Introduction

The liver is the largest abdominal organ. The liver has the final form of a prism or wedge, with its base to the proper and its apex to the left .It is pink brown in color, with a soft consistency, and is extremely vascular and simply friable. The liver carries out several vital functions, like creating vital blood proteins and digestive juice, dynamic food into energy, and cleansing alcohol and poisons from the blood.Liver disease is transmissible (genetic) or caused by a range of things that harm the liver, like viruses and alcohol use. fatness is additionally related to liver damage.Over time, damage to the liver leads to scarring (cirrhosis), which might result in liver failure, a grave condition.

Liver and gall bladder[10,11,12]

The liver is the heaviest gland of the body weighing about 1.4 Kg about 3 lbs and second largest organ of the body.

The gall bladder is a pear shaped sac that is located in a depression of the posterior surface of the liver. It is 7-10 cm long.

Histology of the liver and gall bladder[1-4]

The lobes of the liver are made up of many functional units called lobules. A lobule is typically a six sided structure. (hexagon) that consists of specialized epithelial cells called hepatocytes (hepat – liver cytes –cells)

Instead of capillaries the liver has larger endothelium lined spaces called sinusoids through which blood passes. Also present in the sinusoids are fixed phagocytes called stellate reticulo endothelial (kufpffner) cells.

Bile secreted by hepatocytes enters bile canaliculi, which empty, into small bile ductules. The ductules pass bile into bile ducts at the periphery of the lobules. The bile ducts merge and eventually form the larger right and left hepatic ducts which unit and exit the liver as the common hepatic duct. Further on the common hepatic duct joins the cystic duct from the gall bladder cystic duct from the gall bladder to form the common bile duct. Bile enters the cystic duct and is temporarily stored in the gall bladder. The function of the gall bladder is to store and concentrate bile.

1.2 Role and composition of bile

Each day hepatocytes secrete 800 – 1000 ml of bile, a yellow brownish or olive green liquid. It has a pH of 7.6-8.6 and consists of water, bile acid, cholesterol, a phospholipid called lecithin, bile pigments.

The principal bile pigment is conjugated bilirubin. The phagocytosis of aged red blood cells liberate iron, globin and bilirubin.

1.3 Functions of Liver

The liver also performs many other vital functions.

- **Carbohydrate Metabolism**

Liver maintains a normal blood glucose level. When blood glucose is low, the liver can break down glycogen to glucose and release glucose into the blood stream. The liver also convert amino acids and lactic acid to glucose.

When blood glucose is high, the liver converts glucose to glycogen and triglycerides for storage.

- **Lipid metabolism**

Hepatocytes store triglycerides, break down fatty acid to generate ATP, synthesize lipoproteins, synthesize cholesterol.

- **Protein metabolism**

Hepatocytes remove amino group from amino acids, so that amino acids can be used for ATP production.

Hepatocytes also synthesize most plasma proteins such as α– and β-globulins, albumin, prothrombin and fibrinogen.

- **Processing of drugs and hormones.**

The liver can detoxify substances such as alcohol and excrete drugs such as penicillin, erythromycin and sulfonamides into bile.

- **Excretion of bilirubin**

Bilirubin is derived from the haemo of aged red blood cells and is absorbed by the liver from the blood and secreted into bile.

- **Synthesis of bile salts**

Bile salts are used in the small intestine for the emulsification and absorption of lipids, cholesterol, phospholipids and lipoproteins.

- **Storage**

In addition to glycogen, the liver stores certain vitamins (A, B_{12}, D, E and K) and minerals (Iron and copper).

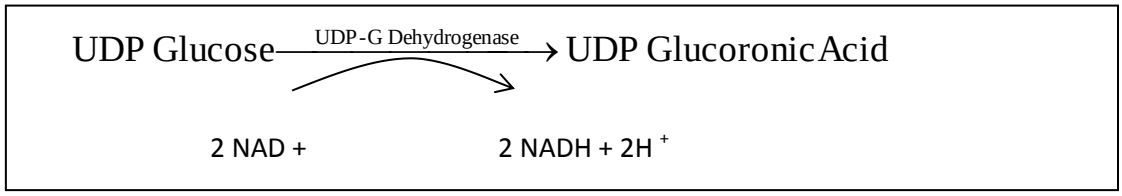
- **Phagocytosis**

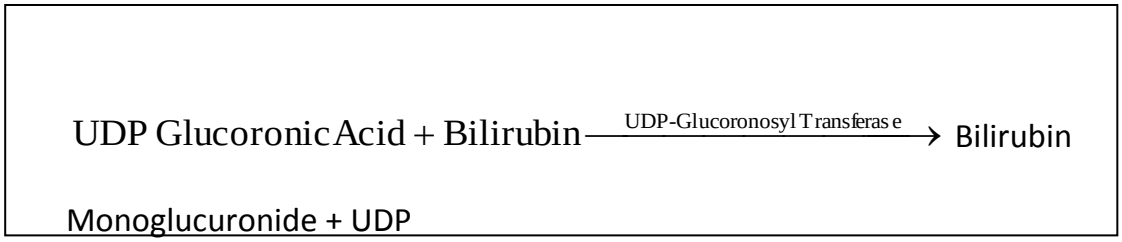
The kupffner cells of the liver phagocytize aged red blood cells, white cells and some bacteria.

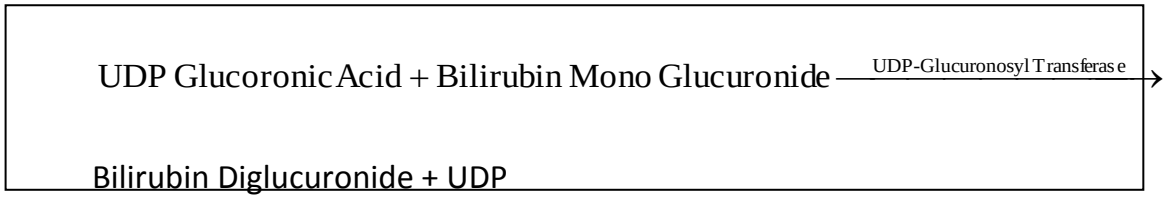
- **Activation of Vitamin D**

The skin, liver and kidney participate in synthesizing the active form of vitamin D.

Conjugated Bilirubin is reduced to urobilinogen by intestinal bacteria.







(2) **Liver disease**

Now vaccines and antiviral drugs are used for the treatment of liver diseases. Hepatitis B vaccines are used only for the prevention. Liver lessions are induced by hepatotoxin, chemicals (ethyl alcohol), peroxides (Peroxides edible oil), toxins in food (alfatoxin). Every year about 18,000 people are reported to die due to liver cirrhosis caused by hepatitis[13]. Liver disorders can be classified as follows. [14]

Hepatitis

It is an inflammation of liver mainly caused by viral infection and may lead to massive hepatic necrosis (death of liver cells).

Hepatoses

This is the non-inflammatory disorder of the liver in which degeneration of liver parenchyma occurs.

Liver Cirrhosis

This can be defined as chronic diseased condition presenting morphological alteration of labeled structure, characterized by destruction and degeneration of parenchymal cells and increased connective tissues.

Fatty liver (Liposis)

This is the condition in which accumulation of triglycerides occurs in the liver due to ceassation of normal movement of triglycerides from liver to plasma.

Jaundice

Jaundice is yellow coloration of the tissues by bile pigments.

Cholestasis

Obstruction of bile flow due to intrahepatic or extrahepatic causes.

Carcinogenesis

This is characterized by cancer induction in liver because of natural substances or man made substances.

Jaundice [15,16]

The word jaundice comes from the French word jaune, which means yellow. Jaundice is yellowish staining of the skin selera and mucous membrane by bilirubin, a yellow orange bile pigment. Bilirubin is formed by a break down product of haemo ring usually from metabolized red blood cells. Serum bilirubin level rises above 3 mg per dl (51.3 umol per L)

Inducers of Jaundice

It can be classified as

1. **Drugs and Chemicals :**

Morphine, Diuretics, chloroform, Acetaminophen, Halothane, Pesticides, Poly-chlorinated biphenyls (PCB), Cycads (methylazony methanol), Coumarins.

2. Infectious

Virus, Bacterial metabolites, Endotoxins.

3. Food poising

e.g : *Amanitia phalloides* (Mushroom), *Senecio jacoboes* (ray wort), *Heliotropium lasiocarpum,* crotalaria sp, *Aspergllus flavus*.

4. Physiological

Damage of liver due to any accident and various liver disease i.e cancer of the head of pancreas, gall stone lodge in the common bile duct.

5. Metals poisoning

Copper, Selenium

Common causes of jaundice

- Blocked bile ducts (by infection, tumour or gall stone)
- Viral Hepatitis

  (Hepatitis A, Hepatitis B, Hepatitis D & Hepatitis E)

- Drug induced cholestasis

  (bile pools in the gall – bladder)

- Drug induced hepatitis

(Hepatitis triggered by erythromycin, sulfa drugs, antidepressants, anti cancer drugs, paracetamol, Tolbutamide oral contraceptives.

- Biliary str
- Alcoholic cirrhosis
- Cancer of pancreas.
- Primary biliary cirrohosis
- In adequate blood flow to the liver
- Hemolytic anaemia
- Gilberts syndrome, Dubin Johnson syndrome, Rotor's syndrome.
- Auto immune Hepatitis.
- Malaria
- Cholangiocarcinoma

- Choledocholithiasis
- Chronic active hepatitis
- Blood transfusion reaction.

Symptoms of Jaundice :

- Yellowish coloration of the sclerate (white of the eyes), skin and mucous membranes
- Brain:- Unconjugated bilirubin can penetrate blood brain barrier which can result in a hyperbilirubinemia toxic encephalopathy or kernictures which can cause mental retardation.
- Blood – conjugated billrubin appears in urine and it became yellowish (dark)
- Faces – Whiteness of faces
- Digestive system – digestion is disturbed, oily food can't be digested, Nausea and vomiting.
- Uneasiness and pain in the region of the stomach.
- Loss of appetite
- Affects fertility
- Enlargement of spleen and liver
- Weight loss
- General languor and lassitude

- Immune system seakness
- Disagreeableness.

Table No.1 : Tests used for identification of liver disorder.[17]

	TESTS	SIGNIFICANCE
I.	**TEST FOR MANUFACTURE AND EXCRETION OF BILE**	
1.	Bilirubin:	
	Serum Bilirubin	Increased in hepatocelluar, obstructive, and haemolytic disease, Giibert's diseae
	In faeces	Absent in biliary obstruction
	In Urine	Conjugated bilirubinuria in patients of hepatitis
2.	Urobilinogen	Increased in hepatocellular and haemolytic diseases, absent in biliary obstruction
3.	Bile acid (Bile saits):	Increased in serum and detectable in Urine in cholestasis
II	**SERUM ENZYME ASSAYS**	
1.	Alkaline phosphatase:	Increased in hepatobiliary diseases (highest in biliary obstruction), bone diseases, pregnancy
2.	Glutamyl transpeptidase	Rise parallels alkaline phosphatase but it specific for hepatobiliary diseases
3.	Transaminases:	
	SGOT(AST)	Increased in tissue injury to liver as well as to other tissues like in myocardial infection
	SGPT(ALT)	Increase is fairly specific for liver cell injury
4.	Other enzymes:	
	5-Nucleotidase	Rise parallels alkaline phosphatase but more specific for diseases of hepatic origin
	Lactic dehydrogenase	Increased in tumors involving the liver
	Cholinesterase	Decreased in hepatocellular disease, malnutrition
III.	**TESTS FOR METABOLIC FUNCTIONS**	
1.	Amino acid and protein metabolism:	
	Serum proteins (total, A/G ratio, Protein electrophoresis)	Hypoalbuminaemia in hepatocelluar diseases; hyperglobulinaemia in cirrhosis and chronic active hepatitis
	Immunoglobulins	Nonspecific alterations in IgA, IgG and igM

	Clotting factors	Prothrombin time and partial thromboplastin time prolonged in patients with hepatocelluar disease
	Serum ammonia	Increased in acute fulminant hepatitis, cirrhosis, hepatic encephalopathy
	Aminoaciduria	In fulminant hepatitis
2.	Lipid and lipoprotein metabolism:	
	Blood lipids (total serum cholesterol, triglycerdes and lipoprotein fractions)	Increased in cholestasis, decreased in acute and chronic diffuse liver disease and in malnutrition
3.	Carbohydrate metabolism:	
	Blood glucose and GTT	Decreased in hepatic necrosis
IV	**IMMUNOLOGIC TESTS**	
1.	Nonspecific Immunologic reactions:	
	Smooth muscle antibody	In hepatic necrosis
	Mitochondrial antibody	In primary billary cirrhosis
	Antinuclear antibody and LE cell test:	In chronic active hepatitis
2.	Antibodies to specific etiologic agents:	
	Antibodies to hepatitis B (HBsAG, HBc, HBeAG)	In hepatitis B
	Amoeba antibodies	Amoebic liver abscess
V	**ANCILIARY DIAGNOSTIC TESTS**	
1.	Ultrasound examination	Cholestasis of various etiologies; SOLs, US-guided FNAC / liver biopsy
2.	FNAC and/ or pecutaneous liver biopsy	Unknown cause of hepatocellular disease, hepatmoegaly and splenomegaly; long standing hepatitis, PUO and SOLs of the liver

Drugs used against hepatitis [18,19,20]

Drugs used in the treatment of Hepatitis

- **Antiviral drugs**

  Immuno globulin

  Interferon α–2a

  Interferon α–2b

  Ribavirin

  Lamivudine

  Adefovir

  Entecavir

- **Glucocorticolds**

  e.g.prednisolone

- **Immunosuppressive agent:**

  e.g. Ciclosporin

  Azathioprine

  Methotrexate

- **Miscellaneous**

e.g. chlordiazepoxide

Diazepam

Ursodeoxycholic acid

Penicillamine

Lactulose

Sod.benzoate

Neomycin

- **Antidotes**

  e.g. Nacetyl cysteine

  Methionine

  Desferrioxamine

Prevention of hepatitis

1. Inhibition of GTP and viral RNA synthesis
2. Direct or indirect suppression of viral protein synthesis
3. Use of Hepatitis B virus surface antigen
4. Replenishment of Glutathione stores of the liver
5. Inhibition of formation of toxic metabolite by inhibiting the enzyme cytochrome $P_{450,}$ alcohol dehydrogenase.
6. Prevention of binding of the toxic metabolite to the cellular constituents (protein, fatty acid).
7. Lowering the level of ammonia in blood.

Evaluation of Hepatoprotective activity of plants :

Hepatoprotective activity can be most easily evaluated/screened with the aid of several model system of liver damage in experimental animals.

In all test model systems conditions for liver damage are implemented and an attempt is made to counteract the toxicosis with the substance/ preparations under test. The magnitude of the protective effects can be measured by estimating the enzyme activities and the rate of survival and can be verified histologically.

Experimental models for hepatoprotective Screening :

The hepatotoxins induce liposis, necrosis, cirrhosis, carcinogenesis & hepatobiliary dysfunction in experimental animals.

The most imp. hepatotoxin are carbon tetrachloride (CCl_4) thioacetamide (TAA), galactosamine, paracetamol, chloroform, ethyl alcohol and pyridine.

1. CCl_4 model :- [21,22,23]

A number of CCl_4 models are devised depending upon its dosage through different routes of administration.

a. Acute hepatic damage :-

Single dose of CCl_4 1.25 ml/kg, b.w.s.c p.o in rats leads to acute hepatic damage. Toxicity is induced after 24 hrs. of administration and can be observed by evaluated enzyme Levels. CCl_4 is normally administered as 50% V/V solution in liquid paraffin or oil.

b. Chronic reversible hepatic damage :

Administration of the dose of 1 ml / kg b.w. s.c to rats twice a week for 8 weeks induces chronic reversible hepatic damage.

c. Chronic irreversible hepatic damage :

Administration of the dose of 1 ml / kg b.w.s.c twice weekly for 12 weeks induces chronic irreversible hepatic damage in rats.

2 Thioacetamide Model : [24]

Adminstration of a single dose of thioacetamide 100 mg / kg b.w.s.c induces acute hepatotoxicity in rats.

3. D. Galactosamine Model : [25]

Single dose of galactosamine 800 mg / kg b.w, i.p. to rats induces hepatotoxicity after 48 administration.

4. Paracetamol Model : [26,27]

a. Acute hepatotoxicity :

This can be induced by administration of single dose of paracetamol 3 gm, kg b.w / p.o. in rats. It takes 48 hours to induce the toxicity.

b. Chronic hepatotoxicity :

Administration of the dose of 1 gm / kg b.w / p.o once a day for 7 days induces chronic hepatotoxicity.

5. Chloroform Model : [28]

It produces hepatotoxicity either by inhalation for 1 hr in atmosphere or by administering 0.4-1.5 ml / kg b.w / s.c.

6. Ethyl alcohol model : [29]

Ethyl alcohol at a single dose of 1 ml / kg b.w/s.c in rats causes fatty degeneration of liver.

Conclusion:

Many liver diseases have long natural histories, and there area unit few treatments which will directly alter their course. to maximise the time to liver disease, decrease the requirement for liver transplantation, and delay death, it becomes necessary to avoid alternative injury to the liver. the prevailing knowledge show that the preventive methods of alcohol shunning, infectious disease vaccination, shunning of NSAIDs, iron supplementation only iron deficiency is incontestible, and a diet area unit prudent in patients with chronic disease.

References:

1. Morton, F.J.; **Major Medicinal Plants**, Botany, Culture and uses.,1.
2. Desmet, A.G.M.P; **Drugs**, 54, 1997, 807-809.
3. Evans, W.L.; Trease and Evans **Pharmacognosy**, 13th Edn,1989, 3.
4. Desmet, A.G.M.P.; **Drugs**, 54, 1997, 801-802.
5. Evans, M.; **Herbal Remedies**, 1st Edn,1997.
6. Handa, S. S.; Kapoor, V. K.; **Pharmacognosy**, Vallabh Prakakshan, 1989. 213.
7. Murthy, R.V.; **Ayurvedic treatment**, 1997, 1st Edn, Cover Page.
8. Handa, S. S.; Kapoor, V. K.; **Pharmacognosy**, Vallabh Prakakshan, 1989, 9.

9. Wagner, H.; Hikiono, H.; Farnsworth, R. Norman; **Economic and Medicinal Plant Research.**, 23, 1999, 13.

10. Grabowski, T.; **Principles of Anatomy and Physiology**, 10th Edn, 877-878.

11. Chaudhuri, K. Sujit; **Pathophysiology**, New Central Book Agency, 5th Edn, 2004, 98.

12. Murray, R.K.; Grammer, D.K; Mayes, P.A; Rodwell, V.W.; Harpers **Biochemistry**, Appeleton and Lance Stanford, 25th Edn, 369-372.

13. Handa, S.S.; **Pharma Times,** 23, 1999, 13.

14. Zimmerman, H.G; **"Hepatotoxicity"** Appletone Century crofts, New York, 1978, 1.

15. Kasper, L. Demmis; Harrison's **Principles of Internal Medicines**, McGraw Hill Medical Publishing Division, 16th Edn., I, 2005, 242.

16. Haslett, Christopher; Chillers R. Edwin; Davidson's **Principles & Practice of Medicine,** Churchill Livingstone Harcourt Publisher, 18th Edn, 1999, 692.

17. Harshmohan; **Pathophysology**, Jaypee Brothers Medical Publisher, 5th Edn, 2005, 614.

18. Katzung, G. Bertam; **Basic Clinical Pharmacology**, McGraw Hill Medical Publishing Division, 9th Edn, 821-823.

19. Rang, H.P; Dale, M. M; **Pharmacology**, Churchill Livingstone Harcourt Publisher, 5th Edn, 2003, 664.

20. Tripathy, K.D.; **Essential Medical Pharmacology**, Jaypee Brothers Medical Publisher, 5th Edn, 2003, 773.

21. Rege.N.; Dahanukar, S.; Karandikar,S.M.; **Indian Drugs**, Vol.27., 1989, 19.

22. Saraf, S.; Dixit, V.K.; **Fitoterapia.**, 62, 1991, 307.

23. Pathak, A.K.; Saraf, S; Dixit, V.K.; **Fitoterapia**, 62,1991, 307.

24. Saraf, S.; Dixit, V.K.; **Fitoterapia**, 63. 1992, 416.

25. Kiso, Y.; Tohkin, M.; Hikino,H; **J. Natural Prtoducts**, 46, 1983, 841.

26. Handa, S.S.; Sharma, A.; **Ind. J.Med.Res.**, 92,1990, 284.

27. Picankar, P. D.; Thesis entitled." **Study of Hepatoprotective Effect of some indigenous plants in experimental animals"** submitted to university of Bombay through Hafkin's Bombay, 1980.

28. Gold Schmidt, S.; Voe, H.M.; Ravdin, I. S.; **J. Clin. Investigation.**, 18. 1939, 227.

29. Goodell, J.P.B.; Hanson, P.C; Hawkins,W.B.; **J. Exper. Med.**, 79, 1944, 625.