Hepatoprotective activity of Natural Products
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ABSTRACT
India is the most eminent in production of medicinal plants or natural products. About 45,000 plant species are available widely, among them several thousand plants are used for many treatments. With the advancements in science and technology wide range of synthetic drugs came into existences. There may be huge advantages and contains some life threatening disadvantages in those drugs. Since from several decades existing in the use of traditional medicine. Advancements in investigations of medicinal plants and formulating the crude drugs become important.

Liver is main essential organ system in the body. It purifies and eliminates the unnecessary material through urine. So it cases more stress to the liver and gets damages due toxin substances. By using medicinal plants can tremendously cure the hepatotoxicity. While using the chemical or synthetic drugs, may cure but causes severe adverse effects. Hence utilizing the medicinal plants, we can achieve the treatment in Hepatoprotective and minimize the adverse effects.

INTRODUCTION
Liver is that the key organ control equilibrium within the body. It’s committed the majority the organic chemistry pathways associated with growth, fight against illness, nutrient offer, energy production and replica. Attributable to its distinctive metabolism and relationship to the digestive tube, the liver is a vital target of the toxicity of medicine, xenobiotic and aerophilous stresses [1, 5]. Over 900 medicine, toxins and herbs are according to cause liver injury and medicines account for two hundredth - four-hundredth of all instances of sudden liver failure. Within the absence of reliable liver protection medicine in trendy drugs, an oversized range of healthful preparations square measure measure suggested for the treatment of liver disorders and very often claimed to supply important relief [6-10]. Makes an attempt square measure being created globally to induce scientific evidences for this historically according flavoring medicine. This situation proves a severe necessity to hold out analysis works associated with hepatotoxicity [11-14].

Aerophilous stress has been known to be the most important explanation for hepatotoxicity that provides that plants with anti-oxidant chemical constituents would be helpful during this regard. Plants have many natural substances, flavonoids, terpinoids and other substituents [15-18]. They can be widely curing the toxicity. Anciently Ayurveda treatment has the milestone, with the many formulations of natural products changes and existence of life span of ancient people [19-21].
Liver is the largest internal organ in the human body and is very much essential for survival. It is the biggest reticulo-endothelial organ in the body which maintains the survival of individual [22-25].

ii. Anatomy

It is the largest gland of the body enclosed within the right lower rib cage beneath the diaphragm. The liver is a soft, pinkish brown triangular organ that normally weighs between 1.4 – 1.6 kg (Robbins, 2007). Liver is divided in two principle lobes, a large right lobe and a smaller left lobe separated by falciform ligament [26-29]. The right lobe is considered by many anatomists to include an inferior quadrate lobe and a posterior caudate lobe [30-34].

iii. Structure:

The lobes of liver are made up of many functional units called lobules. A lobule consists of specialized epithelial cells called hepatic cells or hepatocytes arranged in irregular, branching, interconnected plates around the central vein [35-39]. Rather than capillaries liver has larger space lined by endothelium called sinusoids through which blood passes. The sinusoids are also partly lined with stellate reticuloendothelial (Kupffer’s) cells. These phagocytes destroy worn out white and red blood cells, bacteria and toxic substances [40-45].

Figure 1: Anatomy of Liver (Image Courtesy: http://www.shutterstock.com/s/liver/search.html )

FUNCTIONS OF LIVER

i. Secretion and excretion of bile:

The hepatic cells secrete 800-1000 ml of bile, a yellow, brownish or olive green liquid of pH 7.6-8.6. Bile is partially an excretory product and partially a digestive secretion. The principle bile pigment is bilirubin. Bile mainly consists of water, bile salts, cholesterol, lecithin, bile pigments, and several ions [46-49].

ii. Metabolic functions:
**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 converts amino acid and lactic acid to glucose (gluconeogenesis) when sugar level is low [50-54].

**Lipid metabolism:**

Liver stores some triglycerides (neutral fat) and breaks 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, cholesterol and uses cholesterol to make bile salts [55-58].

**Protein metabolism:**

The liver deaminates (remove the amino group, NH2) amino acids so that they can be used for ATP production. It converts the resulting toxic ammonia (NH3) into much less toxic urea for excretion in urine. Hepatic cells synthesize plasma proteins such as alpha and beta globulins, albumin, prothrombin, and fibrinogen [59-62].

**Drug metabolism:**

Liver plays a vital role in biotransformation of drugs. It converts drug molecules from non-polar to polar. These non-polar drugs can be conjugated with more polar compounds, which make them water soluble for the urinary excretion [63-67].

**PATTERNS OF HEPATIC INJURY**

There many cases of injuries in liver, some are mentioned as below.

i. **Damage and intra cellular accumulation:**

   Damage from toxic and immunologic insult may cause swelling of hepatocytes. In cholestasis liver injury, retained biliary matter may impart a diffuse foamy appearance to the swollen hepatocytes (feathery degeneration). Accumulation occurs in viable hepatocytes, which include iron and copper the accumulation of triglycerides within the hepatocytes is called as steatosis [68-71].

ii. **Necrosis and apoptosis:**

   Any significant insult to the liver can cause hepatocyte necrosis. In apoptotic cell death, isolated hepatocytes round up to form shrunken, pyknotic, and intensely eosinophilic cells containing fragmented nuclei. Hepatocytes may also osmotically swell and rupture, it is called lytic necrosis [72-76].

   Necrosis frequently exhibits a zonal distribution. The most common is necrosis of hepatocytes immediately around the terminal hepatic vein, an injury that is characteristic of ischemic injury and a number of drug and toxic reactions [77-79].

**Inflammation:**
Injury to the liver associated with the acute or chronic inflammatory cells is termed hepatitis. In viral hepatitis, quiescent lymphocytes may collect in portal tracts as a reflection of mild inflammation; spill over into the perioral parenchyma as activated lymphocytes causing a moderately active hepatitis [80-84].

**Regeneration:**

Hepatocytes have long life spans, and they proliferate in response to tissue resection or cell death. Hepatocellular proliferation is marked by mitosis, thickening of the hepatocyte cords, and some disorganization of the parenchymal structure [85-89].

**Fibrosis:**

Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver. Fibrosis is generally irreversible hepatic damage. Deposition of collagen has lasting consequences on patterns of hepatic blood flow and perfusion of hepatocytes. In the initial stages fibrosis may develop around portal tracts or they may be directly deposited within the space. With continuing fibrosis the liver is subdivided into nodules of proliferating hepatocytes surrounded by scar tissue called “cirrhosis” [90-92].

**LIVER DISEASES**

i. **Hepatic failure:**

The most severe clinical consequence of liver disease is hepatic failure. It forms into three main categories:

**Massive hepatic necrosis:**

Acetaminophen, anti-tubercular drugs, anti-depressant, and industrial chemicals such as carbon tetrachloride and poisoning drugs collectively tend the Massive Hepatic necrosis [93]. The mechanism may be direct toxic damage to hepatocytes but more often is a variable combination of toxicity and inflammation with immune mediated hepatocytes destruction [94-96].

**Chronic liver disease:**

This is the most common route to hepatic failure and is the end point of relentless chronic hepatitis ending in cirrhosis.

**Hepatic dysfunction without overt necrosis:**

It causes Reye’s syndrome, tetracycline toxicity, and acute fatty liver of pregnancy.

**Clinical features:**

The clinical signs of hepatic failure include jaundice, hypoalbuminemia, hyperammonemia, fetor hepaticas, impaired estrogenic metabolism and consequent hyperestrogenemia leading to palmar erythema and spider angioma. In males, hyperestrogenemia may lead to hypogonadism and gynaecomastia. Hepatic failure is life threatening and cause multiple organ damages. Respiratory failure
with pneumonia and sepsis combine with renal failure to claim the lives of many patients with hepatic failure.

Cirrhosis:

Cirrhosis is the serious condition, causes death in top countries with the ranking of 10. It is mainly due to alcohol and viral hepatitis. Cirrhosis as the end-stage of chronic liver disease is defined by three characteristics.

Portal hypertension:

Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into prehepatic, intrahepatic and posthepatic causes. The major prehepatic conditions are obstructive thrombosis and narrowing of the portal vein before it ramifies within the liver. The major post hepatic causes are severe right sided heart failure, constrictive pericarditis and hepatic vein outflow obstruction. The dominant intrahepatic cause is cirrhosis, accounting for most cases of hypertension.

Jaundice:

Jaundice is characterized by the yellow coloration of the skin and sclerae due to the retention of pigmented bilirubin, and as cholestasis characterized by systemic retention of not only bilirubin but also other solutes eliminated in bile.

Cholestasis:

Cholestatic conditions which result from hepatocellular dysfunction or intrahepatic or extrahepatic biliary obstruction also may present with jaundice. Pruritis is a presenting symptom related to the elevation in plasma bile acids and their deposition in peripheral tissues particularly skin. Skin xanthomas sometimes vitamins A, D or K improve the results.

Infectious disorders:

Viral hepatitis:

Appear as the result of hyperlipidemia and impaired excretion of cholesterol. Vitamin supplements like Viral hepatitis caused by group of virus having a particular affinity to the liver. These include Infectious mononucleosis, Cytomegalovirus and Yellow fever

Autoimmune hepatitis:

Autoimmune hepatitis is a chronic hepatitis that produce Female predominance particularly in young and postmenopausal problems in women, absence of viral serological marker, Elevated serum IgG and γ-globulin levels, High serum titers of autoantibodies including antinuclear (ANA), antismooth muscle (SMA) and antiliver/kidney microsome antibodies (anti-LKMI)b and Negative antimitochondrial antibody.

Alcoholic liver disease:

Excessive alcohol consumption is the major cause of liver diseases in most developing and developed countries.
**Metabolic liver diseases:**

These include Nonalcoholic fatty liver disease and steatohepatitis, Hemochromatosis, Wilson’s disease, α1-Antitrypsin deficiency and Neonatal cholestasis.

**Intrahepatic biliary tract diseases:**

These include Primary biliary cirrhosis, which is a chronic, progressive, and often fatal cholestatic liver disease characterized by the destruction of intrahepatic bile ducts, portal inflammation and scarring, and the eventual development of cirrhosis and liver failure.

Primary sclerosing cholangitis that is characterized by the inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments[^97-98].

**Hepatic disease associated with pregnancy:**

i. Maternal hypertension, proteinuria, peripheral edema, coagulation abnormalities and varying degrees of disseminated intravascular coagulation

ii. Acute fatty liver of pregnancy which exhibits subclinical hepatic dysfunction to hepatic failure, coma and death.

iii. Intrahepatic cholestasis of pregnancy characterized by pruritis in the third trimester followed by the darkening of urine and occasionally light stools and jaundice.

**Nodules and tumors:**

Hepatic masses may come to attention for a variety of reasons. These include Nodular hyperplasia, benign neoplasms, malignant tumors, Hepatocellular carcinoma, Cholangiocarcinoma and Metastatic tumors.

**Life threatening complications:**

Hepatic failure include multiple organ failure, coagulopathy, hepatic encephalopathy, hepatorenal syndrome rupture Malignancy with chronic disease include hepatocellular carcinoma

**CONCLUSION**

Liver plays a major role in detoxification and excretion of many endogenous and exogenous compounds, any injury or impairment of its function may lead to several implications on one’s health. In treating the hepatoprotective activity many significant medicinal plant extracts are tremendously cure the liver diseases. With the medicinal plant treatment we can reduce the adverse effects of the drugs, as these drugs are naturally available, these may not cause toxicity. Prolong use of medicinal plants may causes some toxicity, but we can cure or minimize the side effects. The drugs Tetracycline, Salicylates, ethanolic agents may causes hepatotoxicity and various adverse effects, comparatively by using medicinal plants may not cause any injury to tissues and other organs.
REFERENCES


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