron transport and fatty acid oxidation, or depletion of anti-oxidant defenses). An indirect result ensuing from mitochondrial participation in programs of cell death. These programs lead to necrosis or apoptosis; they are mediated through signaling mechanisms arising at the cell membrane (e.g., death receptors) or in subcellular compartments (e.g., the endoplasmic reticulum or cell nucleus). Its dysfunction releases excessive amount of oxidants which, in turn, injure hepatic cells. Non-parenchymal cells such as Kupffer cells, fat storing stellate cells, and leukocytes (i.e. neutrophil and monocyte) also have role in the mechanism hepatotoxicity<sup>3</sup>. Medicinal plants play a key role in the human health care system. Pharmacological medicinal plants play a key role in the evaluation of these plants and their taxonomical health care system. Herbal medicines are great demand in various chemicals and drugs disordered hepatic, the developed world for primary health care because of their efficacy, safety, lesser side effects and narrow therapeutic window. Therefore, the use of herbal drugs is much safer than synthetic product available in the market. Herbal remedies support natural healing phenomena through blocking the progression of the degenerative pathological processes. Modern medicine offers limited success in providing effective cure and there is a severe need to develop new drug capable of healing toxic liver damages. In traditional system of medicine, plant were claimed to be effective and used successfully to alleviate multiple liver disorders. Ayurveda has a clinical speciality called rasayana, which prevent disease and counteracts the aging process by means of optimization of homeostasis. It has been reported that rasayanas are rejuvenators, nutritional supplements and

possess strong antioxidant activity. Hepatic injury leads to disturbances in transport function of hepatocytes resulting in leakage of plasma membrane thereby causing an increased enzyme level in serum. All the hepatotoxic used in the present study induced ROS production in the body. This leads to depletion of antioxidant status of hepatic tissue and induced lipid peroxidation degradation of bio membrane in the control group. Administration of antioxidant, which can scavenge the free radicals, could reduced the hepatic injury. There are many herbal medicine plant having antioxidant properties which show hepatoprotective activity<sup>4</sup>.

#### **LIVER AND ITS FUNCTION:**

##### **LIVER:**

The liver is among the most complex and important organs in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. It lies below the diaphragm in the abdominal pelvic region of the abdomen. The liver is a reddish brown organ with four lobes of unequal size and shape. It is both the largest internal organ and the largest gland in the human body. It is connected to two large blood vessels, one called the hepatic artery and one called the portal vein. It constitutes about 2.5% of an adult's body weight. During rest, it receives 25% of the cardiac output via the hepatic portal vein and hepatic artery. The hepatic portal vein carries the absorbed nutrients from the GI tract to the liver, which takes up, stores, and distributes nutrients and vitamins. It produced bile, an alkaline compound which aids in digestion via the emulsification of lipids. Two major types of cells populate the liver lobes: parenchymal and non-parenchymal cells. 80% of the liver volume is occupied by parenchymal cells commonly referred to as hepatocytes. Non-parenchymal cells constitute 40% of the total number of liver cells but only 6.5% of its volume. Sinusoidal endothelial cells, kupffer cells and hepatic stellate cells are some of the non-parenchymal cells that line the hepatic sinusoid<sup>5</sup>.

##### **FUNCTION OF LIVER<sup>6</sup>**

The liver has well over 500 functions and is known as the laboratory of the human body. The liver is tied to all bodily processes because it is responsible for filtration of all incoming foods and fluids. The body relies upon the liver to remove toxins so that nutrients supplied to the body are pure and capable of providing nourishment. Many scientists believe the liver is connected to, or at least aware, of every disease or dysfunction that is happening inside the body.

##### **Metabolic function:**

##### **Carbohydrate metabolism:**

Liver maintains the normal blood glucose level. 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 blood sugar level is low.

##### **Lipid metabolism:**

Liver stores some triglycerides (neutral fat) breakdown fatty acids into acetyl coenzyme-A, this process is called as 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.

##### **Protein metabolism:**

The liver delaminates (remove the amino group, NH<sub>2</sub>) from amino acids so that they can be used for ATP production. It converts the resulting toxic ammonia (NH<sub>3</sub>) into the much

less toxic urea for excretion in urine. Hepatic cells synthesize plasma protein such as alpha and beta globulin, albumin, prothrombin and fibrinogen.

##### **Haematological function:**

The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X and XI, as well as protein C, protein S and antithrombin. In the first trimester fetus, the liver is the main site of red blood cell production. By the 32nd week of gestation, the bone marrow has almost completely taken over that task.

##### **Secretion and excretion of bile:**

Bile is partially an excretory product and partially a digestive secretion. Each day the hepatic cells secrete 800-1000ml of bile, a yellow 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 principle bile pigment is bilirubin. When worn out red blood cells broken down, iron, globin's and bilirubin (derived from haem) are released.

##### **Breakdown:**

The breakdown of insulin and other hormones. The liver glucuronidates bilirubin, facilitating its excretion into bile. The liver breaks down or modifies toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This sometimes results in toxication, when the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine. The liver converts ammonia to urea (urea cycle).

##### **Other functions:**

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 (1-3 years' supply), iron, and copper. The liver is responsible for immunological effects—the reticulo endothelial system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system. The liver produces albumin, the major osmolar component of blood serum. The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure. The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults. The liver is a major site of thrombopoietin production. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by the bone marrow.

##### **LIVER DISEASE:**

##### **Fatty Liver :**

**Fatty liver**, also known as **fatty liver disease (FLD)**, is a reversible condition where large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis (i.e. abnormal retention of lipids within a cell). Despite having multiple causes, fatty liver can be considered a single disease that occurs worldwide in those with excessive alcohol intake and those who are obese (with or without effects of insulin resistance). The condition is also associated with other diseases that influence fat metabolism. Morphologically it is difficult to distinguish alcoholic FLD from non alcoholic FLD and both show micro-vesicular and macrovesicular fatty changes at different stages. Non-alcoholic fatty liver disease occurs when your liver has trouble breaking down fats, causing fat to build up in your liver tissue<sup>7</sup>.

**Pathophysiology of fatty liver disease:**

Defects in fat metabolism are responsible for pathogenesis of FLD which may be due to imbalance in energy consumption and its combustion resulting in lipid storage or can be a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipose tissue to the liver is increased. Impairment or inhibition of receptor molecules (PPAR- $\alpha$ , PPAR- $\gamma$  and SREBP1) that control the enzymes responsible for the oxidation and synthesis of fatty acids appears to contribute towards fat accumulation. In addition, alcoholism is known to damage mitochondria and other cellular structure further impairing cellular energy mechanism. On the other hand non alcoholic FLD may begin as excess of un metabolised energy in liver cells. Hepatic steatosis is considered reversible and to some extent non progressive if there is cessation or removal of underlying cause. Fatty change represents the intra-cytoplasmic accumulation of triglyceride (neutral fats). At the beginning, the hepatocytes present small fat vacuoles (liposomes) around the nucleus (microvesicular fatty change). In this stage liver cells are filled with multiple fat droplets that do not displace the centrally located nucleus. In the late stages, the size of the vacuoles increase pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance (macrovesicular fatty change). These vesicles are well delineated and optically "empty" because fats dissolve during tissue processing. Large vacuoles may coalesce and produce fatty cysts which are irreversible lesions. Macrovesicular steatosis is the most common form and is typically associated with alcohol, diabetes, obesity and corticosteroids. Acute fatty liver of pregnancy and Reye's syndrome are examples of severe liver disease caused by microvesicular fatty change<sup>8</sup>.

**JAUNDICE:**

**Jaundice** (also known as **icterus**; attributive adjective: **icteric**) is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by hyperbilirubinemia (increased levels of bilirubin in the blood). This hyperbilirubinemia subsequently causes increased levels of bilirubin in the extracellular fluid. Concentration of bilirubin in blood plasma does not normally exceed 1 mg/dL (>17 $\mu$ mol/L). A concentration higher than 1.8 mg/dL (>30 $\mu$ mol/L) leads to jaundice. The term jaundice comes from the French word *jaune*, meaning yellow. Jaundice is often seen in liver disease such as hepatitis or liver cancer. It may also indicate leptospirosis or obstruction of the biliary tract, for example by gallstones or pancreatic cancer, or less commonly be congenital in origin. Yellow discoloration of the skin, especially on the palms and the soles, but not of the sclera and mucous membranes (i.e. oral cavity) is due to carotenemia a harmless condition important to differentiate from jaundice. The conjunctiva of the eye are one of the first tissues to change color as bilirubin levels rise in jaundice. This is sometimes referred to as *scleral icterus*. However, the sclera themselves are not "icteric" (stained with bile pigment) but rather the conjunctival membranes that overlie them. The yellowing of the "white of the eye" is thus more properly termed *conjunctival icterus*. The term "icterus" itself is sometimes incorrectly used to refer to jaundice that is noted in the sclera of the eyes, however its more common and more correct meaning is entirely synonymous with jaundice<sup>9</sup>.

**Types of jaundice:**

Jaundice is classified into three categories.

**1) Pre-hepatic (haemolytic jaundice):**

*Pre-hepatic* jaundice is caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells). In tropical countries, malaria can cause jaundice in this manner. Certain genetic diseases, such as sickle cell anemia, spherocytosis, thalassemia and glucose 6-phosphate dehydrogenase deficiency can lead to increased red cell lysis and therefore hemolytic jaundice. Commonly, diseases of the kidney, such as hemolytic uremic syndrome, can also lead to coloration. Defects in bilirubin metabolism also present as jaundice, as in Gilbert's syndrome (a genetic disorder of bilirubin metabolism which can result in mild jaundice, which is found in about 5% of the population) and Crigler-Najjar syndrome. In jaundice secondary to hemolysis, the increased production of bilirubin, leads to the increased production of urine-uro bilinogen. Bilirubin is not usually found in the urine because unconjugated bilirubin is not water-soluble, so, the combination of increased urine-uro bilinogen with no bilirubin (since, unconjugated) in urine is suggestive of hemolytic jaundice.

**2) Hepatocellular (hepatic jaundice):**

*Hepatocellular* (hepatic) jaundice can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug induced hepatitis and alcoholic liver disease. Cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood. Other causes include primary biliary cirrhosis leading to an increase in plasma conjugated bilirubin because there is impairment of excretion of conjugated bilirubin into the bile. The blood contains abnormally raised amount of conjugated bilirubin and bile salts which are excreted in the urine. Jaundice seen in the newborn, known as *neonatal jaundice*, is common in newborns as hepatic machinery for the conjugation and excretion of bilirubin does not fully mature until approximately two weeks of age. Rat fever (leptospirosis) can also cause hepatic jaundice. In hepatic jaundice, there is invariably cholestasis<sup>10</sup>.

**3) Post-hepatic:**

*Post-hepatic* jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" can live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, cholangiocarcinoma, pancreatitis and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome. In complete obstruction of the bile duct, no urobilinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that bilirubin gets converted to urobilinogen to be later released into the general circulation. In this case, presence of bilirubin (conjugated) in the urine without urine-urobilinogen suggests obstructive jaundice, either intra-hepatic or post-hepatic. The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments. However, although pale stools and dark urine are a feature of biliary obstruction, they can occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice<sup>11</sup>.

**Pathophysiology of Jaundice:**

The pathological processes that cause jaundice to take their effect must be understood. Jaundice itself is not a disease, but rather a sign of one of many possible underlying pathological processes that occur at some point along the normal physiological pathway of the metabolism of bilirubin. When red blood cells have completed their life span of approximately 120 days, or when they are damaged, their membranes become fragile and prone to rupture. As each red blood cell traverses through the reticulo-endothelial system, its cell membrane ruptures when its membrane is fragile enough to allow this. Cellular contents, including hemoglobin, are subsequently released into the blood. The hemoglobin is phagocytosed by macrophages, and split into its heme and globin portions. The globin portion, a protein, is degraded into amino acids and plays no role in jaundice. Two reactions then take place with the heme molecule. The first oxidation reaction is catalyzed by the microsomal enzyme heme oxygenase and results in biliverdin (green color pigment), iron and carbon monoxide. The next step is the reduction of biliverdin to a yellow color tetrapyrrole pigment called bilirubin by cytosolic enzyme biliverdin reductase. This bilirubin is "unconjugated," "free" or "indirect" bilirubin. Approximately 4 mg of bilirubin per kg of blood is produced each day. The majority of this bilirubin comes from the breakdown of heme from expired red blood cells in the process just described. However approximately 20 percent comes from other heme sources, including ineffective erythropoiesis, and the breakdown of other heme-containing proteins, such as muscle myoglobin and cytochromes<sup>12</sup>.

**Hepatic events:**

The unconjugated bilirubin then travels to the liver through the bloodstream. Because this bilirubin is not soluble, however, it is transported through the blood bound to serum albumin. Once it arrives at the liver, it is conjugated with glucuronic acid (to form bilirubin diglucuronide, or just "conjugated bilirubin") to become more water soluble. The reaction is catalyzed by the enzyme UDP-glucuronyl transferase. This conjugated bilirubin is excreted from the liver into the biliary and cystic ducts as part of bile. Intestinal bacteria convert the bilirubin into urobilinogen. From here the urobilinogen can take two pathways. It can either be further converted into stercobilinogen, which is then oxidized to stercobilin and passed out in the feces, or it can be reabsorbed by the intestinal cells, transported in the blood to the kidneys, and passed out in the urine as the oxidized product urobilin. Stercobilin and urobilin are the products responsible for the coloration of feces and urine, respectively.

**CIRRHOSIS:**

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated) leading to loss of liver function. Cirrhosis is most commonly caused by alcoholism, hepatitis B and C, and fatty liver disease, but has many other possible causes. Some cases are idiopathic, i.e. of unknown cause. Ascites (fluid retention in the abdominal cavity) is the most common complication of cirrhosis, and is associated with a poor quality of life, increased risk of infection, and a poor long-term outcome. Other potentially life-threatening complications are hepatic encephalopathy (confusion and coma) and bleeding from esophageal varices. Cirrhosis is generally irreversible,

and treatment usually focuses on preventing progression and complications. In advanced stages of cirrhosis the only option is a liver transplant.

**Pathophysiology of cirrhosis:**

The liver plays a vital role in synthesis of proteins (e.g., albumin, clotting factors and complement), detoxification and storage (e.g., vitamin A). In addition, it participates in the metabolism of lipids and carbohydrates. Cirrhosis is often preceded by hepatitis and fatty liver (steatosis), independent of the cause. If the cause is removed at this stage, the changes are still fully reversible. The pathological hallmark of cirrhosis is the development of scar tissue that replaces normal parenchyma, blocking the portal flow of blood through the organ and disturbing normal function. Recent research shows the pivotal role of the stellate cell, a cell type that normally stores vitamin A, in the development of cirrhosis. Damage to the hepatic parenchyma leads to activation of the stellate cell, which becomes contractile (called myofibroblast) and obstructs blood flow in the circulation. In addition, it secretes TGF- $\beta_1$ , which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it secretes TIMP 1 and 2, naturally occurring inhibitors of matrix metallo proteinases, which prevents them from breaking down fibrotic material in the extracellular matrix. The fibrous tissue bands (septa) separate hepatocyte nodules, which eventually replace the entire liver architecture, leading to decreased blood flow throughout. The spleen becomes congested, which leads to hypersplenism and increased sequestration of platelets. Portal hypertension is responsible for most severe complications of cirrhosis<sup>13</sup>.

**HEPATITIS:**

**Hepatitis** (plural **hepatitides**) is a medical condition defined by the inflammation of the liver and 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 fibrosis (scarring) and cirrhosis. Hepatitis may occur with limited or no symptoms, but often leads to jaundice, anorexia (poor appetite) and malaise. Hepatitis is acute when it lasts less than six months and chronic when it persists longer. A group of viruses known as the hepatitis viruses cause most cases of hepatitis worldwide, but it can also be due to toxins (notably alcohol, certain medications, some industrial organic solvents and plants), other infections and autoimmune diseases<sup>14</sup>.

**Acute:**

Initial features are of nonspecific flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhoea, and headache. More specific symptoms, which can be present in acute hepatitis from any cause, are: profound loss of appetite, aversion to smoking among smokers, dark urine, yellowing of the eyes and skin (i.e., jaundice) and abdominal discomfort. Physical findings are usually minimal, apart from jaundice in a third and tender hepatomegaly (swelling of the liver) in about 10%. Some exhibit lymphadenopathy (enlarged lymph nodes, in 5%) or splenomegaly (enlargement of the spleen, in 5%). Acute viral hepatitis is more likely to be asymptomatic in younger people. Symptomatic individuals may present after convalescent stage of 7 to 10 days, with the total illness lasting 2 to 6 weeks. A small proportion of people with acute hepatitis progress to acute liver failure, in which the liver is unable to clear harmful substances from the circulation (leading to confusion and coma due to hepatic encephalopathy) and produce blood proteins (leading

to peripheral edema and bleeding). This may become life-threatening and occasionally requires a liver transplant<sup>15</sup>.

#### **Chronic:**

Chronic hepatitis often leads to nonspecific symptoms such as malaise, tiredness and weakness, and often leads to no symptoms at all. It is commonly identified on blood tests performed either for screening or to evaluate nonspecific symptoms. The occurrence of jaundice indicates advanced liver damage. On physical examination there may be enlargement of the liver. Extensive damage and scarring of liver (i.e. cirrhosis) leads to weight loss, easy bruising and bleeding tendencies, peripheral edema (swelling of the legs) and accumulation of ascites (fluid in the abdominal cavity). Eventually, cirrhosis may lead to various complications: esophageal varices (enlarged veins in the wall of the esophagus that can cause life-threatening bleeding) hepatic encephalopathy (confusion and coma) and hepatorenal syndrome (kidney dysfunction). Acne, abnormal menstruation, lung scarring, inflammation of the thyroid gland and kidneys may be present in women with autoimmune hepatitis<sup>16</sup>.

#### **Non-infection hepatitis-**

All types of inflammation are not bad. The hepatitis caused by alcohol or other toxic material, medication or chemicals is bad for liver and inflames it. Any immune related injury, a metabolic disorder and a genetic problem can result in hepatitis. Liver damage caused as a result of obesity can result in hepatitis. All these types of hepatitis are called non-infectious as they are bound to stay in the body of only one person and not transfer from one person to another.

#### **Infectious hepatitis:**

There are five mainstream types of infectious hepatitis (the hepatitis that can infect from one person to another) that are respectively caused by hepatitis virus A, hepatitis B, hepatitis virus C, hepatitis virus D, and hepatitis virus E where hepatitis virus X and hepatitis virus G also lead to hepatitis.

**Hepatitis A:** It is caused by water or food infected with the virus HAV (hepatitis A Virus). Whether oral or anal contact during sexual intercourse can also lead to the infection. The virus does not lead to chronic disease and almost everyone infected with HAV recovers.

**Hepatitis B:** It is a sexually transmitted disease and is caused by HBV (Hepatitis B Virus). The virus is acquired by contact with any body fluid such as infected blood or semen.

Liver of the infected person swells with HBV. Severe damage to the liver caused by the virus can result in liver cancer. Some patients of hepatitis B gets chronic, remains infected throughout their lives or for very long time. Donated blood must be tested for hepatitis before injecting into a patient. Hepatitis B is acquired by: Unprotected sex, without using condom, with the affect or by the use of a syringe that was already used by the infected patient (it usually happens in the case of drug addicts who exchange syringes and people who inject steroids). In case someone pricked in an accident or pierce his or her skin while making tattoos the virus enters the body if the needle or the surface is not sterilized. All those people who serve in health care projects are at risk of getting infected as a result of any accident. The exchange of toothbrush or razor can also spread the HBV. Milk of the infected mother can affect the baby. Bite of Hepatitis B patient can result in transferring HBV.

**Hepatitis C:** It is caused by the direct contact with the blood of infected person. It is caused by HCV (Hepatitis C Virus) that swells the liver and damages it afterwards. About 20 per

cent of hepatitis C patients get cirrhosis where all those people who acquire cirrhosis are at risk of developing liver cancer. Donated blood must be tested for HCV.

**Hepatitis D:** HDV (Hepatitis D Virus) affects only that person who is already suffering from HBV. Unprotected sexual intercourse, infected blood, and perforation of the skin are once again the causes. Swelling strikes to the liver of hepatitis D patient.

**Hepatitis E:** Water that contains HEV (Hepatitis E Virus) can infect the drinker. Swelling in the liver occur but without any serious consequences. Anal or oral sex is also considered to be a reason for the infection.

**Hepatitis X:** Any infection that is not coming under the category of any of the above viruses are name hepatitis X. Simply narrating it is the inflammation caused by an undiscovered or unknown virus.

**Hepatitis G:** Hepatitis caused by HGV (Hepatitis G Virus) is hepatitis G. Casually there are no signs or symptoms. In case there are symptoms then they are very mild.

#### **Pathophysiology of Hepatitis:**

The liver, like all organs, responds to injury in a limited number of ways and a number of patterns have been identified. Liver biopsies are rarely performed for acute hepatitis and because of this the histology of chronic hepatitis is better known than that of acute hepatitis.

#### **Acute:**

In acute hepatitis the lesions (areas of abnormal tissue) predominantly contain diffuse sinusoidal and portal mononuclear infiltrates (lymphocytes, plasma cells, Kupffer cells) and swollen hepatocytes. Acidophilic cells (Councilman bodies) are common. Hepatocyte regeneration and cholestasis (canalicular bile plugs) typically are present. Bridging hepatic necrosis (areas of necrosis connecting two or more portal tracts) may also occur. There may be some lobular disarray. Although aggregates of lymphocytes in portal zones may occur these are usually neither common nor prominent. The normal architecture is preserved. There is no evidence of fibrosis or cirrhosis (fibrosis plus regenerative nodules). In severe cases prominent hepatocellular necrosis around the central vein (zone 3) may be seen.

In submassive necrosis a rare presentation of acute hepatitis – there is widespread hepatocellular necrosis beginning in the centrilobular distribution and progressing towards portal tracts. The degree of parenchymal inflammation is variable and is proportional to duration of disease. Two distinct patterns of necrosis have been recognised: zonal coagulative necrosis or panlobular (nonzonal) necrosis. Numerous macrophages and lymphocytes are present. Necrosis and inflammation of the biliary tree occurs. Hyperplasia of the surviving biliary tract cells may be present. Stromal haemorrhage is common<sup>17</sup>.

#### **Chronic:**

Chronic active hepatitis was the term used to describe cases of hepatitis for more than 6 months with portal based inflammation, fibrosis, disruption of the terminal plate and piecemeal necrosis. This term has now been replaced by the diagnosis of 'chronic hepatitis with piecemeal (periportal) necrosis (or interface hepatitis) with or without fibrosis. Chronic persistent hepatitis was the term used to describe chronic hepatitis with no significant periportal necrosis or regeneration with a fairly dense mononuclear portal infiltrate. Councilman bodies are frequently seen within the lobule. This condition is now referred to as 'chronic hepatitis without piecemeal necrosis (or interface hepatitis). Chronic lobular hepatitis was the term used to describe chronic hepatitis with

persistent parenchymal focal hepatocyte necrosis (apoptosis) with mononuclear sinusoidal infiltrates. This is now referred to as 'chronic hepatitis without piecemeal necrosis (or interface hepatitis). These terms have since been deprecated. This was done because it was realised that these conditions could alter over time and what might have been regarded as a relatively benign lesion could still progress to cirrhosis. The simpler term 'chronic hepatitis' is now preferred in association with the causative agent (when known) and a grade based on the degree of inflammation, piecemeal or bridging necrosis (interface hepatitis) and the stage of fibrosis. Several grading systems have been proposed but none have been adopted universally. Cirrhosis is a diffuse process characterized by regenerative nodules that are separated from one another by bands of fibrosis. It is the end stage for many chronic liver diseases. The pathophysiological process that results in cirrhosis is as follows: hepatocytes are lost through a gradual process of hepatocellular injury and inflammation. This injury stimulates a regenerative response in the remaining hepatocytes. The fibrotic scars limit the extent to which the normal architecture can be reestablished as the scars isolate groups of hepatocytes. This results in nodules formation. Angiogenesis (new vessel formation) accompanies scar production which results in the formation of abnormal channels between the central hepatic veins and the portal vessels. This in turn causes shunting of blood around the regenerating parenchyma. Normal vascular structures including the sinusoidal channels may be obliterated by fibrotic tissue leading to portal hypertension. The overall reduction in hepatocyte mass, in conjunction with the portal blood shunting, prevents the liver from accomplishing its usual functions – the filtering of blood from the gastrointestinal tract and serum protein production. These changes give rise to the clinical manifestations of cirrhosis<sup>18</sup>.

#### **HEPATOCELLULAR CARCINOMA:**

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver cancer. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis). Liver cancer (hepatocellular carcinoma) is a cancer arising from the liver. It is also known as primary liver cancer or hepatoma. The liver is made up of different cell types (for example, bile ducts, blood vessels, and fat-storing cells). However, liver cells (hepatocytes) make up 80% of the liver tissue. Thus, the majority of primary liver cancers (over 90%-95%) arises from liver cells and is called hepatocellular cancer or carcinoma. Compared to other cancers, HCC is quite a rare tumor in the United States. In countries where hepatitis is not endemic, most malignant cancers in the liver are not primary HCC but metastasis (spread) of cancer from elsewhere in the body, e.g., the colon. Treatment options of HCC and prognosis are dependent on many factors but especially on tumor size and staging. Tumor grade is also important. High-grade tumors will have a poor prognosis, while low-grade tumors may go unnoticed for many years, as is the case in many other organs, such as the breast, where a ductal carcinoma in situ (or a lobular carcinoma in situ) may be present without any clinical signs and without correlate on routine imaging tests, although in some occasions it may be detected on more specialized imaging studies like MR mammography. HCC may present with jaundice, bloating from ascites, easy bruising from blood clotting abnormalities or as loss of appetite,

unintentional weight loss, abdominal pain, especially in the upper -right part, nausea, emesis, or fatigue<sup>19</sup>.

#### **Pathophysiology of Hepatocellular carcinoma:**

Hepatocellular carcinoma, like any other cancer, develops when there is a mutation to the cellular machinery that causes the cell to replicate at a higher rate and/or results in the cell avoiding apoptosis. In particular, chronic infections of hepatitis B and/or C can aid the development of hepatocellular carcinoma by repeatedly causing the body's own immune system to attack the liver cells, some of which are infected by the virus, others merely bystanders. While this constant cycle of damage followed by repair can lead to mistakes during repair which in turn lead to carcinogenesis, this hypothesis is more applicable, at present, to hepatitis C. Chronic hepatitis C causes HCC through the stage of cirrhosis. In chronic hepatitis B, however, the integration of the viral genome into infected cells can directly induce a non-cirrhotic liver to develop HCC. Alternatively, repeated consumption of large amounts of ethanol can have a similar effect. Besides, cirrhosis commonly caused by alcoholism, chronic hepatitis B and chronic hepatitis C. The toxin aflatoxin from certain *Aspergillus* species of fungus is a carcinogen and aids carcinogenesis of hepatocellular cancer by building up in the liver. The combined high prevalence of rates of aflatoxin and hepatitis B in settings like China and West Africa has led to relatively high rates of hepatocellular carcinoma in these regions. Other viral hepatitises such as hepatitis A have no potential to become a chronic infection and thus are not related to hepatocellular carcinoma.

#### **HEPATIC ENCEPHALOPATHY:**

**Hepatic encephalopathy** (also known as **portosystemic encephalopathy**) is the occurrence of confusion, altered level of consciousness and coma as a result of liver failure. In the advanced stages it is called **hepatic coma** or **coma hepaticum**. It may ultimately lead to death. It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver. The diagnosis of hepatic encephalopathy requires the presence of impaired liver function and the exclusion of an alternative explanation for the symptoms. Blood tests (ammonia levels) may assist in the diagnosis. Attacks are often precipitated by an intercurrent problem, such as infection or constipation. Hepatic encephalopathy is reversible with treatment. This relies on suppressing the production of the toxic substances in the intestine and is most commonly done with the laxative lactulose or with non-absorbable antibiotics. In addition, the treatment of any underlying condition may improve the symptoms. In particular settings, such as acute liver failure, the onset of encephalopathy may indicate the need for a liver transplant. Ammonia, which is produced by the body when proteins are digested, is one of the harmful substances that is normally made harmless by the liver. Many other substances may also build up in the body if the liver is not working well. They can cause damage to the nervous system. Hepatic encephalopathy may occur suddenly in people who previously had no liver problems when damage occurs to the liver<sup>20</sup>.

#### **Pathophysiology of Hepatic Encephalopathy:**

There are various explanations why liver dysfunction or portosystemic shunting might lead to encephalopathy. In healthy subjects, nitrogen-containing compounds from the intestine, generated by gut bacteria from food, are transported by the portal vein to the liver, where 80–90% is metabolised through the urea cycle and/or excreted

immediately. This process is impaired in all subtypes of hepatic encephalopathy, either because the hepatocytes (liver cells) are incapable of metabolising the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt. Nitrogenous waste products accumulate in the systemic circulation (hence the older term "portosystemic encephalopathy"). The most important waste product is ammonia ( $\text{NH}_3$ ). This small molecule crosses the blood-brain barrier and is absorbed and metabolised by the astrocytes, a population of cells in the brain that constitutes 30% of the cerebral cortex. Astrocytes use ammonia when synthesising glutamine from glutamate. The increased levels of glutamine lead to an increase in osmotic pressure in the astrocytes, which become swollen. There is increased activity of the inhibitory  $\gamma$ -aminobutyric acid (GABA) system, and the energy supply to other brain cells is decreased. This can be thought of as an example of brain oedema of the "cytotoxic" type<sup>21</sup>. Despite numerous studies demonstrating the central role of ammonia, ammonia levels don't always correlate with the severity of the encephalopathy; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low. Other waste products implicated in hepatic encephalopathy include mercaptans (substances containing a thiol group), short-chain fatty acids and phenol. Numerous other abnormalities have been described in hepatic encephalopathy, although their relative contribution to the disease state is uncertain. Benzodiazepine-like compounds have been detected at increased levels as well as abnormalities in the GABA neurotransmission system. An imbalance between aromatic amino acids (phenylalanine, tryptophan and tyrosine) and branched-chain amino acids (leucine, isoleucine and valine) has been described; this would lead to the generation of false neurotransmitters (such as octopamine and 2-hydroxyphenethylamine). Dysregulation of the serotonin system, too, has been reported. Depletion of zinc and accumulation of manganese may play a role. Inflammation elsewhere in the body may precipitate encephalopathy through the action of cytokines and bacterial lipopolysaccharide on astrocytes<sup>22</sup>.

#### DIFFERENT MODELS OF HEPATOTOXICITY

##### **$\text{CCl}_4$ induced hepatotoxicity:**

Carbon tetrachloride was formerly used for metal degreasing and as a dry-cleaning fluid, fabric-spotting fluid, fire-extinguisher fluid, grain fumigant and reaction medium. Carbon tetrachloride ( $\text{CCl}_4$ ) induced liver damage has been lengthily used as an experimental model.  $\text{CCl}_4$  is used as a model drug for the study of hepatotoxicity in acute and chronic liver failure.  $\text{CCl}_4$  is metabolized by CYP2E1, CYP2B and possibly CYP3A, to form the trichloromethyl radical,  $\text{CCl}_3$ . This  $\text{CCl}_3$  radical can bind to cellular molecules damaging crucial cellular progression. This radical can also react with oxygen to form the trichloromethylperoxy radical  $\text{CCl}_3\text{OO}$ , a highly reactive species. The metabolites of  $\text{CCl}_4$  cause the hepatic injury in the  $\text{CCl}_4$  liver injury model. Single dose of  $\text{CCl}_4$  to a rat produces centrilobular necrosis and fatty changes. The poison reaches its maximum concentration in the liver within 3 hrs of administration<sup>23</sup>. Dose of  $\text{CCl}_4$ : 1 ml/kg carbon tetrachloride, dissolve in olive oil 1 : 1 ratio, administered orally twice a week for over a period of 8 weeks. Dose of  $\text{CCl}_4$ : 0.1 to 3 ml/kg I.P. for a period of 7 days.  $\text{CCl}_4$  in liquid paraffin (30% v/v) 1 ml/kg. I.P. administered every 72 hours, for a period of 10 days.

Single dose of  $\text{CCl}_4$  (2.5 ml/kg body wt, diluted with equal volume of lipid paraffin; I.P.) to induce acute hepatotoxicity dose administered on 7 days.

##### **Thioacetamide induced hepatotoxicity:**

Thioacetamide has been used as an organic solvent in the leather, textile, and paper industries, as an accelerator in the vulcanization of buna rubber (synthetic polybutadiene), and as a stabilizer of motor fuel. Thioacetamide is an organosulfur compound. This white crystalline solid is soluble in water and serves as a source of sulfide ions in the synthesis of organic and inorganic compounds. It is a prototypical thioamide. Thioacetamide, a selective hepatotoxic within a short period of time after the administration of the drug. It experiences an extensive metabolism to acetamide and thioacetamide S-dioxide by the mixed function oxidase system. Acetamide does not have liver necrotizing properties while thioacetamide S-oxide is further metabolized to cytochrome P-450 mono oxygenase to sulfene, thioacetamide S-dioxide. The thioacetamide S-dioxide is a very extremely reactive compound. Thioacetamide is oxidized to a reactive metabolite that is further oxidized to thioacetamide S-dioxide, which covalently binds to liver, macromolecules and initiates liver injury. Mechanism of thioacetamide toxicity is due to the formation of thioacetamide S-oxide which is responsible for the amendment in cell permeability and the concentration of  $\text{Ca}^{++}$  increases intracellular in nuclear volume and also obstructs mitochondrial activity which leads to cell death<sup>24</sup>. Dose of Thioacetamide: 200 mg/kg body weight administered intraperitoneal twice weekly, for 8 weeks<sup>25</sup>. Dose of thioacetamide: 600 mg/kg body weight administered orally<sup>26</sup>.

##### **Galactosamine induced hepatotoxicity:**

D – Galactosamine (D-Gal) is a well-established hepatotoxicant, it induced a diffuse type of liver injury closely resembling human viral hepatitis and acute self-limiting hepatitis with necrosis, inflammation and regeneration, resembling a drug-induced disease in human. The toxicity of D-Gal is mainly related to the depletion of uridine pools that are associated with limited ribonucleic acid (RNA) and protein synthesis, thus altering hepatocellular function<sup>27</sup>. This mechanism of toxicity increases in cell membrane porosity leading to cell death. Galactosamine decreases the bile flow and it's gratified i.e. bile salts, cholic acid and deoxycholic acid. Dose of D-galactosamine: 400 mg/kg, I.P.<sup>28</sup>. Single Dose of Galactosamine 800 mg/kg I.P. administered on 21st day of experiment<sup>29</sup>. Dose of Galactosamine 500 mg/kg i.p. three times weekly for over a period of one to 3 months<sup>30</sup>.

##### **Alcohol induced hepatotoxicity:**

Liver is among the organs most susceptible to the toxic effects of ethanol. Alcohol consumption is known to cause fatty infiltration, hepatitis and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Hepatitis and cirrhosis may occur because of enhanced lipid peroxidative reaction during the microsomal metabolism of ethanol. It is generally accepted that alcohol can induce *in vivo* changes in membrane lipid composition and fluidity, which may eventually affect cellular functions. Among the mechanisms responsible for effects of alcohol, an increase in hepatic lipid peroxidation leads to alteration in membrane phospholipid composition. The effects of ethanol have been suggested to be a result of the enhanced generation of oxygen free radicals during its oxidation in liver. The peroxidation of membrane

lipids results in loss of membrane structure and integrity. This results in elevated levels of glutamyl transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decrease the activity of catalase, superoxide dismutase, along with increase in levels of glutathione in liver. The decrease in activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol. Alcohol pre-treatment stimulates the toxicity of  $\text{CCl}_4$  due to increased production of toxic reactive metabolites of  $\text{CCl}_4$ , namely tri chloro-methyl radical by the microsomal mixed function oxidative system. This activated radical binds covalently to the macromolecules and induces peroxidative degradation of membrane lipids of endoplasmic reticulum rich in polyunsaturated fatty acids. This lipid peroxidative degradation of biomembranes is the principle cause of hepatotoxicity<sup>31</sup>. Dose of ethanol 20% ethanol (7.5g/kg body wt, 5 ml in the forenoon and 5ml in the afternoon; oral) for six month. Dose of ethanol: 3g/kg body weight, 30%v/v; p.o, for 20 days<sup>32</sup>. The initial dose of ethanol was 6g.kg-1.day-1 (solutions maximally containing 56% alcohol), and the dose was progressively increased during week 1 to a maintenance dose of 8 g/kg/day that was continued for 5 more weeks<sup>33</sup>.

#### **Paracetamol induced hepatotoxicity:**

Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl- P-benzoquinoneimine, an oxidative product of Paracetamol to sulphhydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver. Dose of Paracetamol 1mg/kg p.o<sup>34</sup>. Single Dose of Paracetamol 3 g/kg p.o administrated on 10<sup>th</sup> day of experiment<sup>35</sup>. Single dose of Paracetamol 2g/kg p.o administrated on 5<sup>th</sup> day of experiment<sup>36</sup>. Single dose of Paracetamol, 3g/kg p.o. administrated on 3<sup>rd</sup> day of experiment<sup>37</sup>.

#### **Lithocholic acid induced hepatotoxicity:**

The mechanism of hepatobiliary injury in the lithocholic acid progressively used model of cholestatic liver injury. The etiology of LCA induced cholestasis in rat include biochemical alterations of the bile canaliculi membrane. Due to the poor solubility of LCA the crystalline plugs develop in bile canaliculi and impaired transferring. Administration of LCA can outcome in hepatocellular necrosis with significant reductions in basolateral bile acid uptake (Ntcp,Oatp1) and sinusoidal bile acid efflux transporters (Mrp3) increased. These changes in the liver represent an inherent toxicity of accumulating bile acids. Dose of lithocholic acid: single dose of 4 $\mu\text{mol}/100\text{g}$  body wt, administrated intravenously<sup>38</sup>.

#### **Antimicrobial drug induced hepatotoxicity:**

Drug induced hepatotoxicity is a potentially serious adverse effect of the currently used antitubercular therapeutic regimens containing Isoniazid (INH), Rifampicin and Pyrazinamide. Adverse effects of antitubercular therapy are sometimes potentiated by multiple drug regimen. Thus, though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is enhanced. INH is metabolized to monoacetyl

hydrazine, which is further metabolized to a toxic product by cytochrome  $\text{P}_{450}$  leading to hepatotoxicity. Patients on concurrent rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to rifampicin-induced cytochrome  $\text{P}_{450}$  enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half life of AcHz (metabolite of INH) is shortened by rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and rifampicin in combination. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. Pharmacokinetic interactions exist between rifampicin and pyrazinamide in tuberculosis patients, when these drugs are administered concomitantly. Pyrazinamide decrease the blood level of rifampicin by decreasing its bioavailability and increasing its clearance. Pyrazinamide, in combination with INH and rifampicin, appears to be associated with an increased incidence of hepatotoxicity<sup>39</sup>. Dose of antitubercular drug (Isoniazid 7.5mg/kg, rifampicin 10mg/kg, pyrazinamide 35 mg/kg, p.o.) for 2 weeks<sup>40</sup>. Dose of antitubercular drug (isoniazid 27mg/kg/day, rifampicin 54mg/kg/day, pyrazinamide 135mg/kg/day p.o.) administrated for 30 days, dose extrapolated from daily human dose using the conversion table based on body surface area<sup>41</sup>. Dose of antitubercular drug (isoniazid and rifampicin 200mg each/kg body weight/day, p.o.) for 45 days.

#### **Azathioprine induced hepatotoxicity:**

AZA is an important drug used in the therapy of autoimmune disorder and in preventing graft rejection. The nitro-conjugated double bond of imidazole ring of AZA is a Michael acceptor. AZA is cleaved in vitro to 6-MP non enzymatically by a nucleophilic attack of sulphhydryl groups primarily GSH, on the b carbon in the activated double bond. AZA toxicity to rat hepatocytes was preceded by depletion of GSH. Prior GSH depletion enhanced toxicity while supplemental GSH was protective. In hepatocytes GSH is consumed during metabolism of AZA to 6-MP. The mechanism of AZA toxicity to mitochondrial injury with profound depletion of ATP and cell death by necrosis. Lipid peroxidation as well as altered levels of some endogenous scavengers are taken as indirect in vivo reliable indices for the contribution of free radical generation and in turn oxidative stress<sup>42</sup>.

#### **Ranitidine induced hepatotoxicity :**

Liver injury induced by ranitidine is due to its metabolite which may leads to hepatic oxidative damage and one of its metabolite is generating immunoallergic reaction. It also produces a reaction as reflected by infiltration of hepatocytes with ranitidine dose of either 50 or 30 mg/kg. Severe inflammatory changes with collagenous septa beginning to form after pronounced centrilobular and bridging necrosis in the parenchyma there was focal liver cell necrosis with some accumulation of histocytic elements and slight steatosis and cholestasis. Portal tract shows fibrosis, bile duct proliferation and infiltrate consisting of lymphocytes, plasma cells, polymorphs and eosinophils. Liver injury is manifested in terms of increase in levels of serum aminotransferases, modest hepatic infiltration by both lymphocytes and eosinophils and slight focal hepatocellular necrosis also causes liver cholestasis associated with increased plasma bilirubin and alkaline phosphatase<sup>43</sup>.

**Mercury induced hepatotoxicity:**

Human activities play a major role in polluting the environment by toxic and carcinogenic metal compounds. These are evidences that these metals by accumulating contaminate waters sources and food chain with their compounds. Mercury and its compounds are widely used in industries and their hazards to animals have been documented. Mercury is a transition metal and it promotes the formation of reactive oxygen species (ROS) such as hydrogen peroxides. These ROS enhance the peroxides and hydroxyl radicals. These lipid peroxides and hydroxyl radical may cause cell membrane damage and thus destroy the cell. Mercury also inhibits the activities of free radical quenching enzyme such as catalase, superoxide dismutase and glutathione peroxidase. Mercury causes cell membrane damage like lipid peroxidation which leads to the imbalance between synthesis and degradation of enzyme protein. The excess production of ROS by mercury may be explained by its ability to produce alteration in mitochondria by blocking the permeability transition pore<sup>44</sup>. Dose of mercuric chloride : 5mg/kg body weight, through intra peritoneal injection for twenty days. Mercuric chloride dose: 2mg/kg body weight, administrated orally for thirty days<sup>45</sup>.

**Lead induced hepatotoxicity :**

Many metals play important roles in the functioning of enzyme, cell-signaling processes and gene regulation. Lead is a blue-gray and highly toxic divalent metal that occurs naturally in the earth's crust and is spread throughout the environment by various human activities. Lead induced hepatic damage is mostly rooted in lipid peroxidation (LPO) and disturbance of the prooxidant antioxidant balance by generation of reactive oxygen species (ROS)<sup>46</sup>. Lead toxicity lead to free radical damage by two separate pathway: (1) generation of ROS, including hydroperoxides, singlet oxygen, and hydrogen peroxide and (2) the direct depletion of antioxidant reserves. The cell membrane is the main target of the oxidative damage produced by heavy metals. This is mainly due to changes in polyunsaturated fatty acids having double bonds, largely present in the phospholipids of membranes. Lead is known to produce oxidative damage by enhancing peroxidation of membrane lipids, and LPO is a deleterious process carried out by free radicals. LPO is an outcome of the chain of events involving initiation, propagation, and termination reactions. GSH depletion is another important mechanism of lead toxicity. GSH is a tripeptide –containing cysteine with a reactive –SH group and reductive potency. It can act as a non-enzymatic antioxidant by direct interaction of the –SH group with ROS, or it can be involved in the enzymatic detoxification reaction for ROS as a cofactor or a coenzyme. Lead bind exclusively to the –SH group, which decreases the GSH level and can interfere with the antioxidant activity of GSH<sup>47</sup>. Oral treatment with lead nitrate at a dose of 50mg/kg body weight daily for 40 days<sup>48</sup>.

**Bromobenzene induced hepatotoxicity:**

Bromobenzene (BB), an industrial solvent and an additive in motor oils, causes necrosis in liver. Bromobenzene is subjected to biotransformation in the liver and metabolites of BB are highly hepatotoxic. Bromobenzene is hydrolyzed by cytochrome p450 monooxygenases (CYPs), and inhibitors of CYPs were found to decrease the hepatotoxicity. CYPs mediated epoxidation yields the highly electrophilic BB 3,4-epoxide. The irreversible binding of this of this very reactive metabolite to proteins like glutathione S-transferase (GST), liver fatty acid binding proteins (L-FABP), carbonic anhydrase, is highly correlated to pathological effect. The

alternative, more stable, BB 2,3-epoxide was found to covalently bind soluble protein like haemoglobin. Drug metabolizing GSTs catalyze the sequestration of the reactive epoxides through conjugation to glutathione. The level of glutathione (GSH) conjugates excreted in the bile correlated with the BB dosage and the hepatotoxic effects. The epoxides are also hydrolyzed by the microsomal epoxide hydrolase and CYPs. The resulting bromophenols can be oxidized to hydroquinones and conjugated to GSH. At high doses, conjugation to the metabolites depletes the hepatic GSH pool, and the intracellular protection against reactive oxygen species (ROS) and hazardous xenobiotic metabolites is lost. This lead to a number of secondary events that damage the cell, like lipid peroxidation, ATP depletion, mitochondrial dysfunction, energy imbalance, and altered intracellular calcium levels<sup>49</sup>. Dose of bromobenzene (0.5, 2.0 and 5.0mmole/kg body weight, dissolved in corn oil, 40%v/v) administered orally for 10 – 12 weeks<sup>50</sup>.

**CONCLUSION**

Hepatotoxicity implies chemical-driven liver damage. There are many chemical agents that cause hepatotoxicity and these agents called hepatotoxins. These cause hepatotoxicity by the generation of free radicals and damage the liver cells and causes of many liver diseases. Mechanism of action of different chemical agents that cause liver damage and related liver diseases are discuss in this article.

**REFERENCES:**

- Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davron JT, Steven HB, Timothy M and Reish J. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002; 137: 947–954
- Ahsan, M.R, K.M. Islam, I.J. Bulbul, M.A. Musaddik and E. Haque .Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride-induced hepatotoxicity in rats. *Eur. J. Sci. Res.* 2009; 37: 302-310.
- Patel T, Roberts L. R, Jones B. A. and Gores G. J. Dysregulation of apoptosis as a mechanism of liver disease: an overview. *Semin. Liver Dis.* 1998; 18: 105-114.
- Krinsky NI, Mathews-Roth MM, Welankiwar S, Sehgal PK, Lausen NCG and Russett M .The metabolism of [14 C]β-carotene and the presence of other carotenoids in rats and monkeys. *J Nutr.* 1990; 120: 81-87.
- Kmiec Z (2001). "Cooperation of liver cells in health and disease". *Adv Anat Embryol Cell Biol* 161: III–XIII, 1–151.
- Friedman scott E, Grendell James h, McQuaid, Kenneth R. Current diagnosis & treatment in gastroenterology. New York: lang medical book/ mcgraw-hill.2008; Pp. 664-679.
- Reddy JK, Rao MS. "Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation". *Am. J. Physiol. Gastrointest. Liver Physiol.* 2006; 290: 852–8.
- Goldman, Lee. Cecil Textbook of Medicine -- 2-Volume Set, Text with Continually Updated Online Reference. Philadelphia: W.B. Saunders Company; 2003.
- Carotenemia, Author: Robert A Schwartz, MD, MPH; Chief Editor: Dirk M Elston.
- Collier J, Longore M, Turmezei T, Mafi AR. "Neonatal jaundice". *Oxford Handbook of Clinical Specialties.* Oxford University Press; 2010.
- O'Keefe, Lori. "Increased vigilance needed to prevent kernicterus in newborns". *American Academy of Pediatrics*; 2001; 18 : 231.
- Pashankar D, Schreiber RA. "Jaundice in older children and adolescents". *Pediatrics in Review*; 2001; 22: 219–226.
- Iredale JP. "Cirrhosis: new research provides a basis for rational and targeted treatments". *BMJ*; 2001; 327: 143–147.
- K. Sembulingam, prema sembulingam. Liver and Gallblader, chapter 40 In: essentials of medical physiology, 3<sup>rd</sup> edition, jaypee brothers medical publishers (p)ltd: new delhi;2004. page no.200-201.
- Bain VG, Ma M. "Ch. 14: Acute Viral Hepatitis". *First principle of gastroenterology.*
- Chronic hepatitis at Merck Manual of Diagnosis and Therapy Home Edition.
- Nakanuma Y, Sasaki M, Terada T, Harada K. "Intrahepatic peribiliary glands of humans. II. Pathological spectrum". *J. Gastroenterol. Hepatol.* 1994; 9 (1): 80–6.

18. Gastroenterology IWPotWCo. "Terminology of chronic hepatitis, hepatic allograft rejection, and nodular lesions of the liver: summary of recommendations developed by an international working party, supported by the World Congresses of Gastroenterology, Los Angeles, 1994". *Am. J. Gastroenterol.*1994; **89**: S177-81.
19. Chien-Jen Chen, Hwai-I. Yang, Jun Su, Chin-Lan Jen, San-Lin You, Sheng-Nan Lu, Guan-Tarn Huang, Uchenna H. Iloeje. "Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level". *JAMA.* 2006; 295: 65-73.
20. Polson J, Lee WM."AASLD position paper: the management of acute liver failure". *Hepatology.*2005; 41: 1179-97.
21. Ryan JM, Shawcross DL. "Hepatic encephalopathy". *Medicine.*2011; 39: 617-620.
22. Sundaram V, Shaikh OS. "Hepatic encephalopathy: pathophysiology and emerging therapies". *Med. Clin. North Am.*2009; **93**: 819-36.
23. Dawkins MJ. Carbon tetrachloride poisoning in the liver of the new born rat. *J.path.bact.*1963; 85:189.
24. Ambrose A.M, DeEds F, Rather L.J. further studies on toxicity of thioacetamide in rats. *Proc. Soc. Exp. Boil. Med* 1950; 74: 134-140.
25. Predrag L, Hui S, Uri C, Hassan A, Arie B. The effects of aqueous extracts prepared from the leaves of *Pastacia lentiscus* in experimental liver disease. *J Ethnopharmacol.* 2005;100: 198-204.
26. Minnady Muthulingam, Paulraj Dominic Savio, Thomas Sathanantha Seeli, Natarajan Indra and Subramanian Sethupathy. Therapeutic role of edible mushroom *Pleurotus florida* (Mont.) on thioacetamide induced hepatotoxicity in rats. *International journal of current issue* 2010;5: 041-046.
27. Keppler DO, paush J, decker K. effect on ribonucleic acid synthesis: selective uridine triphosphate deficiency induced by D- galactosamine in liver and reversed by pyrimidine nucleotide precursors. *J. boil. Chem.* 1974; 249: 211-216.
28. Saraswat B, visen PK, dayal R, Agarwal DP, patnaik GK. Protective action of ursolic acid against chemical induced hepatotoxicity in rats. *Ind. J. pharmacol* 1996; 28:232-237.
29. Madro A, Kurzepa J, Czechowska G, Słomka M, Celiński K, Szymonik-Lesiuk S. Erythropoietin inhibits liver gelatinases during galactosamine-induced hepatic damage in rats. *Pharmacol Rep.* 2009; 61:917-2
30. Vogel H. Gerhard. Activity on gastrointestinal tract. *Drug Discovery and Evaluation: Pharmacological Assays.* page 944.
31. A Pandey, P Bigoniya, V Raj, KK Patel. Pharmacological screening of *Coriandrum sativum* Linn. for hepatoprotective activity. *J Pharm Bioall Sci* 2011;3:435-41.
32. Sandhir R and Gill KD. Hepatoprotective effects of Liv-52 on ethanol induced liver damage in rats. *Ind. J. Expt. Biol.* 1999; 37:762-66.
33. Kapur V, Pillai KK, Hussain SZ and Balani DK. Hepatoprotective activity of Jigrine on liver damage caused by alcohol-carbon tetrachloride and paracetamol in rats. *Ind. J. Pharmacol.* 1994; 26:35-40
34. J. de Vries J. de Jong, F.M. Lock, L. van Bree, H. Mullink, R.W. Veldhuizen Protection against paracetamol-induced hepatotoxicity by acetylsalicylic acid in rats. *Toxicology.*1984; 30: 297-304.
35. Kapur V, Pillai KK, Hussain SZ and Balani DK. Hepatoprotective activity of Jigrine on liver damage caused by alcohol-carbon tetrachloride and paracetamol in rats. *Ind. J. Pharmacol.* 1994; 26:35-40.
36. Handa SS and Sharma A. Hepatoprotective activity of *Andrographolide* from *Andrographis paniculata* against CCl<sub>4</sub>. *Ind. J. Med. Res.* 1990; 92: 276-92.
37. Kakis G, Phillips MJ, yousef IM. The respective roles of membrane cholesterol and of sodium potassium adenosine triphosphatase in the pathogenesis of lithocholate induced cholestasis. *Lab invest.* 1980; 43: 73-81.
38. Bonvicini F, gautier A, gardiol D, borel GA. Cholesterol in acute cholestasis induced by tauroolithocholic acid: a cytochemical study in transmission and scanning electron microscopy. *Lab invest.* 1978; 38: 487-495.
39. Padma VV, Suja V, Shyamala DCS and Prema. Hepatoprotective effect of Liv-52 on antitubercular drug-induced hepatotoxicity in rats. *Fitoterapia.* 1998; 69: 520-22.
40. Kabutarwala, Divyang N. Evaluation of antioxidant and hepatoprotective effect of herbal formulations. *Dspace.*2010.
41. Mudgal A K, Razvi S U, Jugalkishor B J, AND Mateenuddin MD. Effect of the antioxidant alpha – tocopherol acetate and sodium selenite on hepatotoxicity induced by antitubercular drugs in rats. *Indian j physiol Pharmacol.* 2004; 48:119-122.
42. M raza, M ahmad, A gado, OA AL- shabanah. A comparison of hepatoprotective activities of amino guanidine and N- acetyl cysteine in rats against the toxic damage induced by azathioprine. *Comparative biochem physiol* 2003; 134: 451-456.
43. Hemieda faried AE, abdel hady E1- sayed. Biochemical and histological studies on H2- receptor antagonist ranitidine – induced hepatotoxicity in rats. *Ind J Exp Bio* 2005;43: 782-785.
44. Nilcolli, A, E. Basso, V. Petronilli, R.M. Wenger and P. Bernard: interaction of cyclophilin with the mitochondrial inner membrane and regulation of the permeability transition pore and cyclosporine A-sensitive channel. *J. Boil .chem.*1995; 271: 2185-2192.
45. Jagadeesan. G and Sankarsami Pillai.S. Hepatoprotective effects of taurine against mercury induced toxicity in rats. *Journal of Environmental Biology.* October 2007; 28: 753-756.
46. Gurer H, ercal N. Can antioxidants be beneficial in the treatment of lead poisoning? *Free radic boil med.* 2000; 29:927-45.
47. Gurer H, ozgunes H, neal R, spitz DR, ercal N. Antioxidant effect of N-acetylcysteine and succimer in red blood cells from lead exposed rats. *Toxicology* 1998; 181-189.
48. Sharma A, Sharma V, Kansal L. Amelioration of lead-induced hepatotoxicity by *Allium sativum* extracts in Swiss albino mice. *Libyan J Med.* 2010;7:5-10.
49. Locke, S.J., and brauer, M. The response of the rat liver in situ to bromobenzene in vivo proton magnetic resonance imaging and 31P magnetic resonance spectroscopy studies. *Toxicol. Appl. Pharmacol.*1991; 110: 416-428.
50. Wang, B.H., Zuzel, K.A., Rahman, K., and billington, D. Protective effect of aged garlic extract against bromobenzene toxicity to precision cut rat liver slices. *Toxicology.*1998; 126: 213-222.