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REVIEW ARTICLE

Hepatoprotective models and screening methods: a review

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ABSTRACT

Liver, the largest organ in the body is being evolved to maintain the body's internal milieu and also protect itself from the challenges it faces during its implementation. It is a essential organ having assorted functions. It theater a significant position not only in the metabolism, production and storage other than in the detoxification of a lot of endogenous and exogenous compounds and converting them to less toxic substances for excretion. A number of herbal preparations are available in the market Liver cell injury caused by a range of toxic chemicals (certain chemotherapeutic agents, anti-biotic, carbon tetrachloride (CCL_4), paracetamol (PCM), thioacetamide (TAA) etc.), excessive alcohol consumption and microbes is well-studied. The present review is aimed on liver, its function, liver diseases, types of drug induced hepatotoxicity and their mechanisms of liver damage and clinical scenario.

Keywords: Hepatotoxicity, Carbon tetrachloride, Hepatoprotective, Liver injury, Paracetamol.

1. INTRODUCTION:

LIVER

Liver is the biggest reticulo-endothelial organ in the body as such has important immune function in maintaining body integrity. The liver plays an astonishing array of vital functions in the continuation, performance and adaptable homeostasis of the body. It is concerned with approximately all the biochemical pathway to enlargement, fight in opposition to disease, nutrient contribute, energy stipulation and reproduction[1].

Anatomy

The liver is the largest gland of the body enclosed within the right lower rib cage beneath the diaphragm. It is approximately totally enclosed via visceral peritoneum and a thick irregular connective tissue layer that lies deep to the peritoneum. Liver is separated within two principle lobes, a huge right lobe along with a smaller left lobe alienated through falciform tendon. The right lobe is consider through a lot of anatomists to comprise an lower quadrate lobe and a posterior caudate lobe. Liver have five surfaces as posterior anterior, inferior superior, also right[1].

Functions of liver[2]

1. Secretion and excretion of bile
2. Metabolic functions
   - Carbohydrate metabolism
   - Lipid metabolism
   - Protein metabolism
3. Haematological functions- (Haematopoeisis and coagulation)
4. Circulatory function
5. Detoxication and protective functions
6. Drug metabolism.

Liver diseases

Liver is a essential organ has a decisive in the metabolism of xenobiotics that causes it to succumb to numerous hepatic diseases.

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Table 1: Type of Liver diseases and their cause

LIVER DISEASE	**Jaundice**[2]			
Type of Jaundice	**Haemolytic Jaundice** (Prehepatic Jaundice)	**Hepatocellular Jaundice** (cholestatic jaundice)	**obtrusive Jaundice** (extra cholestatic jaundice)	
Causes	destruction of RBC and increases in bilirubin level in blood	bilirubin is conjugated which cannot excrete	Bile cannot be poured into small intestine and bile salts results conjugated bilirubin in blood	
Determination	Yellow pigmentation of the skin, mucous membrane.			
LIVER DISEASE	**Hepatitis**[3]			
Type of Hepatitis	Hepatitis A, Hepatitis E	Hepatitis B, Hepatitis C, Hepatitis D		
Causes	Intake of contaminated water or food	Sharing needles with contaminated person, accidental stab through contaminated needle, having insecure sex with contaminated person and blood transfusion from infected donors		
Determination	swelling and inadequate functioning of liver			
LIVER DISEASE	**Cirrhosis** [4]			
Characterized by:	progessive hepatocyte injury folllowed by regeneration and fibrosis lead to disorganization of lobular design, pseudo lobule development and acquired vascular malformation.			
Result	Degenerate inflammation and damage of parenchyma of liver ion of hepatic cells and dysfunction of liver.			
Liver Diseases	**Tumors of Liver**[4]			
Types of tumors	Benign tumors	Malignant tumors		
Benign haemangioma	Focal hyperplasia	Adenoma	Primary tumors	Secondary metastasis
LIVER DISEASE	**Hepatocellular Failure**[6]			
Occurrence	Ultra structural lesions of hepatocytes reye's disorder. Chronic liver diseases, unrelieved hepatitis, cirrhosis, Wilson's disease. enormous hepatic necrosis fulminate virus hepatitis.			
LIVER DISEASE	**Hepatic Encephalopathy**[4]			
Clinical features	Nonspecific, electro encephalo graphic (EEG) changes. Troubled consciousness moving ahead to coma. Fluctuating neurologic signs. Progressive perplexity, lethargy and coma which may lead to death.			
LIVER DISEASE	**Portal Hypertension**[4]			
Causes	Enhance resistance for the portal blood flow			
Occurance	i) Prehepatic ·Portal vein thrombosis ·Splenomegaly	ii) Intrahepatic ·Cirrhosis ·Miliary Tuberculosis ·Idiopatic	iii) Post Hepatic ·Severe right heart failure	
LIVER DISEASE	**Hepatocellular Carcinoma**[4]			
Etiology and Pathogenesis	Protracted infection with hepatitis B virus. Cirrhosis Environmental toxins. alpha toxin B, produced through Aspergillus flavus. Oral contraceptive questionable role.			

HEPATOTOXICITY:

Hepatotoxicity implies chemical-driven liver injured. convinced medicinal agent, when in use in overdoses and sometimes even when introduced within beneficial ranges, may possibly damage the organ. additional chemical agent, such as those used in laboratories (e.g. CCl_4, paracetamol, alcohol) and industries (e.g. lead, arsenic), natural chemicals (e.g., microcystins, aflatoxins) and herbal remedies (*Cascara sagrada*) can also induce hepatotoxicity. chemical that effect liver injury are known as hepatotoxins. Further 900 drugs have been occupied in causing liver injury.

Chemicals that cause liver injury are called hepatotoxins. These agents be renovate in chemically immediate metabolities 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[8].

Classification of Hepatotoxins

Table 2: Type of Hepatotoxins and their mechanism with examples

Type of Toxicity	Histological Lesions	Mechanism	Examples
INTRINSIC TOXICITY[5, 6]			
1.Direct hepatotoxins	Necrosis (zonal)and /or steatosis	Membrane injury destruction of structural basis of cell metabolism	CCl_4, $CHCl_3$, phosphorus
2.Indirect hepatotoxins	Steatosis or Necrosis	Interference with specific metabolic pathway leads to structural injury	Ethionine,Thioacetamide, Paracetamol, Ethanol
3. Cholestatic	Bile duct injury	Iinterference with hepatic excretory pathway leads to cholestasis	Rifampicine, Steroids
HOST IDIOSYNCRASY[7]			
1. Hypersensitivity	Necrosis or cholestasis	Drug allergy	Sulfonamides Halothane
2.Metabolic Abnormality	Necrosis or cholestasis	Production of hepatotoxic metabolites	Isoniazid

DRUG INDUCED HEPATOTOXICITY

Drug-induced hepatotoxicity is the most important cause of acute liver failure in many countries[9,10]. Almost all drugs are identified as foreign substances by the body which subjects them to various biochemical transformations involving reduction of fat solubility and change of biological activity. Adverse drug reactions [ADRs] can be considered as Type A reactions [predictable or high incidence or pharmacological] or Type B reactions [unpredictable or low incidence or idiosyncratic; [IADRs]. Type first reaction are dose-dependent and occur in a relatively regular time-frame. All persons are susceptible to Type A reactions which are generally a result of direct liver toxicity of the parent drug or its metabolites[11] eg acetaminophen-induced hepatotoxicity[12] or phenytoin-induced hepatotoxicity[13]. Type B reactions are unrelated to the pharmacological action of the drug[14].

Table 3: Drug Induced Hepatotoxicity and their mechanism.

S. No.	Class of Drug	Drug Name	Mechanism	Ref. No.
1.	**Anti-Tuberculosis Drugs**	Rifampicin, Isoniazid,	Rifampicin induces isoniazid hydrolase, when rifampicin is combined with isoniazid thus explaining the higher toxicity of the combination.	**15**
		Pyrazinamide	Pyrazinamide inhibite CyP-450 isoenzymes.	
2.	**Non Steroidal Anti-Inflammatory Drugs (NSAIDs)**	Diclofenac	Impairment of ATP synthesis by mitochondria and production of active metabolities.	**16**
		Sulindac	Inhibits canalicular bile salt progress, and such reserve may possibly supply to cholestatic liver injury.	
	Aniline analgesics	Acetaminophen (paracetamol)	Formation of a reactive metabolite and acetyl benzoquinamine through cytochrome P-450 pathway.	**17**
3.	**Anaesthesia**	Halothane, Isoflurane, Enflurane, Desflurane, Nitrous oxide	Cause Idiosyncratic Liver toxicity by forming a reactive trifluoroacetyl chloride reactive metabolite by cytochrome P450 and suggests an immune-mediated reaction. This unstable toxic metabolite binds to liver proteins causing cellular injury.	**18**
5.	**Aniline antibiotics**	Sulfonamides	HIV infection was probably caused through growing the oxidation to poisonous metabolites by the CyP-450 pathway.	**19**
6.	**Anticoagulants**	Warfarin, Heparin	Direct damage of hepatocytes by reactive metabolites which resulted in augmented antigenicity and consequent immunoallergic reaction.	**20**
7.	**Anti-hyperlipidemic drugs**	Lovastatin	Direct effect or productions by enzyme–drug addict leads to cell dysfunction, membrane dysfunction cytotoxic T-cell response.	**21**
		Pravastatin	Pravastatin cause acute intrahepatic Cholestasis	
8.	**Anti-Epileptic Drugs**	Carbamazepine	Lead to direct cytotoxicity and liver cell rapture.	**22, 23, 24**
		Valproic acid	VPA interference with the β– oxidation of the endogenous lipid. VPA form an ester conjugate by means of carnitine that may lead to secondary carnitine deficiency.	
		Phenytoin	The level of lactic dehydrogenase, aminotransferas, alkaline phosphatase, bilirubin, and prothrombin time in serum.	

DIFFERENT MODELS OF HEPATOTOXICITY[25]

Hepatoprotective cause was studied against chemicals and drugs induced hepatotoxicity in rats like carbon tetrachloride (CCl_4), alcohol, paracetamol, galactosamine, etc[2]. There are following experimental models explained by employing some of the important hepatotoxins.

1) Carbon tetra chloride (CCl_4) model: A number of Carbon tetra chloride models are invented, depending

upon its dosage through different routes of administration.

a) Acute hepatic damage: Acute liver damage, regarded as beside ischemia, hydropic deterioration and central necrosis is caused by oral or subcutaneous administration of CCl_4 (1.25ml/kg). The maximum elevation of biochemical parameters are found to be 24 hours after the CCl_4 administration normally administered as 50% v/v solution in liquid paraffin or olive oil.

b) Chronic reversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 8 weeks generates chronic, reversible liver injury.

c) Chronic, irreversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 12 weeks produce chronic, irreversible liver injury.

2) Thioacetamide model: Thioacetamide (100mg/kg S.C.) induces acute hepatic damage after 48 hrs of administration by causing sinusoidal congestion and hydropic swelling with increased mitosis.

3) Paracetamol model (PCM model): Paracetamol induces acute hepatotoxicity depending upon its dosage through different routes of administration.

- Paracetamol (800mg/kg i.p.) induces centrilobular necrosis without steatosis.
- Paracetamol at a single dose (3g/kg p.o.) produces acute hepatic injury. It get 48 hours to provoke the toxicity.

4. Chloroform model: It produces hepatotoxicity with extensive central necrosis, hepatic cell degeneration, fatty metamorphosis and necrosis either by inhalation or by subcutaneous administration (0.4-1.5ml/kg).

5. Ethanol model: Ethanol induces liposis to a different degree depending on its dose, route and time of administration such as:

- A single dose of ethanol (1ml/kg) induces fatty degeneration.
- Administration of 40%v/v ethanol (2 ml/100gm per day p.o.) for 21 days makes fatty liver.
- Administration of country made liquor (3ml/100 gm per day p.o.) for 21 days makes liposis.

LIVER FUNCTION TESTS[26]

In keeping with the multiplicity of their liver role, selections of tests are accessible to right to use them. The variety of the test is subjective by its effortlessness, reliability, and compassion as well as particular function one is interested in accessing.

S. No.	Liver Function Tests	Details
1.	Test of bilirubin metabolism Estimation of serum bilirubin	Bilirubin levels are elevated in all types of Jaundice.
	Urinary bilirubin	Elevation of water soluble conjugated bilirubin glucoronides in urine occur in obstructive jaundice.
	Urine urobilinogen	Abnormally low level or absence of urobilinogen in urine is diagnostic of biliary obstruction
2.	Test of protein synthesis and metabolism Estimation of plasma protein	Electrophoresis is very useful in detection of impaired liver function or hepatic failure.
	Albumin Globulin ratio (A/G ratio)	It is usually 1.2 to 1.4 and may possibly reverse in liver disorder.
	Flocculation tests	The most commonly used are the Thymol turbidity and Zinc sulphate turbidity tests.
	Plasma prothrombin and prothrombin time	Liver dysfunction, prothrombin synthesis impaired due to poor absorption of vitamin K leading to low plasma prothrombin levels and a prolonged prothrombin point. Coagulation time further more prolonged.
3.	Test based on excretory function Serum alkaline phosphatase	Alkaline phosphatase levels in serum are abnormally high in biliary obstruction.
	Bromsulphthalein (BSP) Excretion	Used to assess the liver cell dysfunction in the absence of jaundice.
4.	Test to assess hepato- cellular damage Serum enzyme estimation	Serum transminase levels (SGOT & SGPT) are markedly elevated in active hepatitis.

5. Parameters Reflecting Liver Condition and Their Interpretation:

a) **Transaminases**[27]: Transaminase is a process in which an amino group is transferred from an amino acid to an alpha – keto acid. It is an important step in the metabolism of amino acids. The enzymes responsible for transamination are called tranaminases (Now call amino-transverses). Two diagnostically helpful transaminases are glutamate oxaloacetate transaminase or SGOT and glutamate pyruvate transminase or SGPT. These enzymes catalyze the following reaction.

b) GOT/AST

L- aspartate +Oxoglutarate----------Oxaloacetate + Glutamate (or ketoglutarate)

L- alkanine + Oxoglutarate----------Pyruvate + Glutamate (or ketoglutarate)

Clinical significance

Increased serum transaminase activity is seen in liver dysfunction. Greater activity of SGOT (AST) over SGPT (ALT) is typical of myocardial infarction.

Serum glutamate pyruvate transaminase (SGPT)

Principle

SGPT (ALT) catalyzes the transfer of amino group from L-alanine to alpha- ketoglutarate to yield pyruvate and L glutamate. Lactates dehydrogenises then convert pyruvate and NADH into NAD and lactate. The transfer taking place NADH to NAD decrease the fascination at 340 nm. The rate of reduces in absorbance is measured and is proportional to the SGPT activity.

GPT (ALT)

L-alanine + ketoglutarate----------L-Glutamate + pyruvate

LDH

Pyruvate +NADH +H^+ ⟶ Lactate + NAD^+

Clinical significance

Elevation of SGPT (ALT) activity is found in liver and kidney diseases such as infectious or noxious hepatitis, contagious cirrhosis and mononucleosis. Extreme amplify is also originate in obtrusive jaundice, metastasis carcinoma, hepatic obstruction and myocardial infarction. SGPT levels may be decrease in patients undergoing long term hemodialysis without supplemental vitamin therapy.

Normal value: SGOT (AST): 7 – 21 U/L; SGPT (ALT): 6 –21 U/L

Serum glutamate oxaloacetate transaminase (SGOT)

Principle

SGOT (AST) catalyzes the transfer of the amino group from L- aspartate to alpha – ketoglutarate to yield oxaloacetate and L- glutamate. Malate dehydrogenises (MDH), then convert oxaloacetate and NADH in the direction of NAD and malate. The adaptation of NADH toward NAD decreases the absorbance on 340 nm, the time of which relative towards the SGOT movement.

GOT (AST)

L- aspartate + ketoglutarate ⟶
Oxaloacetate + L-glutamate

MDH

Oxaloacetate +NADH +H^+ ⟶
L- malate +NAD^+

Clinical significance

Organ rich in SGOT are hear, liver or skeletal strength. when a few of these organs are dented, serum GOT intensity rise in proportion to the severity of damage. In myocardial infarction SGOT starts increasing by 3-9 hours, peaks on second day returnto normal on 4^{th}-6^{th} day. In hepatitis, SGOT peaks usually between 7-12 days and any increase up to 100 times. Increased levels SGOT are also found in pancreatitis mononucleosis, and trauma of renal necrosis skeletal muscle, and cerebral necrosis.

Phosphatases[27]

Phosphates belong to the class of enzyme called hydrolyses and they are characterized by their ability to hydrolyse a large variety of organic phosphate with the formation of an alcohol and phosphate ions. Phosphates of diagnostic significance are- alkaline phosphates and acid phosphates. These are distinguish through their reaction in acidic and alkaline medium. The PH for determining the alkaline phosphates' action is 10 and in favor of acid phosphates it is 5.

Alkaline Phosphatase (ALP)

Principle

The substrate, p-nitrophenyl phosphate (PNPP) is hydrolysed by ALPto p- nitrophenol and phosphoric acid. Some divalent ions like Mg^{++} are added to the system which act like activators. PNPP is colorless into acidic medium or alkaline medium while PNP is yellow in colour in the alkaline medium and colourless in the acid medium.

ALP/ACP

P-Nitrophenyl phosphate + H_2O ⟶
p- nitrophenol + H_3PO_4
(Colourless) (Yellow)

Clinical significance

Increased alkaline phosphatase activity may be related to hepatobiliary abed bone sickness. Very elevated alkaline phosphates' movement in serum is seen in patients with bone cancer and marked increased also occur in obstructive jaundice and biliuary cirrhosis. Moderate elevations have been noted in case of Hodgkin's sickness, infective congestive hepatitis, heart failure, and abdominal troubles.

Normal value: Alkaline phosphatase (ALP**)**: 20 to 100 U/L

Gamma-Glutamyl Transpeptidase (GGTP)

Principle

Gamma –glutamyl transpeptise catalyses transfer of gamma- glutamyl group from the substrate gamma-glutamyl para – nitroanilide to glycylglycine releasing free P- nitroaniline which absorbs illumination at 405 nm. Enzyme activity is comparative to the enhance absorbance at this wave length.

GGTP

g-glutamyl nitroanilide + glycylglycine ⟶
P-nitroaniline + Glutamyl glucylglycine

Clinical significance

Elevated serum GGTP levels appear to be indicative of infection of liver, biliary area and pancreas. Serum GGTP action is usully elevated in the cases of cholangitis, cholesystitis, cholelithiasis, viral hepatitis chronic hepatitis, and netastatic carcinoma.

GGTP is particularly helpful in clinical assessment of alcoholic cirrhosis. while serum GGTP is not eminent in any appearance of bone disorder, it examine has been important in differentiating bone and liver disease in conjunction with alkaline phosphatase determination.

Normal values: Gamma-glutamyl transpeptidase (GGTP): 5 –24 IU/L

Serum Bilirubin

Bilirubin in serum would only react with daizo reagent in the existence of alcohol, after the proteins have been uninvolved by precipitation. adding of alcohol just before the reaction give positive test for both conjugated and unconjugated bilirubin stain. Unconjugated bilirubin altitude is after estimate by subtracting direct bilirubin value from this total value.

Normally, 0.25 mg/dlof conjugated bilirubin is present contained by the blood of an growing person. Bilirubin gets higher in disease of hepatocyte, obstacle to biliary secretion into duodenum, within hemolytic and defect of hepatic uptake and conjugation of bilirubin treatment such as Gilbert's disease.[28]

Serum Protein

Liver cells synthesise albumin, prothrombin fibrinogen, hepatoglobin, alpha- 1antitrypsin, transferring alpha foetoproteins ceruloplasm, and acute stage proteins. The blood levels of these plasma proteins are decreased in extensive liver injured. A consistently predictable whole protein is in the ordinary vary of 5.5 to 8 gram/dl. Hypoalbuminanemia may possibly take place in liver disease having significant destruction of hepatocytic. Hyperglobulinaemia may possibly current in unceasing inflammatory disorders such as in cirrhosis and chronic hepatitis.[28]

CONCLUSION

Hepatotoxicity implies chemical-driven liver damage. There are many chemical agent that cause hepatotoxicity and these agents called Hepatotoxins. These cause hepatotoxicity by the generation of free radicals and damage the liver cells and cause of m any liver diseases. The list of hepatotoxic drugs is huge and a complete coverage is complicated, To addition thus near by a large group of drugs used for different therapeutic indications which are toxic to the liver and thus should be cautiously administered; particularly when given at high doses or used for chronic or long term administration. The liver, its function, liver diseases, types of drug induced hepatotoxicity and their mechanisms of liver damage and clinical scenario are discuss in this article.

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