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SCREENING ANIMAL MODELS OF HEPATOPROTECTIVE AGENTS – A REVIEW

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ABSTRACT

The liver is the body's largest and most essential organ, responsible for food and medication metabolism. Humans are susceptible to liver disorders, which can be fatal. Excessive alcohol use, toxic chemicals (some chemotherapeutic medicines, anti-biotics, carbon tetrachloride (CCl_4), paracetamol (PCM), thioacetamide (TAA), and microorganisms, among others) have all been linked to liver cell harm. The current review focuses on the liver, its function, hepatic illnesses, drug-induced hepatotoxicity, and the mechanisms that cause liver damage, as well as the clinical situation.

Keywords: Liver, Hepatotoxicity, Paracetamol, Liver Damage, Carbon tetrachloride

INTRODUCTION

Liver

The liver is the body's biggest gland, weighing approximately 1.4 kg (3 lb.) in an average adult. It is only second in size to the skin among all of the body's organs. The liver is located beneath the diaphragm, and it takes up the majority of the right hypochondriac and epigastric portions of the abdominopelvic cavity **[1]**.

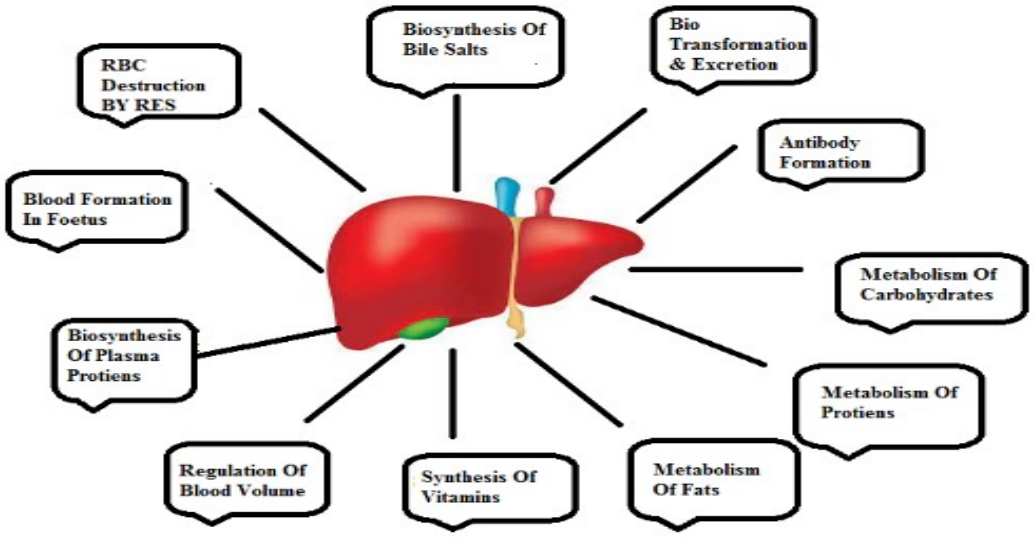

Figure 1: Physiology of Liver

Anatomy of Liver

The visceral peritoneum almost fully covers the liver, which is completely covered by a dense irregular connective tissue layer, deep within the peritoneum. The liver is split into two halves. The falciform has two lobes—a big right lobe and a smaller left lobe. a fold of the mesentery's ligament. Despite the fact that the right many anatomists believe that the lobe includes the inferior quadrate lobe (Kwa-DRA-T) and a posterior caudate lobe (KAW-dt), according to the findings. morphology of the internal (primarily the distribution of blood vessels), The quadrate and caudate lobes belong to the left side of the brain lobe. The falciform ligament connects the undersurface of the diaphragm to the superior surface of the liver, assisting in the suspension of the liver in the abdominal cavity. The ligamentum teres (round ligament), a remnant of the fetus's umbilical vein, runs along the free border of the falciform ligament and extends from the liver to the umbilicus **[2]**.

Liver Diseases

Liver disease is any trouble of liver that causes sickness. The liver is in charge of a number of important functions in the body, and if it becomes ill or damaged, those functions will cease to function, causing serious harm to the body. Hepatic disease is a term used to describe liver disease.

Liver disease is a general concept that encompasses any issue that causes the liver to stop performing its intended functions. Until a reduction in activity happens, more than 75 percent, or three quarters, of the liver tissue must be pretentious.

The liver is the body's most solid organ, and it is often classified as a gland because it produces and secretes bile among its many functions. The liver is covered by the rib cage in the superior right part of the abdomen. It has two major lobes, each of which is made up of several small lobules.

The liver cells receive blood from two different outlets. The hepatic artery transports oxygen-rich blood from the heart to the liver, while the portal vein transports nutrients from the intestine and spleen **[3-6]**.

Hepatotoxicity

Hepatotoxicity (from hepatic toxicity) refers to liver damage caused by chemicals. The most prevalent reason for a drug's withdrawal from the market after approval is drug-induced liver injury, which is a cause of acute and chronic liver disease caused primarily by drugs. More than 900 medications have been linked to liver damage, making it the most prevalent reason for a drug's withdrawal from the market. Hepatotoxicity and drug-induced liver injury are also responsible for a significant number of compound failures, emphasizing the need for toxicity prediction models (e.g., DTI) and drug screening assays (e.g., stem cell-derived hepatocyte-like cells) that can detect toxicity early in the drug development process. Chemicals frequently induce liver harm that only emerges as abnormal liver enzyme readings.5 percent of all hospital admissions and 50% of all acute liver failures are due to drug-induced liver damage **[7-10]**.

Drug Induced Hepatotoxicity

In patients with acute liver injury with no evident cause, drug-induced liver injury (DILI) is a common differential diagnosis. Apart from ruling out competing etiologies, knowledge about the agent's known and potential hepatotoxicity is critical in the diagnostic process. Hepatotoxicity data, on the other hand, is not always readily available **[12]**.

Table 1

Sr. No.	Class Of Drug	Drug Name	Mechanism
1.	Analgesic	Paracetamol	Formation of a reactive metabolite and acetyl benzo quinamine through cytochrome P-450 pathway [11]
2.	Immunosuppressants	Azathioprine	The mechanism of AZA toxicity is mitochondrial damage with severe ATP depletion and necrotic cell death. Changes in the levels of several endogenous scavengers, as well as lipid peroxidation, are used as indirect in vivo valid markers for the contribution of free radical formation and, thus, oxidative stress. [12-13]
3.	Non-Steroidal Anti-Inflammatory Drugs	Diclofenac	Mitochondrial ATP synthesis and active metabolite production are impaired.
		Sulindac	Inhibits canalicular bile salt production, which may contribute to cholestatic liver damage.

4.	**Anti-Tuberculosis Drugs**	**Rifampicin, Isoniazid**	**When rifampicin is combined with isoniazid, it activates isoniazid hydrolase, which explains the combination's increased toxicity.**
		Pyrazinamide	**Cyp-450 isoenzymes are inhibited by pyrazinamide.[11]**
5.	**Anaesthesia**	**Halothane, Isoflurane, Enflurane, Desflurane, Nitrous oxide**	**Results into an Idiosyncratic liver toxicity by cytochrome P450 producing a reactive trifluoro acetyl chloride reactive metabolite, which supports an immune-mediated reaction. This poisonous metabolite attaches to liver proteins and causes cellular damage.[14]**
6.	**Antibiotics**	**Sulphonamides**	**This drug activates Cyp-450 pathway which likely induced liver infection by increasing the oxidation of toxic compounds.[15]**
		Erythromycin	**During its main elimination route is bile & a small portion in the urine& its side-effects associated with the drug is diarrhoea, nausea, vomiting, &massive liver failure. [16]**
7.	**Anticoagulants**	**Warfarin, Heparin**	**Hepatocytes were directly damaged by reactive metabolites, resulting in increased antigenicity and an immune-allergic response.[17]**
8.	**Anti-hyper lipidemic drugs**	**Lovastatin**	**Cell malfunction, membrane dysfunction, and cytotoxic T-cell response are all caused by the direct action or products of enzyme–drug addicts. Cell malfunction, membrane dysfunction, and cytotoxic T-cell response are all caused by the direct action or products of enzyme–drug addicts.**
		Pravastatin	**Acute intrahepatic cholestasis is caused by pravastatin.[11]**
9.	**Anti-Epileptic Drugs**	**Carbamazepine**	**Direct cytotoxicity and rupture of liver cells**
		Valproic acid	**VPA hinders with the β- oxidation of the endogenous lipids. VPA and carnitine produce an ester conjugate, which can lead to secondary carnitine insufficiency.**
		Phenytoin	**Lactic dehydrogenase, aminotransferase, alkaline phosphatase, bilirubin, and prothrombin time all are elevated in the blood.[11]**
10.	**Anti-Cancer Drugs**	**Cisplatin**	**Elevated CYP2El enhances production of R.O.S & oxidative stress which induces Hepatotoxicity.[18]**
		Doxorubicin	**During its oxidative metabolism, it has been found to undergo redox cycling between semiquinone and quinone radicals. A single dose of Adriamycin (10 mg/kg) was found to cause hepatotoxicity in rats.[13]**
11.	**H2 Blockers**	**Ranitidine**	**It causes liver injury due to its metabolite which may lead to hepatic oxidative damage & also produced infiltration of hepatocytes.[13]**

Various Models of Hepatotoxicity: A variety of hepatotoxic models have been studied, including chemically induced, drug induced, metal induced, radiation induced, and genetic models, among others. However, a model that accurately simulates human hepatotoxicity is required.

Carbon tetrachloride (CCl_4) Induced

Carbon tetrachloride has the chemical formula CCl_4 and is an inorganic substance. It's a clear liquid with a sweet odour that dissipates quickly. It (CCl_4) is a common industrial solvent with a reputation for causing liver damage **[19-20]**.

Principle

CCl_4 is the most extensively utilised hepatic toxicant in laboratory animals for the experimental research of liver injury. Cytochrome P-450 2E1 (CYPE2E1) in hepatocytes produces CCl_3, a toxic metabolite of CCl_4. This free radical subsequently reacts with cellular lipids and proteins to generate the trichloromethyl peroxyl radical, which targets lipids on the endoplasmic reticulum membrane more quickly than the trichloromethyl free radical, resulting in acute centrilobular necrosis. Significant fibrosis occurs after 2–4 weeks, severe bridging fibrosis after 5–7 weeks, and cirrhosis after 8–9 weeks, according to histopathology investigations **[21]**.

Procedure

Rats of either sex were fed a standard diet and housed in a temperature (25 °C) and light/dark cycle of 12 hours. Animals were denied food prior to the experiment. Varied concentrations of CCl_4 were used to cause hepatotoxicity in animals, as well as different routes and time periods, as shown in the table. The animals were anaesthetized and euthanized on the last day of the study, and biochemical parameter and histological analyses were done **[22-23]**.

Table 2

Animals Used	Dose & Route
Male Sprague-Dawley rats	CCl_4 0.5 ml/kg i.p. for 3 days [23]
Male Sprague-Dawley rats	CCl_4 0.2 ml/100 g i.p. for 2 weeks [24]
Male Wistar rats	CCl_4 0.5 ml/kg i.p. twice a week for a period of 4 weeks [25]
Male Wistar rats	CCl_4 0.125 ml/kg i.p. for 7 days [26]
Male Wistar rats	CCl_4 1.0 ml/kg i.p. after every 72 h for 10 days [27]
Male Wistar rats	CCl_4 2 ml/kg, s.c. at every 72 h for 10 days [28]

Thioacetamide (TAA) Induced

Thioacetamide is a white crystalline solid organosulfur chemical that is soluble in water and is used to synthesize organic and inorganic compounds as a source of sulphide ions **[29]**.

Principle: TAA is not harmful to the liver; instead, thioacetamide-s-oxide, a TAA intermediate metabolite, covalently binds to hepatic macromolecules, altering cell permeability and increasing intracellular Ca_2 concentration, causing cellular damage and necrosis in both zone 1 and zone 3 hepatocytes **[19-20]**.

Procedure: Animals of either sex were fed a regular food and given water prior to the experiment, and they were kept in a

temperature-controlled environment with a 12-hour light-dark cycle. The animals were given TAA in various concentrations, methods, and time periods to cause thioacetamide (TAA)-induced hepatotoxicity, as shown in the table below **[30]**.

Table 3

Animals Used	Dose & Route
Male Wistar rats	Thioacetamide 200 mg/kg i.p. twice a week for 12 weeks [31]
Male Wistar rats	Thioacetamide 300 mg/kg i.p. on day 14[32]
Male Wistar rats	Thioacetamide 400 mg/kg i.p. for 2 weeks [33]

Paracetamol Induced

Paracetamol is most widely prescribed drug. It is use in reliving of mild grade pain, fever etc. Overdosing on these medicines resulted in toxic damage to multiple organ systems, including the gastrointestinal tract, kidneys, and liver.

Principle: Hepatotoxicity caused by paracetamol (PCM) causes centrilobular necrosis, congestion, and failure. PCM is largely transformed to inactive molecules via Phase II metabolism by conjugation with sulphate and glucuronide, with a tiny fraction oxidized via the Cytochrome P450 enzyme system. PCM is converted to the highly reactive intermediate metabolite N-acetyl-p-benzo-quinone imine (NAPQI) by Cytochrome P450 2E1 (CYP2E1) and 3A4 (CYP3A4). Semiquinone radicals, formed by one electron reduction of N-acetyl-p-benzquinamides, attach covalently to cellular membrane macromolecules and enhance lipid peroxidation, causing tissue damage. Higher doses of PCM and N-acetyl-p-benzquinamides can alkylate and oxidizes intracellular glutathione (GSH), leading to a depletion of the liver GSH pool, which leads to enhanced lipid peroxidation and liver injury **[33]**.

Procedure: Rats of either sex were fed a regular chaw diet and had unlimited access to water. They were given a 12-hour light/dark cycle to acclimatize before being used. Hepatotoxicity was induced by giving different doses of PCM (3 mg/kg, p.o. for 7 days–3 weeks). The effects of hepatotoxicity on several parameters were investigated **[34-35]**.

Anti-TB Drugs Induced

Rifampicin with isoniazid in treatment of Tuberculosis is still a major public health issue in poor countries.

Principle: Isoniazid is metabolized into acetyl isoniazid and hydrolyzed to acetyl hydrazine in the presence of N-acetyltransferase. Hepatocyte damage is caused by CYP2E1 metabolizing acetyl hydrazine into a reactive acylating species that binds covalently to liver cell macromolecules **[36]**.

Procedure: Wistar rats weighing 150–200 g were housed at a constant temperature (25 °C) and on a 12-hour light/dark cycle for one week before to and during the studies, and were fed a regular food and water ad libitum. Rats were given 50–100 mg/kg i.p./o.p. for 10–28 days of isoniazid (INH) co-administered with rifampicin to induce hepatotoxicity **[37]**.

Radiation Induced

Machines can produce energy in the form of waves or streams of particles, which is known as radiation.

Principle: Acute liver injury progresses to radiation-induced liver damage. It was thought that when exposed to radiation, central vein endothelium and sinusoidal endothelial cells activate the coagulation cascade, resulting in fibrin buildup and clot formation in the central veins and hepatic sinusoids.

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Azathioprine Induced

AZA is an important drug used in the therapy of autoimmune disorder and in preventing graft rejection.

Principle: The mechanism of AZA toxicity is mitochondrial damage with severe ATP depletion and necrotic cell death. Changes in the levels of several endogenous scavengers, as well as lipid peroxidation, are used as indirect in vivo valid markers for the contribution of free radical formation and, thus, oxidative stress.

Procedure: It has been reported that the administration of AZA (15 mg/kg orally) for 4 weeks induced hepatotoxicity in rats. Alternately administration of AZA (50 mg/kg i.p) single dose also induces hepatotoxicity **[13]**.

Alcohol Induced

Sugar fermentation is used to make alcohol. Alcohol can operate as a stimulant in low quantities, causing sensations of euphoria. Alcohol has an immediate and potentially deadly sedative effect on every organ in the body, and these effects are dependent on the blood alcohol content (BAC) over time.

Principle: Alcohol after absorption converted into acetaldehyde & it is toxic & may causes membrane damage & cell necrosis via generation of Highly ROS.

Procedure: Rats of either sex were fed a regular chaw diet and had unlimited access to water. They were given a 12-hour light/dark cycle to acclimatize before being used.

Alcohol was used to cause hepatotoxicity in the animals, as shown in **Table 4**.

Table 4

Animals Used	Dose & Route
Male albino Wistar rat	Ethanol 7.9 g/kg p.o. daily for 45 days
Male albino Wistar rat	Ethanol 2.0 ml/l00 g p.o. for 21 days
Male albino Wistar rat	Ethanol 5 g/kg/day p.o. for 60 days
Female albino Wistar rat	Ethanol 3.76 gm/kg twice a day p.o. for 25 days [40]

Liver Function Tests

Table 5

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	Obstructive jaundice causes an elevation in water-soluble conjugated bilirubin glucuronides in the urine.
	Urine urobilinogen	Biliary blockage is diagnosed by an abnormally low level or lack of urobilinogen in the urine.
2.	Test of protein synthesis and metabolism Estimation of plasma protein	Electrophoresis is particularly useful in detecting hepatic failure or reduced liver function.
	Albumin Globulin ratio (A/G ratio)	It is usually 1.2 to 1.4 and may possibly reverse in liver disorder.
	Flocculation tests	Thymol turbidity and Zinc sulphate turbidity tests are the most widely utilized.
	Plasma prothrombin	Prothrombin synthesis is hampered due to inadequate vitamin K absorption, resulting in low plasma prothrombin levels and a protracted prothrombin point. Coagulation time is now even longer.
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 evaluate 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.	Serum glutamate oxaloacetate transaminase (SGOT) /AST	Increase in case of liver dysfunction. Myocardial infarction is marked by higher SGOT (AST) activity than SGPT (ALT). SGOT (AST): 7 – 21 U/L (Normal Value)
6.	Serum glutamate pyruvate transaminase (SGPT)/ALT	Infectious or noxious hepatitis, contagious cirrhosis, and mononucleosis are all conditions that cause an increase in SGPT (ALT) activity. Obtrusive jaundice, metastatic cancer, hepatic blockage, and cardiac infarction can all cause extreme increase. SGPT (ALT): 6 –21 U/L (Normal Value)
7.	Alkaline Phosphatase (ALP)	Hepatobiliary abed bone illness as well as obstructive jaundice & biliary cirrhosis may be linked to increased alkaline phosphatase activity. Alkaline phosphatase (ALP): 20 to 100 U/L (Normal Value)
8.	Gamma-Glutamyl Transpeptidase (GGTP)	Serum GGTP levels that are elevated appear to be symptomatic of infection in the liver, biliary system, and pancreas. Gamma-glutamyl transpeptidase (GGTP): 5 –24 IU/L (Normal Value) [11]

CONCLUSION

Hepatotoxicity refers to liver damage caused by chemicals. Hepatotoxicity is caused by a variety of chemical agents, which are known as hepatotoxins. Hepatotoxicity is caused by the formation of free radicals, which damage the liver cells and cause a variety of liver illnesses. The list of hepatotoxic drugs is extensive, and comprehensive coverage is difficult to achieve. Furthermore, there is a large group of drugs used for various therapeutic indications that are toxic to the

liver and should be used with caution, especially when given in high doses or for chronic or long-term administration. This article discusses the liver, its function, liver illnesses, kinds of drug-induced hepatotoxicity, their processes of liver damage, and clinical scenarios.

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