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Chemically and pharmacologically induced liver toxicity models in experimental animals and observed changes

Hilmi Nuhoglu[1]*

[1]Kafkas University, Faculty of Veterinary Medicine, Department of Pathology, Kars, Türkiye
*Corresponding: hilminuhoglu@gmail.com

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Abstract
Toxicity models conducted using laboratory animals are widely preferred in biomedical research to understand the effects of toxic substances on biological systems, to make safety assessments, and to test therapeutic approaches. Another reason is the physiological and anatomical similarities of mice, rats, and rabbits to humans. Although there are many experimental liver toxicity models, toxicity models created with drugs and chemicals are preferred over surgical models. These models aim to simulate many conditions such as acute or chronic toxicities, drug toxicities, hepatitis, steatosis, and cirrhosis. Toxicology models have a special importance because the liver is considered one of the most vulnerable organs to toxic substances due to its metabolic functions. In this context, experimental toxicity models created with many drugs and chemicals such as acetaminophen, cadmium, ethanol, carbon tetrachloride, and diclofenac have been evaluated. In experimental studies, although different among models, biochemically elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and malondialdehyde (MDA) levels indicate liver damage, while decreased glutathione (GSH) levels reflect weakened antioxidant defenses. Histopathologically, although different among models, necrosis, fibrosis, fat accumulation and inflammation have been observed, depending on the type of toxin. Experimental liver toxicity models are indispensable for understanding liver pathophysiology, identifying potential risks and advancing hepatoprotective therapies. Their findings will improve biomedical research and clinical practice in addressing toxin-induced liver damage.
Keywords: *Liver Toxicity, ALT, AST, MDA, GSH*

1. Introduction

Toxicity models conducted using laboratory animals are widely utilized in biomedical research to understand the effects of toxic substances on biological systems, perform safety evaluations, and test therapeutic approaches.[1,2] The liver, due to its metabolic functions, is considered one of the most vulnerable organs to toxic substances. Consequently, animal models are invaluable for elucidating the mechanisms of liver toxicity.[3,4] These models enable researchers to investigate the biochemical pathways, cellular effects, and tissue-level damage caused by toxic agents, thereby providing insights into potential risks that humans may encounter.[5,6]

The primary species used in toxicity models include mice, rats, and rabbits. These species are preferred due to their physiological and anatomical similarities to humans, ease of handling, and relatively low cost.[7] Experiments conducted on these animals facilitate understanding the effects of substances such as acetaminophen, cadmium, and ethanol, which are commonly used in liver toxicity studies. By administering these substances at specific doses and durations, a toxic response can be induced. Subsequently, detailed investigations can be conducted on tissue damage, biochemical alterations, molecular responses, and histopathological changes observed post-toxicity.[8,9]

Toxicity processes typically involve biological mechanisms such as oxidative stress, inflammation, cell death (apoptosis), and organ dysfunction. These processes can vary depending on the type of toxic agent, its dosage, and the duration of exposure. For instance, high doses of acetaminophen can lead to extensive cellular necrosis and oxidative damage in the liver, while heavy metals like cadmium cause biochemical imbalances through oxidative stress.[10,11] These pathological and biochemical alterations allow for direct observation of the effects of toxic agents on liver tissue.

Toxicity models applied to experimental animals are also utilized to evaluate the efficacy of protective treatments aimed at preventing or mitigating toxic effects.[12] This study comprehensively examines the mechanisms, pathogenesis processes, and the histopathological and biochemical alterations resulting from toxicity in experimental animal models. This review aims to contribute to the development of more effective and reliable models and systems for experimental liver toxicity studies.

2. Normal histology and biochemistry of the liver in experimental animals

The liver, with its critical metabolic functions and detoxification processes, is one of the most vital organs in the body. Consequently, it is frequently studied in toxicology research. The structural characteristics and biochemical functions of the liver provide essential insights into its

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responses to toxic agents and its mechanisms of toxicity. In experimental animals, particularly in mouse and rat models, the normal histological structure and biochemistry of the liver exhibit many similarities to those of the human liver, making these models highly suitable for research purposes.[1,3]

3. The normal histological structure of the liver

The liver has a lobular structure, composed histologically of lobules organized around a central vein. Each lobule contains hepatic cords formed by radially arranged hepatocytes, with sinusoids located between these cords. The sinusoids facilitate the flow of blood toward the central vein, supporting the liver's metabolic processes.[13] The walls of the sinusoids house Kupffer cells, which are the liver's resident macrophages responsible for immune functions. Additionally, the liver contains Ito cells (stellate cells) within the perisinusoidal spaces; these cells store lipids and vitamin A and become activated during the development of fibrosis.[14]

Hepatocytes are the primary functional cells of the liver, responsible for critical functions such as detoxification, protein synthesis, lipid metabolism, and glycogen storage. These cells are characterized by their large, round nuclei, abundant mitochondria, and well-developed rough endoplasmic reticulum. In normal liver histology, hepatocytes are neatly organized, sinusoids are open, and Kupffer cells remain active. These structural features are essential for maintaining the liver's healthy functioning.[15,16]

4. Normal biochemical functions of the liver

The liver serves as a central hub for numerous biochemical reactions, playing a pivotal role in protein, carbohydrate, and lipid metabolism. The primary biochemical functions of the liver include:

Detoxification: The liver plays a critical role in metabolizing and neutralizing toxins that enter the body. Cytochrome P450 enzymes are key players in the biotransformation of toxic substances. These enzymes are particularly active in drug metabolism, facilitating the conversion of toxic compounds into more water-soluble forms, which can then be excreted via the kidneys.[16]

Protein synthesis and albumin production: The liver plays a crucial role in synthesizing plasma proteins such as albumin and fibrinogen. Albumin regulates the osmotic pressure of blood, while other plasma proteins are essential for coagulation mechanisms. Low levels of albumin can indicate impaired liver function, serving as a marker for hepatic dysfunction.[17]

Carbohydrate metabolism: The liver is the primary organ responsible for regulating blood glucose levels. Through its ability to store glucose as glycogen, it helps maintain blood sugar balance during both hypoglycemia and hyperglycemia. Additionally, the liver supports glucose production when needed through gluconeogenesis, ensuring a stable energy supply.[18]

Lipid metabolism: The liver plays a critical role in the synthesis and storage of triglycerides and cholesterol. It is also the site of lipoprotein production and fatty acid oxidation, processes that are essential for energy production and the maintenance of cellular membrane integrity.[15]

Bile production: The liver produces bile, which is essential for the digestion and absorption of fats. Bile salts emulsify fats, facilitating their breakdown by digestive enzymes and enhancing their absorption in the intestine.[15]

Biochemical indicators of a healthy liver: A healthy liver maintains specific enzyme levels and protein production to support optimal function. Under normal conditions, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are typically low in a healthy liver. Elevated levels of these enzymes can indicate liver damage. Albumin and other plasma proteins are maintained within normal ranges. A decrease in albumin levels may suggest liver dysfunction or failure. Bilirubin levels remain low because a healthy liver efficiently metabolizes bilirubin and excretes it through bile.

In experimental animals, the normal histological and biochemical state of the liver serves as a reference point for comparing and identifying abnormal conditions in toxicity studies. These foundational structures and functions provide insights into how the liver responds to toxic agents and are essential benchmarks in numerous toxicity studies.

5. Liver toxicity models in experimental animals

Liver toxicity studies in experimental animals are conducted using various models, including chemical, pharmacological, surgical, genetic, dietary, and oxidative stress-based approaches. Among these, chemical and pharmacological models are the most widely used. Each model provides valuable insights into the liver's response to toxic agents and helps elucidate the distinct biological processes triggered by toxicity.

5.1. Carbon tetrachloride (CCl_4) toxicity

Carbon tetrachloride (CCl_4) is an industrial solvent with the capacity to induce oxidative stress and necrosis in the liver. It triggers oxidative stress through lipid peroxidation, playing a crucial role in studying liver fibrosis and cirrhosis.[19,20]

Experimental protocol: Commonly used species include rats and mice, particularly Wistar rats and C57BL/6 mice. Administered at 0.2–2 ml/kg, typically as a 50% solution mixed with olive oil, either intraperitoneally or orally and twice weekly for 4–12 weeks. This animals structural changes in the liver, such as fibrosis, necrosis, and inflammation, are evaluated. Biochemical parameters like ALT and AST are measured to assess liver function. The administration of CCl_4 increases reactive oxygen species (ROS) production, leading to liver damage and triggering fibrogenic processes.[21,22,23]

5.1.1. Mechanism of CCl_4 toxicity

Carbon tetrachloride undergoes biotransformation in the liver via cytochrome P450 enzymes, particularly CYP2E1. This process generates a highly reactive metabolite, the trichloromethyl radical (CCl_3•). CCl_3• promotes the production of reactive oxygen species (ROS), leading to oxidative damage within hepatocytes. CCl_3• interacts

with unsaturated fatty acids in cell membranes, initiating lipid peroxidation. This damages the structural integrity of cellular membranes and intracellular organelles. Lipid peroxidation disrupts membrane integrity, increases intracellular calcium levels, and causes mitochondrial dysfunction, ultimately resulting in hepatocyte necrosis.

Additionally, CCl_4 exposure increases the migration of inflammatory cells into sinusoids. Chronic exposure triggers collagen production and the accumulation of extracellular matrix, leading to fibrosis and, eventually, cirrhosis.[20,21,24]

5.1.2. Pathogenesis of CCl_4 toxicity

Carbon tetrachloride is a potent hepatotoxin that induces lipid peroxidation in the liver. It is metabolized by cytochrome P450 enzymes into the $CCl_3\bullet$, a highly reactive species that initiates lipid peroxidation in hepatocyte membranes, leading to cellular damage.[21] The trichloromethyl radical disrupts the structural integrity of cell membranes by oxidizing unsaturated fatty acids. This damage increases intracellular calcium levels and triggers mitochondrial dysfunction. Impaired mitochondrial function reduces energy production, causing necrosis in liver tissue. Prolonged exposure to CCl_4 leads to the accumulation of inflammatory cells and enhanced collagen production, resulting in fibrosis and progression to cirrhosis.[19,24]

This sequence of events underscores the significant impact of CCl_4 on liver function and structure, making it a valuable model for studying liver toxicity and related pathological processes.

5.1.3. Biochemical changes in CCl_4 toxicity

Carbon tetrachloride is a toxin that induces lipid peroxidation and severe oxidative stress in the liver. It is metabolized by cytochrome P450 enzymes into reactive free radicals, which enhance lipid peroxidation and cause damage to cell membranes.

Animals exposed to CCl_4 exhibit significantly elevated levels of ALT, AST, and malondialdehyde (MDA), indicating hepatic injury. Additionally, reduced levels of glutathione (GSH) reflect a weakened cellular antioxidant defense system.

These biochemical alterations highlight the profound impact of CCl_4 on liver function and oxidative balance, providing critical markers for assessing hepatotoxicity.[19,21]

5.1.4. Histopathological changes in CCl_4 toxicity

Carbon tetrachloride is a severe toxic agent that causes extensive necrosis and fibrosis in the liver. It induces lipid peroxidation, resulting in damage to cell membranes. Histopathologically observed changes: formation of fibrotic tissue around the portal areas and sinusoids, Increased deposition of collagen in the liver, reduction in sinusoidal space due to fibrosis and prolonged CCl_4 exposure accelerates the fibrotic process, ultimately leading to the development of cirrhosis.

These histopathological changes illustrate the profound structural alterations caused by CCl_4 toxicity and its utility in studying liver fibrosis and cirrhosis.[19,21,23,24]

5.2. Paracetamol

Paracetamol is a widely accessible analgesic and antipyretic, often used in overdose cases, including suicide attempts. At high doses, it induces toxicity and is commonly employed to study acute liver failure. This toxicity occurs via a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which depletes glutathione stores, leading to liver damage.[25,26]

Experimental protocol: The most commonly used animals for modeling paracetamol toxicity are BALB/c and C57BL/6 mice, although rats are also utilized. Typically, 300–2000 mg/kg as a single dose, administered intraperitoneally or orally and as an acute toxicity model, is given, and the liver is analyzed 24–48 hours post-administration. Liver tissue is collected for biochemical analysis (e.g., ALT and AST levels) and histopathological examination. Paracetamol toxicity is mediated by the production of the reactive metabolite NAPQI, which causes oxidative stress and cellular necrosis in the liver.[27]

Paracetamol-induced liver injury is a well-established experimental model that mimics drug-induced liver damage observed in humans, providing a valuable tool for understanding the mechanisms of hepatotoxicity and evaluating potential therapeutic interventions.

5.2.1. Mechanism of paracetamol toxicity

Paracetamol is metabolized in the liver by cytochrome P450 enzymes, producing a reactive metabolite called N-acetyl-p-benzoquinone imine (NAPQI). Under normal conditions, NAPQI is detoxified by conjugation with GSH. However, in cases of high-dose paracetamol intake, the liver's GSH reserves are rapidly depleted, leaving NAPQI unneutralized. Excess NAPQI binds covalently to hepatocyte proteins when GSH is exhausted, leading to direct cellular damage. NAPQI disrupts the integrity of cell membranes and organelle structures by forming covalent bonds with proteins. This damage results in hepatocyte death. NAPQI accumulation induces oxidative stress and lipid peroxidation, which further compromise cellular membranes. Oxidative stress impairs mitochondrial function, reducing cellular energy levels and causing necrosis. The metabolism of paracetamol through cytochrome P450 2E1 (CYP2E1) enhances the production of ROS, exacerbating oxidative stress and overwhelming cellular defense mechanisms.

Paracetamol toxicity is a widely used experimental model for studying acute liver injury. Its primary mechanism involves the accumulation of NAPQI due to GSH depletion, leading to oxidative damage, mitochondrial dysfunction, and eventual hepatocyte necrosis.[26,27,28,29]

5.2.2. Pathogenesis of paracetamol toxicity

The depletion of GSH leads to increased oxidative stress in hepatocytes and mitochondrial dysfunction. This mitochondrial impairment results in cellular energy loss and ATP depletion, ultimately causing cell death. Paracetamol toxicity primarily affects the centrilobular (central lobular) region of the liver, leading to hepatocyte necrosis. Necrosis causes the release of liver enzymes such as ALT and AST into the bloodstream, serving as biochemical markers of liver injury. Inflammation and widespread hepatocyte death can progress to acute liver failure. In

severe cases, this condition may become fatal.

Paracetamol-induced hepatotoxicity highlights the importance of oxidative stress and mitochondrial damage in liver injury, making it a critical model for studying acute liver failure and its underlying mechanisms.[25]

5.2.3. Biochemical changes in paracetamol toxicity

Paracetamol toxicity, when administered at high doses, induces oxidative stress and mitochondrial damage in the liver. It is metabolized into the toxic metabolite NAPQI, which depletes GSH stores in the liver.[26] The reduction in GSH levels weakens the cell's antioxidant defense system, leading to an increase in ROS. Biochemical analyses of experimental animals treated with paracetamol show elevated levels of serum ALT and AST, indicating hepatocyte damage.[27,28,29]

These biochemical changes are hallmarks of paracetamol-induced hepatotoxicity and serve as critical indicators for assessing liver injury in experimental models.

5.2.4. Histopathological changes in paracetamol toxicity

Paracetamol toxicity is widely used to model acute liver injury and is characterized by centrilobular necrosis in hepatocytes. This condition arises from the accumulation of NAPQI, a toxic metabolite of paracetamol metabolism, which induces oxidative stress and cellular necrosis.[27] Necrotic areas are observed around the central vein, reflecting severe hepatocyte damage. Expansion of the sinusoids due to structural damage. Presence of inflammatory cells infiltrating the liver tissue, contributing to further injury.[26,29,30]

These histopathological changes illustrate the extent of liver damage caused by paracetamol toxicity and serve as key features in experimental models for studying drug-induced liver injury.

5.3. Alcohol-induced liver injury model using ethanol

Ethanol induces alcoholic liver disease (ALD), characterized by fat accumulation, inflammation, and fibrosis in the liver. The ethanol-induced toxicity model is commonly used to study steatosis and inflammation in the liver.

Experimental protocol: Ethanol toxicity studies are commonly used rats and 5–10% ethanol is provided via drinking water or liquid diet. this experimantal protocol administered daily for 4–8 weeks. At the end of the 4–8 week period, liver tissue is collected for histological analysis to examine fat accumulation, ballooning hepatocytes, and fibrosis. Biochemical markers such as ALT, AST, and GGT levels are measured to assess liver damage.[31]

5.3.1. Mechanism of ethanol toxicity

Ethanol toxicity mimics ALD, characterized by fat accumulation, inflammation, and fibrosis. Ethanol is metabolized by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) enzymes, producing acetaldehyde as a reactive intermediate. Acetaldehyde induces oxidative stress in hepatocytes by increasing the production of ROS, triggering lipid peroxidation, which disrupts cellular membrane integrity and leads to hepatocyte necrosis.[32] Additionally ethanol metabolism causes an accumulation of NADH, which promotes fatty acid synthesis, resulting in steatosis (fat accumulation) in hepatocytes. If chronic ethanol consumption activates Kupffer cells (liver macrophages) and increases the release of inflammatory cytokines. This inflammatory response contributes to the progression of fibrosis and cirrhosis, characteristic of chronic liver disease.[33]

This model is a valuable tool for studying the pathophysiology of alcoholic liver disease and evaluating therapeutic interventions targeting ethanol-induced liver damage.

5.3.2. Pathogenesis of ethanol toxicity

Acetaldehyde, a byproduct of ethanol metabolism, is a key factor in triggering inflammatory and fibrotic responses in the liver. Acetaldehyde increases the production of ROS in hepatocytes, leading to oxidative stress. Oxidative stress causes lipid peroxidation, damaging cellular membranes and exacerbating inflammation.[32] Chronic ethanol consumption activates Kupffer cells (liver macrophages), promoting the release of inflammatory cytokines. The inflammatory response amplifies liver damage and creates a pro-fibrotic environment. The persistent inflammatory and oxidative damage contributes to the development of fibrosis and cirrhosis, hallmark features of chronic liver diseases associated with ethanol toxicity.[31,33]

This pathogenic pathway illustrates the significant role of acetaldehyde and oxidative stress in the progression of ethanol-induced liver injury, emphasizing its utility in studying alcoholic liver disease.

5.3.3. Biochemical changes in ethanol toxicity

Ethanol toxicity is associated with fat accumulation and oxidative stress in the liver. Acetaldehyde, a byproduct of ethanol metabolism, increases ROS production, leading to oxidative stress. Experimental animals exposed to ethanol exhibit elevated levels of AST, ALT, GGT, and MDA, markers of liver damage and oxidative stress.[32,34] Ethanol toxicity increases lipid peroxidation and serum triglyceride levels, reflecting enhanced fat accumulation in the liver. Ethanol metabolism leads to NADH accumulation, stimulating fatty acid synthesis and resulting in steatosis (fat accumulation in the liver).[33,34]

These biochemical changes highlight the dual impact of ethanol toxicity: promoting oxidative damage and metabolic dysregulation, which collectively drive liver injury and steatosis.

5.3.4. Histopathological changes in ethanol toxicity

Ethanol toxicity is characterized by fat accumulation, hepatocyte ballooning, and inflammation in the liver. Acetaldehyde, a byproduct of ethanol metabolism, triggers lipid peroxidation, leading to steatosis. Both microvesicular and macrovesicular fat deposits are observed in hepatocytes. Hepatocytes show swelling and ballooning, indicative of cellular injury. Inflammatory cells infiltrate liver tissue, contributing to further damage. Chronic ethanol exposure leads to severe histopathological changes, including fibrosis and the development

of cirrhosis.[32,33,35]

These histopathological findings underline the progressive nature of ethanol-induced liver injury, from steatosis to advanced stages like fibrosis and cirrhosis, making this model critical for studying chronic liver diseases.

5.4. Diclofenac (Non-steroidal anti-inflammatory drug - NSAID) model

Diclofenac, a widely used NSAID, can cause hepatotoxicity at high doses. This model is employed to study the effects of long-term NSAID use on liver function.

Experimental protocol: Diclofenac toxicity studies are used mice or rats. Administered orally or intraperitoneally at 10–50 mg/kg typically daily for 7–14 days. Animals are treated daily with diclofenac, after which liver tissue is collected for histopathological analysis. Biochemical markers, including ALT, AST, alkaline phosphatase (ALP), and bilirubin levels, are measured to evaluate liver dysfunction. Diclofenac induces hepatic toxicity by causing oxidative stress and mitochondrial damage.[36]

5.4.1. Mechanism of diclofenac toxicity

Diclofenac-induced hepatotoxicity involves its metabolism in the liver through hydroxylation and glucuronidation by cytochrome P450 enzymes, resulting in the formation of reactive intermediates. Reactive metabolites interact with mitochondrial membrane proteins, leading to oxidative stress and impaired mitochondrial function.[36] Mitochondrial dysfunction reduces ATP production, disrupting the energy balance in hepatocytes. Energy depletion and oxidative damage culminate in hepatocyte necrosis.[37] Diclofenac-induced hepatotoxicity serves as a model to explore NSAID-related liver injuries and understand the underlying mechanisms of oxidative damage and mitochondrial impairment.

5.4.2. Pathogenesis of diclofenac toxicity

Diclofenac exhibits hepatotoxic effects by inducing mitochondrial damage and oxidative stress in the liver. Diclofenac metabolites interact with mitochondrial membrane phospholipids, impairing mitochondrial function. This disruption leads to reduced ATP production and depletion of cellular energy reserves.[37] Mitochondrial damage increases ROS production. Depletion of intracellular glutathione reserves exacerbates oxidative stress and triggers lipid peroxidation, compromising cellular membrane integrity.[36]

These processes collectively highlight the acute hepatotoxic effects of diclofenac, driven by energy depletion and oxidative damage at the cellular and mitochondrial levels.

5.4.3. Biochemical changes in diclofenac toxicity

Diclofenac is an NSAID that causes mitochondrial damage and oxidative stress. Reactive intermediates formed during diclofenac metabolism contribute to hepatic oxidative stress by inducing mitochondrial dysfunction and depleting GSH reserves.[36] Increased levels of ALT and AST indicate liver cell damage. Elevated MDA levels reflect enhanced lipid peroxidation, a hallmark of oxidative stress.[37]

These biochemical markers serve as critical indicators of diclofenac-induced liver damage and highlight the role of oxidative and mitochondrial stress in hepatotoxicity.

5.4.4. Histopathological changes in diclofenac toxicity

Diclofenac-induced hepatotoxicity is associated with mitochondrial damage and oxidative stress, resulting in hepatocyte necrosis and inflammation. Presence of inflammatory cell infiltration in the portal and periportal areas. Swelling and ballooning of hepatocytes, indicative of cellular injury. Observation of focal necrotic areas within the liver tissue.[36,37] This histopathological profile is critical for understanding the toxic effects of diclofenac on the liver and provides insights into the mechanisms underlying NSAID-induced hepatotoxicity.

5.5. Cadmium exposure model

Cadmium is a heavy metal known for its toxic effects linked to environmental pollution. It induces oxidative stress in the liver, leading to tissue damage. The cadmium toxicity model is widely used to study the effects of environmental toxins on the liver.

Experimental protocol: Rats and rabbits are commonly used for cadmium toxicity studies. Cadmium administered at 1–10 mg/kg via intraperitoneal or oral routes. Typically 4–6 weeks, with daily or weekly administration, though extended protocols up to 28 weeks are also used. Cadmium toxicity is studied as a chronic model. After 4–6 weeks of cadmium administration, liver tissue is collected. Oxidative stress markers such as MDA and superoxide dismutase (SOD) levels are analyzed. Histopathological examination reveals indicators of liver damage, including necrosis, inflammation, and fibrosis.[11,39]

5.5.1. Mechanism of cadmium toxicity

Cadmium, an environmental pollutant and industrial heavy metal, induces significant oxidative stress and inflammation in the liver. Cadmium depletes GSH reserves and reduces the activity of antioxidant enzymes such as SOD.[11] Although cadmium does not directly generate ROS, it increases oxidative stress indirectly by inhibiting cellular antioxidant systems.[39] Cadmium disrupts intracellular calcium homeostasis, triggering apoptosis and leading to cell death.[40] Prolonged cadmium exposure results in chronic liver damage, including fibrosis. This process involves an inflammatory response in hepatocytes, accompanied by increased cytokine release.[41]

The mechanism highlights cadmium's role in disrupting cellular balance and its contribution to both acute and chronic liver injury through oxidative stress, apoptosis, and inflammation.

5.5.2. Pathogenesis of cadmium toxicity

Cadmium toxicity leads to liver damage through mechanisms involving oxidative stress and inflammation. Cadmium increases oxidative stress by inhibiting the activity of antioxidant enzymes such as GSH and SOD.[40] Suppression of antioxidant defenses and increased ROS production trigger lipid peroxidation in cell membranes, leading to cellular damage and death. Cadmium exposure enhances cytokine production and promotes the accumulation of inflammatory cells in hepatic tissue.

This inflammatory response contributes to chronic liver damage, including fibrosis.[41]

These interconnected processes of oxidative stress and inflammation underline the progression of cadmium-induced liver toxicity, culminating in acute injury and chronic conditions such as fibrosis.

5.5.3. Biochemical changes in cadmium toxicity

Cadmium toxicity induces oxidative stress and disrupts cellular energy balance in the liver. Cadmium accumulation decreases the activity of antioxidant enzymes such as GSH and SOD, exacerbating oxidative stress.[40] Serum levels of ALT, AST, and GGT are significantly increased, serving as biochemical indicators of liver cell damage.[42] Oxidative stress caused by cadmium enhances lipid peroxidation, leading to elevated MDA levels.

These biochemical changes reflect the hepatotoxic effects of cadmium, highlighting oxidative damage and impaired liver function as central features of its toxicity.

5.5.4. Histopathological changes in cadmium toxicity

Cadmium toxicity triggers oxidative stress, apoptosis, and inflammatory responses, leading to significant structural damage in the liver. Hepatocyte ballooning and apoptotic bodies are commonly observed. Inflammatory cell infiltration is evident in portal areas, reflecting an active immune response.[40] Perisinusoidal collagen accumulation and fibrosis are notable consequences of cadmium toxicity. Chronic exposure can progress to severe structural changes such as fibrosis and cirrhosis.[41,42]

These histopathological alterations underline the progression of cadmium-induced liver damage, from acute oxidative injury to chronic conditions like fibrosis and cirrhosis.

5.6. Bromobenzene model

Bromobenzene is a chemical used as an industrial and laboratory solvent that induces significant liver toxicity. This model is commonly employed to study cellular necrosis and oxidative stress effects in the liver.

Experimental protocol: Bromobenzene toxicity studies are used mice or rats. and 500–1000 mg/kg, administered as a single dose via intraperitoneal or oral routes. Administration with 24–72 hours after administering a single dose of bromobenzene, liver tissue is collected for histopathological and biochemical analysis. Biochemical parameters, including ALT, AST, GSH levels, and oxidative stress markers, are evaluated. Bromobenzene induces hepatic cell damage through increased ROS production.[43]

5.6.1. Mechanism of bromobenzene toxicity

Bromobenzene is an industrial solvent with significant hepatotoxic effects, primarily mediated through its metabolism in the liver. Bromobenzene is metabolized by cytochrome P450 enzymes in the liver, producing reactive epoxide intermediates. These intermediates require conjugation with GSH for detoxification.[43] If GSH reserves are depleted, reactive metabolites persist and induce oxidative stress, damaging cellular membranes. Oxidative damage leads to lipid peroxidation, cellular necrosis, and inflammation, exacerbating liver injury.

This mechanism highlights the role of oxidative stress and glutathione depletion in bromobenzene-induced hepatotoxicity, making it a valuable model for studying acute liver injury.

5.6.2. Pathogenesis of bromobenzene toxicity

Bromobenzene is metabolized by cytochrome P450 enzymes in the liver, producing reactive epoxide intermediates. The reactive epoxides generated are detoxified through conjugation with GSH. When GSH reserves are depleted, the epoxides persist and induce oxidative damage.[43] The reactive metabolites trigger lipid peroxidation in cellular membranes, leading to hepatocyte necrosis. Bromobenzene metabolites stimulate inflammatory responses in the liver, exacerbating tissue damage and promoting the spread of cellular injury.

This pathway underscores the critical role of oxidative stress, GSH depletion, and inflammation in the hepatotoxic effects of bromobenzene.

5.6.3. Biochemical changes in bromobenzene toxicity

Bromobenzene toxicity results in significant oxidative stress and lipid peroxidation in the liver. Reduced GSH levels are observed, reflecting impaired antioxidant defenses. Elevated MDA levels indicate enhanced lipid peroxidation, a hallmark of oxidative stress.[43,44] Increased serum levels of ALT and AST serve as biochemical markers of hepatocyte damage.

These biochemical alterations highlight the oxidative damage and hepatocyte injury induced by bromobenzene, emphasizing its role as a model for studying acute liver toxicity.

5.6.4. Histopathological changes in bromobenzene toxicity

Bromobenzene toxicity leads to oxidative stress and lipid peroxidation in liver cells, resulting in notable histopathological alterations. Extensive necrotic areas are observed in liver tissue, indicating severe cellular damage. Narrowing of sinusoids due to structural damage and cellular alterations. Infiltration of inflammatory cells seen within the liver, reflecting an active immune response.

These histopathological changes are closely linked to glutathione depletion and the resultant oxidative stress, highlighting the severe cellular injury caused by bromobenzene toxicity.[43,44]

5.7. Tetrachloroethylene (PCE) model

Tetrachloroethylene (PCE) is an industrial solvent used in environmental toxicity studies to investigate its effects on the liver, particularly focusing on oxidative stress and biotransformation processes.

Experimental protocol: Mice or rats are commonly used in PCE toxicity models. Administered at 500–2000 mg/kg via intraperitoneal or oral routes and typically applied for 1–4 weeks, 2–3 times per week. After PCE administration, liver tissue is collected for analysis. Biochemical parameters such as AST, ALT, and MDA are measured to

assess oxidative stress. Histopathological examination reveals structural changes such as hepatocyte necrosis and sinusoidal dilation. PCE induces oxidative stress by increasing reactive oxygen species (ROS), leading to lipid peroxidation in the liver.[45]

5.7.1. Mechanism of PCE toxicity

Tetrachloroethylene is an industrial solvent that contributes to environmental pollution and induces oxidative stress in the liver. PCE undergoes biotransformation in the liver, leading to the generation of ROS. The increased ROS production triggers oxidative stress.[45] ROS induces lipid peroxidation, damaging cellular membranes and disrupting hepatocyte integrity. The oxidative damage and membrane disruption result in hepatocyte necrosis, contributing to liver injury.

This mechanism highlights the critical role of oxidative stress and lipid peroxidation in PCE-induced hepatotoxicity, making it a valuable model for studying the toxic effects of environmental pollutants.

5.7.2. Pathogenesis of PCE toxicity

Tetrachloroethylene induces liver damage through oxidative stress and lipid peroxidation, resulting from its biotransformation in the liver. PCE metabolism increases the production of ROS. ROS trigger lipid peroxidation, leading to structural damage to cellular membranes and disrupting cellular function.[45] Membrane damage and cellular dysfunction result in hepatocyte death. PCE exposure activates inflammatory responses, contributing to chronic liver damage and potentially progressing to fibrosis or cirrhosis.

This pathogenic mechanism highlights the role of oxidative stress and inflammation in PCE-induced liver injury, underlining its significance in environmental toxicity studies.

5.7.3. Biochemical changes in PCE toxicity

Tetrachloroethylene induces oxidative stress and lipid peroxidation in the liver, leading to significant biochemical alterations. Increased levels of ALT and AST indicate hepatocyte damage. Elevated MDA levels reflect enhanced lipid peroxidation, a marker of oxidative stress.[45,46] Decreased GSH levels indicate weakened antioxidant defense mechanisms, exacerbating cellular injury.

These biochemical changes demonstrate the oxidative and metabolic disruptions caused by PCE, highlighting its hepatotoxic effects.

5.7.4. Histopathological changes in PCE toxicity

Tetrachloroethylene induces lipid peroxidation and membrane damage in the liver, leading to hepatocyte apoptosis and necrosis. Sinusoidal dilation is observed, reflecting structural changes in liver vasculature. Necrotic areas within hepatocytes indicate severe cellular damage. Accumulation of inflammatory cells in portal areas suggests an active immune response. Prolonged PCE exposure can lead to fibrotic changes and chronic liver damage.[45,46]

These histopathological findings highlight the severe impact of PCE on liver structure and function, illustrating its potential to cause both acute and chronic hepatic injury.

5.8. Trichloroethylene (TCE) model

Trichloroethylene is an industrial solvent and cleaner known for its hepatotoxic effects. The TCE toxicity model is particularly useful for studying long-term effects such as fat accumulation (steatosis) and fibrosis.

Experimental protocol: Rats are commonly used in TCE toxicity studies. TCE administered at 1000 mg/kg either orally or via inhalation and experimental animals daily exposure for 4–6 weeks. Liver tissue is analyzed histopathologically for lipid accumulation and fibrosis. Biochemical parameters, including ALT, AST, and lipid peroxidation markers, are measured to assess liver function. TCE disrupts lipid metabolism, contributing to steatosis and fibrosis.[47]

5.8.1. Mechanism of TCE toxicity

Trichloroethylene is a chemical solvent known for its hepatotoxic effects, including steatosis and fibrosis. TCE is metabolized in the liver by the cytochrome P450 system, leading to the production of reactive intermediates. These intermediates increase lipid peroxidation and trigger oxidative stress. TCE disrupts lipid homeostasis, contributing to fat accumulation in hepatocytes (steatosis). Prolonged TCE exposure exacerbates oxidative damage, leading to fibrosis and impairing liver function.[47]

This mechanism highlights TCE's role in promoting chronic liver damage, emphasizing its use in models exploring the effects of industrial pollutants on hepatic health.

5.8.2. Pathogenesis of TCE toxicity

Trichloroethylene disrupts lipid metabolism in the liver, promoting steatosis (fat accumulation) and inflammation. During TCE metabolism, toxic intermediates are formed, which increase ROS production. The elevated ROS levels initiate lipid peroxidation, damaging cellular membranes and promoting oxidative stress.[47] The oxidative damage triggers chronic inflammatory responses in the liver, exacerbating tissue injury. Persistent inflammation and oxidative stress contribute to the development of fibrosis, significantly increasing the risk of chronic liver diseases and eventual liver failure.

This pathogenic process highlights the role of TCE in inducing long-term liver damage, making it a critical model for studying steatosis, fibrosis, and their underlying mechanisms.

5.8.3. Biochemical changes in TCE toxicity

Trichloroethylene induces lipid peroxidation and oxidative stress in the liver, leading to notable biochemical alterations. Increased levels of ALT, AST, GGT, and MDA are observed, indicating hepatocyte damage and oxidative stress.[47,48] Decreased GSH levels reflect suppressed cellular defense mechanisms and increased vulnerability to hepatocyte injury.

These biochemical markers highlight the oxidative and metabolic disruptions caused by TCE, underlining its hepatotoxic effects.

5.8.4. Histopathological changes in TCE toxicity

Trichloroethylene exposure induces fat accumulation and inflammation in the liver, leading to significant histopathological alterations. Both microvesicular and macrovesicular fat accumulation (steatosis) is observed in hepatocytes. Narrowing of sinusoids due to structural alterations and tissue remodeling. Accumulation of inflammatory cells in the portal areas reflecting an active immune response. Prolonged TCE exposure results in fibrosis and loss of liver function, contributing to chronic liver damage.[47,48]

These histopathological changes underline the progressive nature of TCE-induced liver injury, from acute steatosis and inflammation to chronic fibrosis and functional impairment.

5.9. Methotrexate (Chemotherapeutic agent) model

Methotrexate is a chemotherapeutic drug widely used in cancer treatment, with a known risk of hepatotoxicity. Chronic use of methotrexate can trigger liver fibrosis and contribute to hepatotoxicity. This model is employed to study effects such as liver fibrosis and necrosis.

Experimental protocol: Rats are commonly used in this model, though mice (e.g., C57BL/6) may also be utilized. Administered at 10–20 mg/kg intraperitoneally, once a week and weekly administration for 4–6 weeks. After methotrexate treatment, liver tissue is collected for analysis. ALT, AST, and MDA levels are measured to evaluate oxidative stress and lipid peroxidation. Liver sections are analyzed for hepatocyte necrosis, fibrosis, and inflammation. Methotrexate induces liver damage by promoting oxidative stress and inflammation.[49,50]

5.9.1. Mechanism of methotrexate (MTX) toxicity

Methotrexate (MTX) exerts its hepatotoxic effects through enzyme inhibition, oxidative stress, and inflammation. MTX inhibits Dihydrofolate Reductase (DHFR), disrupting folate metabolism and impairing DNA and RNA synthesis. This effect is particularly toxic to rapidly dividing cells, leading to cell death.[50] During MTX metabolism, reactive oxygen species (ROS) are generated. ROS increase oxidative stress and trigger lipid peroxidation, damaging cellular membranes.[50] Folate deficiency hampers DNA repair and cell division, exacerbating cellular damage and promoting hepatocyte death. MTX increases inflammatory cytokine levels, contributing to chronic liver damage and the development of fibrosis.

This multifaceted mechanism explains the hepatotoxic potential of methotrexate, emphasizing its impact on oxidative balance, inflammation, and cellular repair processes.

5.9.2. Pathogenesis of MTX toxicity

Methotrexate is a chemotherapeutic agent that inhibits folate metabolism, disrupting DNA synthesis and repair in liver cells. MTX suppresses cellular replication processes by depleting folate, leading to increased oxidative stress in hepatocytes.[50] Depletion of antioxidant defenses, including GSH, exacerbates oxidative damage, resulting in hepatocyte death and hepatic inflammation. Folate deficiency promotes intracellular ROS production, triggering lipid peroxidation and further damaging cellular membranes. Prolonged MTX use increases the release of fibrogenic cytokines such as TGF-β, which activates hepatic stellate cells. Activated stellate cells produce collagen and extracellular matrix proteins, contributing to fibrosis. As fibrosis progresses, liver stiffening and chronic damage occur, potentially advancing to cirrhosis.

This pathogenic mechanism illustrates the multi-step process by which MTX induces liver injury, encompassing oxidative stress, inflammation, and fibrogenesis, ultimately leading to chronic liver disease.

5.9.3. Biochemical changes in MTX toxicity

Methotrexate inhibits folate metabolism, leading to increased oxidative stress and disruption of DNA synthesis. Significant increases in ALT and AST levels indicate hepatocyte damage and compromised liver function. Higher levels of MDA reflect enhanced lipid peroxidation, a hallmark of oxidative stress.[50,51] Decreased GSH levels indicate diminished cellular defense mechanisms, exacerbating oxidative damage and vulnerability to hepatocyte injury.

These biochemical alterations underscore the role of oxidative stress and antioxidant depletion in MTX-induced liver toxicity, serving as critical markers for assessing its hepatotoxic effects.

5.9.4. Histopathological changes in MTX toxicity

Methotrexate induces cellular damage and mitosis inhibition in hepatocytes due to folate deficiency. Perisinusoidal fibrosis is observed, reflecting extracellular matrix deposition and tissue remodeling. Infiltration of inflammatory cells into liver tissue, indicating an active immune response to cellular injury. Presence of apoptotic cells highlights the extent of hepatocyte death caused by MTX toxicity.[50,51] Prolonged MTX use leads to progressive fibrosis and severe tissue damage, potentially resulting in chronic liver disease.

These histopathological changes illustrate the structural damage caused by MTX toxicity, emphasizing its impact on liver function and the progression toward fibrosis with long-term use.

5.10. Isoniazid toxicity model

Isoniazid, a drug used in tuberculosis treatment, can cause hepatotoxicity with prolonged use. This model is employed to study acute drug-induced liver damage.

Experimental protocol: Rats are commonly used in isoniazid toxicity studies. Administered at 50–200 mg/kg via oral or intraperitoneal routes and daily administration for 4–8 weeks. Liver tissue is analyzed to evaluate the toxic effects of drug metabolites. ALT, AST, and total bilirubin levels are measured to assess liver function. Liver samples are evaluated for hepatocyte necrosis, cellular infiltration, and steatosis as indicators of liver damage.[52,53]

5.10.1. Mechanism of isoniazid (INH) toxicity

Isoniazid (INH), an antituberculosis agent, induces hepatotoxicity through its metabolism and subsequent

immune response. INH is metabolized in the liver by N-acetyl transferase (NAT2) to produce reactive metabolites. These metabolites covalently bind to hepatocyte proteins, forming adducts that are recognized by the immune system, triggering an immune response.[53] Reactive metabolites increase oxidative stress, depleting glutathione (GSH) reserves and weakening cellular defenses. This leads to lipid peroxidation and further cellular damage. The combination of immune-mediated damage and oxidative stress culminates in hepatocyte necrosis, a hallmark of INH-induced liver injury.

This mechanism highlights the dual contribution of immune activation and oxidative stress in isoniazid hepatotoxicity, making it a valuable model for studying drug-induced liver injury.

5.10.2. Pathogenesis of INH toxicity

Isoniazid, used in tuberculosis treatment, causes hepatotoxicity with prolonged use through its metabolism and subsequent cellular and immune-mediated damage. INH is metabolized in the liver by N-acetyl transferase (NAT2), resulting in the production of toxic metabolites. These metabolites form covalent bonds with hepatocyte proteins, creating adducts that activate the immune system, triggering hepatic inflammation.[53] Reactive metabolites induce oxidative stress by depleting antioxidant reserves such as GSH. This leads to lipid peroxidation, causing structural damage to cellular membranes and further compromising hepatocyte integrity. Activation of inflammatory cells exacerbates liver injury, amplifying tissue damage and contributing to hepatocyte necrosis.

This pathogenic pathway highlights the combined effects of immune activation, oxidative stress, and inflammation in INH-induced liver toxicity, explaining its hepatotoxic potential in long-term usage.

5.10.3. Biochemical changes in INH toxicity

Isoniazid toxicity induces immune activation and oxidative stress, leading to significant biochemical alterations in the liver. INH depletes GSH levels, weakening cellular antioxidant defenses. Elevated MDA levels indicate enhanced lipid peroxidation, a hallmark of oxidative stress.[53] ALT and AST levels rise significantly, indicating hepatocyte damage. Total bilirubin levels increase, reflecting impaired liver function and bile excretion.

These biochemical markers illustrate the oxidative damage and immune-mediated injury associated with INH toxicity, emphasizing its impact on hepatocyte function and antioxidant balance.

5.10.4. Histopathological changes in INH toxicity

Isoniazid induces the production of toxic metabolites that form covalent bonds with proteins in hepatocytes, triggering an immune response and structural damage in the liver. Swelling of hepatocytes, indicative of cellular injury. Widespread necrotic areas in the liver tissue, reflecting significant hepatocyte death. Accumulation of inflammatory cells in portal areas, highlighting the immune response to drug-induced injury.

These histopathological findings demonstrate the extent of liver damage caused by INH toxicity, emphasizing the role of immune activation and oxidative stress in drug-induced hepatotoxicity.[53]

5.11. Tamoxifen (Endocrine therapeutic) model

Tamoxifen, used in breast cancer treatment, poses a risk of hepatotoxicity with long-term use. Its effects on lipid metabolism make it a valuable model for studying hepatic steatosis and liver fat accumulation.

Experimental protocol: Mice and rats are commonly used in tamoxifen toxicity studies. Administered at 20–50 mg/kg via oral or intraperitoneal routes and 6–8 weeks, applied 2–3 times per week. Liver tissue is collected for histopathological analysis after tamoxifen administration. ALT, AST, and bilirubin levels are measured to assess liver function. Signs of hepatocyte necrosis, fat accumulation (steatosis), and fibrosis are evaluated. Tamoxifen induces liver damage through lipid peroxidation and mitochondrial dysfunction.[54,55]

5.11.1. Mechanism of tamoxifen toxicity

Tamoxifen, a selective estrogen receptor modulator (SERM) used in breast cancer treatment, induces hepatotoxicity through oxidative stress and mitochondrial dysfunction. During tamoxifen metabolism in the liver, ROS are produced. Increased ROS levels lead to lipid peroxidation, causing damage to cellular membranes.[55] Tamoxifen disrupts mitochondrial function, reducing ATP production and impairing cellular energy balance. Energy depletion contributes to hepatocyte necrosis and apoptosis.

This dual mechanism of oxidative damage and mitochondrial dysfunction highlights the hepatotoxic potential of tamoxifen, particularly during long-term use.

5.11.2. Pathogenesis of tamoxifen toxicity

Tamoxifen is widely used in the treatment of breast cancer; however, it can also lead to toxic effects in the liver. The underlying mechanisms of hepatotoxicity include oxidative stress, inflammation, mitochondrial dysfunction, and apoptotic processes. These pathways result in significant liver cell damage and enhanced inflammatory responses.

The toxic effects of tamoxifen in the liver are mediated through increased production of ROS, which induces oxidative stress. This phenomenon triggers lipid peroxidation, protein oxidation, and DNA damage. Famurewa et al. demonstrated that oxidative imbalance and inflammatory pathways, such as the NO/iNOS/NF-κB signaling axis, play a central role in tamoxifen-induced hepatotoxicity.[56] Mitochondrial dysfunction is a critical component of tamoxifen metabolism's toxic effects. Ribeiro et al. reported that the activation of mitochondrial permeability transition pores and the reduction in ATP production disrupt energy metabolism in hepatocytes, triggering cellular death pathways.[57] Inflammation represents another key aspect of hepatotoxicity. Ahmed et al. highlighted that tamoxifen administration increases the levels of inflammatory cytokines, including TNF-α and IL-6, thereby initiating inflammatory responses that can lead to liver fibrosis.[58] Apoptotic mechanisms associated with liver damage are also notable. Gao et al. revealed

that tamoxifen activates apoptotic pathways, resulting in significant morphological changes in hepatocytes.[59] Moreover, studies by Karam et al. suggested that tamoxifen-induced toxicity is linked to dysregulation in cellular signaling pathways, such as Nrf2 and NF-κB. These pathways may serve as potential therapeutic targets for mitigating hepatotoxicity.[60]

5.11.3. Biochemical changes in tamoxifen toxicity

Tamoxifen induces cellular damage in the liver by increasing lipid peroxidation. Increased ALT and AST levels indicate hepatocyte damage. Elevated MDA levels reflect enhanced lipid peroxidation, a hallmark of oxidative stress. Decreased GSH levels indicate impaired cellular antioxidant defense, exacerbating oxidative damage.[55,61]

These biochemical changes highlight the oxidative stress and metabolic disturbances caused by tamoxifen, serving as critical indicators of its hepatotoxic effects.

5.11.4. Histopathological changes in tamoxifen toxicity

Long-term tamoxifen use carries a risk of hepatotoxicity, primarily through lipid peroxidation and damage to cellular membranes. Fat accumulation is observed in hepatocytes, indicative of disrupted lipid metabolism. Swelling of hepatocytes, reflecting cellular injury. Fibrosis in the perisinusoidal regions, signaling extracellular matrix deposition and chronic liver damage.[55,61]

These histopathological changes highlight the structural and metabolic alterations in the liver due to tamoxifen, emphasizing its potential to cause chronic liver injury.

6. Conclusion

Liver toxicity models in experimental animals play a vital role in biomedical and toxicological research. These models provide a detailed understanding of the toxic effects of various chemicals on the liver at molecular, cellular, and tissue levels. Toxins such as acetaminophen, cadmium, ethanol, carbon tetrachloride, and diclofenac cause liver damage through distinct mechanisms, creating specific biochemical and histological changes that are observed through a variety of biomarkers and histopathological evaluations.

For instance, acetaminophen at high doses induces centrilobular necrosis, while cadmium triggers oxidative stress, apoptosis, and inflammation. Chronic exposure to ethanol leads to conditions such as steatosis and fibrosis. Chemicals like carbon tetrachloride cause lipid peroxidation, resulting in extensive cellular damage and long-term effects such as cirrhosis. These diverse models reveal the complex pathophysiological processes triggered by different toxins and highlight their unique biochemical and histological damage profiles.

Liver biochemical changes reflect the metabolic pathways and stress responses to toxins. Elevated levels of enzymes such as ALT and AST indicate hepatocyte damage, while increased MDA levels mark enhanced lipid peroxidation. Decreased GSH levels signal weakened antioxidant defenses, correlating with heightened oxidative stress. Furthermore, reduced activities of enzymes like SOD demonstrate a compromised defense mechanism against free radicals. These biochemical alterations provide critical insights into liver function deterioration and the initiation of cellular damage.

Each toxin presents a unique damage profile. Acetaminophen toxicity often shows centrilobular necrosis and sinusoidal dilation, whereas ethanol toxicity is marked by fat accumulation and hepatocyte ballooning. Carbon tetrachloride induces structural changes such as perisinusoidal fibrosis and collagen deposition, while diclofenac toxicity features mitochondrial damage and inflammation. Such variations in histological damage reveal the extent and type of injury caused by toxins and offer a detailed map of the liver's response, aiding in understanding the progression and chronic potential of the damage.

These models also provide foundational knowledge for preclinical drug evaluations and the development of hepatoprotective agents. For instance, studies showing glutathione supplementation mitigating acetaminophen toxicity or antioxidants reducing lipid peroxidation in carbon tetrachloride toxicity offer potential therapeutic strategies. Thus, liver toxicity models not only elucidate toxin effects but also guide protective and therapeutic interventions.

Findings from these models significantly enhance our understanding of the detrimental effects of chemicals on liver health. Detailed examinations of biochemical and histological changes due to toxins contribute to the prevention of toxic effects and the development of liver protection strategies. These insights also assist in identifying new therapeutic targets for minimizing liver damage, underlining the indispensable role of experimental liver toxicity models in both fundamental research and clinical applications. As a result, these models form a valuable basis for future research aimed at safeguarding liver health and combating toxin-induced damage effectively.

Ethical approval

This study does not require approval from the Ethics Committee for Animal Experiments.

Authors contribution

HN: Research, planning, article scanning, writing-original draft & review.

Conflict of interest

There are no conflicts of interest associated with this re-search publication, according to the authors.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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