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Review Article

Preclinical Models of Hepatic Injury: A Comprehensive Review of Chemically, Immunologically, and Pharmacologically Induced Liver Damage in Rat Models

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ABSTRACT

The hepatic organ plays a vital role in maintaining the body's homeostasis by facilitating intricate biochemical reactions. Hepatic impairment, a pervasive condition in diverse liver disorders, poses considerable challenges due to its propensity for recurrence and potential to progress to debilitating conditions, including fibrotic scarring, cirrhotic degeneration, and hepatic failure or malignancy. To elucidate the underlying mechanisms and develop efficacious therapeutic strategies, it is crucial to establish a murine model that accurately recapitulates the clinical manifestations and pathophysiological processes of liver damage. The goal of this study is to present a thorough analysis of the many liver damage models, encompassing chemically induced, immune-mediated, alcohol-related, and drug-induced paradigms, with a focus on their methodologies, molecular mechanisms, and relative merits and limitations. By developing robust animal models, researchers can investigate novel hepatoprotective interventions and garner valuable insights into the management of liver damage disorders, thereby enhancing patient care and outcomes.

Keywords: Hepatotoxicity, Rodent Models, Liver Injury Mechanisms, Experimental Pathology, Signaling Pathways.

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INTRODUCTION

The hepatic organ is a sophisticated entity that fulfills a vital function in numerous physiological processes, encompassing protein synthesis, detoxification, and metabolic regulation (Shingina *et al.*, 2023). Hepatic impairment is a significant clinical concern, especially considering the COVID-19 pandemic's impact on liver health (Li and Fan 2020). The liver's extensive vascular network and pivotal role in metabolic homeostasis render it susceptible to injury from various endogenous and exogenous substances, potentially leading to hepatic disorders and damage (Damm and Kramer 2016). Globally, hepatic diseases account for a substantial mortality rate, with cirrhosis, hepatocellular carcinoma, and complications arising from liver damage being prominent causes of death (Asrani *et al.*, 2019; Sun *et al.*, 2019). Hepatic damage can stem from diverse etiologies, including cholestatic, autoimmune hepatitis, liver disease, viral hepatitis, non-alcoholic steatohepatitis, and ethanol consumption, ultimately resulting in anomalous wound healing responses, hepatic inflammation, and compromised liver function (Crabb *et al.*, 2020; Zhang *et al.*, 2019). Hepatic injury can be dichotomized into endogenous and exogenous categories,

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precipitating hepatocellular damage, dysfunction, inflammation, and architectural alterations (Duarte *et al.*, 2015; Thomson *et al.*, 2017). Acute and chronic hepatic injury represent two distinct forms of liver damage, with the latter potentially progressing to cirrhosis and life-threatening sequelae (Giordano and Zervos 2013; Guicciardi and Gores 2005; Thomson *et al.*, 2017). Given the considerable burden of hepatic disease, developing effective therapeutic strategies is paramount (Hussaini and Farrington 2007; R. J. Lu *et al.*, 2016). Animal models, particularly murine models, are essential tools for advancing clinical medicine and elucidating hepatic disease mechanisms (Sakowicz *et al.*, 2022; Wang *et al.*, 2021). At present, chemical, immunological, alcoholic, and drug-induced liver injury are commonly used in rodent models (Figure 1) (Mao *et al.*, 2024). The goal of this review is to present a thorough summary of various murine models of hepatic injury, including chemically induced, immunological, alcoholic, and drug-induced models, highlighting their underlying mechanisms, modeling methodologies, advantages, and disadvantages, as well as signaling pathways implicated in hepatic damage (Weiler-Normann, Herkel, and Lohse 2007; Wu *et al.*, 2023; Zhai *et al.*, 2023). By synthesizing the current state of knowledge on hepatic injury models, this review seeks to inform researchers in selecting suitable models for their investigations.

RODENT MODEL OF CHEMICAL LIVER INJURY

Model of liver damage caused by carbon tetrachloride

Carbon tetrachloride (CCl_4) is a potent liver toxin commonly utilized in industrial settings, primarily gaining entry into the body through gastrointestinal absorption or respiratory inhalation. This substance can precipitate hepatocellular damage in both animals and humans, and associated model of liver damage bears a striking resemblance to the clinical presentation of Acute Liver Injury (ALI) (Yu *et al.*, 2011). Rodent models commonly employed in research investigating liver injury is explained in Table 1.

Mechanism

The hepatotoxic effects of CCl_4 are attributed to its metabolic activation by the Cytochrome P450 (CYP450) enzyme system, which generates trichloromethyl radicals. These highly reactive species initiate a cascade of lipid peroxidation reactions, compromising membrane fluidity and permeability, and disrupting cellular calcium homeostasis. The ensuing cellular damage encompasses cytoskeletal disruption, phospholipase activation, and oxidative modifications to biomolecules, including proteins, lipids, and nucleic acids. Furthermore, the covalent binding of trichloromethyl radicals to DNA and hepatic proteins can precipitate cellular dysfunction, ultimately culminating in hepatocellular injury and necrosis (Figure 2A) (Zhang *et al.*, 2017).

The modeling technique

Experimental models of acute hepatic impairment have been established utilizing CCl_4 administration in rodents. Specifically, male Wistar/SD rats (6-8 weeks old) received a solitary dose of CCl_4 (1 mL per kilogram, 40-50% plant-based oil used) via intraperitoneal or subcutaneous injection (Y. Lu *et al.,* 2016). In a different study, CCl_4 (2 mL/kg, 10% in olive oil) was injected intraperitoneally once to cause acute liver injury in C57BL/6 mice (8-9 weeks old) (Wang *et al.,* 2017). For chronic hepatic injury models, rodents were administered CCl_4 (1 mL/kg, 40% in plant oil) twice weekly for 8-12 weeks via intraperitoneal injection or oral gavage (Weber, Boll, and Stampfl 2003). Notably, co-administration of phenobarbital, acetone, or CYP450 enzyme inducers can potentiate CCl_4 hepatotoxicity and abbreviate the duration required for chronic hepatic injury model establishment (Yu *et al.,* 2022).

Advantages or disadvantages

The CCl_4-induced liver damage model is a traditional and widely used approach. The ALI model is characterized by a short modeling cycle, high repeatability, and economic feasibility, accurately reflecting hepatic cellular activity, metabolic processes, and morphological changes. In contrast, the Chronic Liver Injury (CLI) model has a longer modeling cycle and requires careful handling due to potential hazards. To ensure safe operation, it is essential for researchers to follow standard operating procedures and take necessary precautions (R. Zhang *et al.,* 2012).

Model of liver damage caused by D-galactosamine

D-Galactosamine (D-GalN) is a chemical compound that impairs liver cell function by interfering with uridine nucleotide metabolism, resulting in inflammatory responses and extensive liver damage. The histopathological features induced by D-GalN are similar to those seen in human viral hepatitis, providing a useful model for investigating liver pathology (Gupta *et al.,* 2022).

Mechanism

D-GalN disrupts uridine nucleotide metabolism, causing liver cell damage and necrosis. It also binds to liver cell membranes, altering ion balance, activating phospholipase, and increasing oxidative stress. The resulting decrease in glutathione levels triggers TNF-α production, leading to cell death (Figure 2B) (Cengiz *et al.,* 2015).

The modeling technique

Commonly used are adult SDF grade Balb/c mice or Wistar/SD rats. Physiological saline is used to generate a 10% solution of D-GaIN, It is subsequently brought to pH 7.0 with 1 mmol/L NaOH. After 24 to 28 hr of execution, 600 mg/kg to 900 mg/kg are all administered intraperitoneally at once and ALI model was created (Colakoglu *et al.,* 2016). This category includes rates of acute hepatotoxicity caused by a single dose of D-GalN (300 mg/

kg·body weight, i.p.). Widespread liver necrosis frequently results from doses more than 1000 mg/kg (Zhuge *et al.,* 2020).

Advantages and disadvantages

The D-GalN method is a specific and relevant tool for studying liver disease, with minimal effects on non-hepatic tissues. It is useful for investigating viral hepatitis, hepatic encephalopathy, and liver failure, but is relatively expensive and challenging to reverse (Al-Qahtani and Binobead 2019).

Model of liver damage caused by thioacetamide

Thioacetamide (TAA) is a hepatotoxic agent that can cause liver cell injury and increase oxidative stress through lipid peroxidation. The TAA-induced liver fibrosis model is a relevant and widely used model for investigating the pathogenesis of acute liver failure and hepatic fibrosis, with similarities to human liver fibrosis (Cheng *et al.,* 2021).

Mechanism

TAA induces liver injury by promoting oxidative damage, reducing glutathione levels, and increasing free radical formation. This causes a disturbance in calcium homeostasis, enhanced ROS production, and mitochondrial dysfunction, leading to cellular damage through interconnected mechanisms (Figure 2C) (Wijesundera *et al.,* 2016).

Modeling method

Various rodent models, including BALB/c mice, C57BL/6 mice, Sprague-Dawley rats, and Wistar rats aged 6-8 weeks, are utilized to investigate TAA-induced hepatotoxicity. TAA can be administered by a variety of methods, such as intraperitoneal and subcutaneous injection, and oral gavage, thanks to its high aqueous solubility. TAA can be prepared in normal saline at a concentration equal to 0.03% for parenteral administration, whereas highly purified water is used for oral gavage. The standard treatment protocol involves administering 200 mg/kg doses 2-3 times weekly, with treatment durations typically exceeding four weeks, irrespective of the administration route (Deng *et al.,* 2018; Hessien *et al.,* 2010).

Advantages and disadvantages

The advantages of the TAA model include its excellent repeatability, stability, and durability of the induced damage. Nevertheless, the model has some drawbacks, such as the potential for TAA to act as a weak carcinogen and the requirement for careful protocol adherence. Furthermore, the model's scope is limited by its predominant use in small animal models (Tennakoon *et al.,* 2015).

A model of α-Naphthyl isothiocyanate-induced liver damage

An indirect toxin that targets bile duct epithelial cells causes the release of bile acids, which in turn causes liver damage in the ANIT model of liver injury. Similar to real intrahepatic cholestasis, this model is characterized by high levels of both total and direct bilirubin, which can harm liver and bile duct cells. The ANIT model is frequently used to investigate jaundice and intrahepatic cholestasis (Xa *et al.,* 2004).

An indirect toxin that targets bile duct epithelial cells causes the release of bile acids, which in turn causes liver damage in the ANIT model of liver injury. Similar to human intrahepatic cholestasis, this model is characterized by high levels of both total and direct bilirubin, which can harm liver and bile duct cells. Intrahepatic cholestasis and Jaundice are commonly studied using the ANIT model.

Mechanism

The hepatotoxic effects of ANIT are attributed to its accumulation in bile, which damages intrahepatic bile duct epithelial cells, leading to hyperplasia, inflammation, and bile duct obstruction. This ultimately results in the accumulation of toxic bile components in the liver, causing hepatobiliary damage and mitochondrial dysfunction (Figure 2D) (Palmeira *et al.,* 2003).

Method of modelling

ANIT-induced liver injury can be studied in a range of rodent models, including Wistar rats and BALB/c mice. The compound can be administered orally in olive oil at doses of 60-100 mg/kg to induce acute liver injury, or intraperitoneally at 80 mg/kg once weekly for 16 weeks to induce chronic liver injury (Gijbels *et al.,* 2021; Zhao *et al.,* 2013).

Advantages and disadvantages

The benefits of this model include its simplicity, consistency, and high reliability, making it a valuable tool for assessing medications that support liver health and bile production. However, the model's drawbacks include the hazardous nature of the substance, the extended duration of the study, and the necessity for rigorous adherence to established protocols (Ding *et al.,* 2012).

Model of liver damage caused by dimethylnitrosamine

Dimethylnitrosamine is a highly toxic compound that can cause liver damage and is known to induce hepatocarcinogenesis and mutagenesis. The DMN-induced liver disease model is appropriate for studying the pathogenesis of liver fibrosis due to its resemblance to human liver fibrosis. Additionally, this model can be utilized to study acute liver failure and the transition from liver cirrhosis to hepatocellular carcinoma (Jahan *et al.,* 2022).

Mechanism

The bioactivation of DMN by liver CYP2E1 results in the formation of toxic metabolites that cause cellular damage and liver injury. By stimulating hepatic stellate cells, elevated MMP-2 expression and activity are essential for the development of liver fibrosis, promoting collagen deposition, and enhancing cell proliferation. Additionally, MMP-2 contributes to liver damage by inducing capillarization of hepatic sinusoids (Figure 2E) (Liu *et al.,* 2017; Shane *et al.,* 2000).

Method of modelling

Researchers can choose from several animal models, including SD rats, and C57BL/6 mice Wistar rats, BALB/c mice to study liver disease. After being diluted to a 1% solution in 0.15 mol/L NaCl, DMN is given three times a week for three to four weeks at a dose of 10 mg/kg, primarily to cause hepatic fibrosis or damage (Bao *et al.,* 2021; Zhang *et al.,* 2016).

Advantages and disadvantages

The advantages of this model include its capacity to induce a stable and persistent form of liver fibrosis that is resistant to reversal. However, the model's limitations include its potential hazards, which demand meticulous handling and strict adherence to safety protocols to mitigate risks (You *et al.,* 2021).

Diethylnitrosamine induced liver injury model

Diethylnitrosamine is a well-known cancer-causing substances that poses significant health risks to humans and animals, causing liver damage, toxicity, and immune system suppression (Fuchs *et al.,* 2014). Research has shown that even low doses of DEN can induce liver fibrosis and promote liver cancer development by altering liver structure and enhancing growth of cells (Moyle 2000). Animal models of liver disease, including liver cancer and liver fibrosis, are therefore commonly made using DEN (Figure 2F).

Mechanism

The metabolic activation of DEN by CYP2E1 generates reactive species that cause oxidative stress and damage to liver cells, leading to necrosis (Piao *et al.,* 2012). DEN metabolism also produces diazo compounds that can alkylate DNA, leading to genetic mutations and aberrant transcriptional activity, which can drive liver tumorigenesis (Gao *et al.,* 2013). Moreover, DEN-mediated suppression of increasing cell proliferation and preventing apoptosis, NCOA5 expression can trigger the IL-6/STAT3 signaling pathway, which increases inflammation and upregulates anti-apoptotic genes like Bcl-2, hence promoting the development of liver cancer (Bingül *et al.,* 2013).

Method of modelling

DEN can be used to induce various stages of liver disease in animal models. One large dose administered intraperitoneally (200 mg/kg body weight) can cause acute liver injury within 4-6 weeks (Barbisan *et al.,* 2002; Pradeep *et al.,* 2007). Repeated administration of a lower dose (100 mg/kg body weight, intraperitoneally, once weekly for 6 weeks) can induce liver fibrosis (Didamoony, Atwa, and Ahmed 2023). Hepatocellular Carcinoma (HCC) may develop after a sustained exposure to a

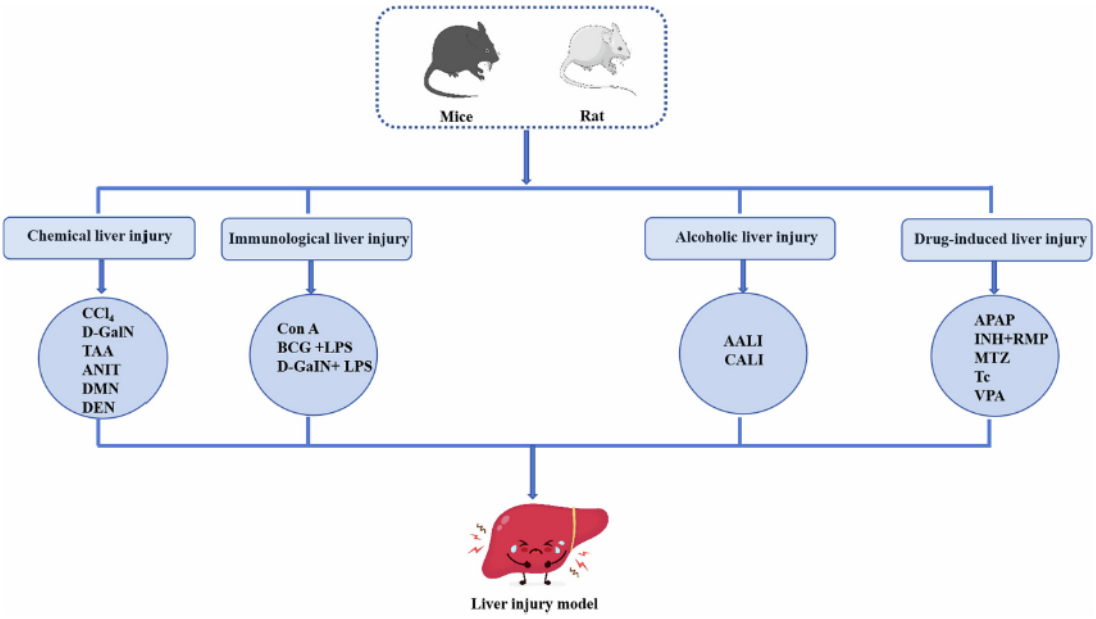

Fig. 1. The types of liver injury in rodent models.

Figure 1: The types of liver injury in rodent models (Mao *et al.,* 2024).

Table 1: Rodent models commonly employed in research investigating liver injury.

Substance	Animal Models	Modeling Method	References
VPA (Valproic Acid)	Kunming mice, C57BL/6J mice, Wistar rats	100-500 mg/kg intraperitoneally every day for 7-14 days, or 500 mg/kg taken orally for 14 days.	(Alqarni *et al.*, 2022; Fuchs *et al.*, 2014; Gama *et al.*, 2022; Gao *et al.*, 2022; Gheena *et al.*, 2022; He *et al.*, 2017; Iqbal *et al.*, 2022; Lee *et al.*, 2008; Vitins *et al.*, 2014)
CCl_4 (Carbon Tetrachloride)	Wistar or Sprague-Dawley rats, C57BL/6 mice	Administered intraperitoneally or subcutaneously at 1-2 mL/kg using a 40%-50% solution in vegetable oil. Observed for ~24 hr.	(Y. Lu *et al.*, 2016; Weber *et al.*, 2003)
D-GalN (D-Galactosamine)	Wistar or SD rats, Balb/c mice	600-900 mg/kg intraperitoneally, or 300 mg/kg over a 24-hr period.	(Colakoglu *et al.*, 2016; Zhuge *et al.*, 2020)
TAA (Thioacetamide)	C57BL/6 mice, Wistar rats, SD rats, and BALB/c	Administered intraperitoneally two to three times each week for four weeks at a dose of 200 mg/kg.	(Deng *et al.*, 2018; Hessien *et al.*, 2010)
ANIT (Alpha-Naphthylisothiocyanate)	C57BL/6 mice, Wistar rats, SD rats, and BALB/c	Orally at 60-100 mg/kg, observed for 24-28 h; or intraperitoneally at 80 mg/kg for up to 16 weeks.	(Gijbels *et al.*, 2021; Zhao *et al.*, 2013)
DMN (Dimethylnitrosamine)	C57BL/6 mice, Wistar rats, SD rats, and BALB/c	Three times a week for three to four weeks at a dose of 10 mg/kg intraperitoneally	(Bao *et al.*, 2021; Zhang *et al.*, 2016)
DEN (Diethylnitrosamine)	Wistar or SD rats	200 mg/kg intraperitoneally for four to six weeks.	(Barbisan *et al.*, 2002; Didamoony *et al.*, 2023; Ghufran *et al.*, 2021; Pradeep *et al.*, 2007)
Con A (Concanavalin A)	BALB/c and C57BL/6 mice	Tail vein injection at 15-20 mg/kg for acute model (12 h), or 10 mg/kg weekly for 8 weeks for chronic induction.	(Tamura *et al.*, 2016; Tu *et al.*, 2012)
BCG + LPS	C57BL/6 or Kunming mice	Tail vein BCG injection (5×10^6-10^7 bacteria) on day 1; LPS (7.5-10 µL in saline) via tail vein on day 10.	(Hu *et al.*, 2020)
D-GalN + LPS	Balb/c mice	LPS (50-100 µg/kg) and D-GalN (300-700 mg/kg) intraperitoneally for 16 hr; or 400 mg/kg D-GalN and 0.1 mg/kg LPS given after 14 days of HSA pretreatment.	(Liu *et al.*, 2015; Zhao *et al.*, 2019)
Alcohol (ALI model)	Wistar or SD rats	Oral gavage of 56° Baijiu at 7-20 mL/kg twice daily for 7 days; or intraperitoneal injection, observed over 72 h.	(Zhao *et al.*, 2022)
Alcohol (CLI model)	Wistar or SD rats	Ethanol in water (5 g/kg/day) for 8 weeks; or ethanol-rich liquid diet for 4-12 weeks. May include 10-day adaptation, then ethanol gavage on day 11.	(Brandon-Warner *et al.*, 2012; DeCarli and Lieber 1967; Füllgrabe *et al.*, 2007; Ikewuchi *et al.*, 2021; Keegan *et al.*, 1995; Liu *et al.*, 2021; Ore *et al.*, 2020; Voigt *et al.*, 2018; Xiaoxia Wang *et al.*, 2020; Zhang *et al.*, 2023)

Substance	Animal Models	Modeling Method	References
APAP (Acetaminophen)	C57BL/6 mice	Single intraperitoneal injection of 250 mg/kg, monitored over 12-16 h.	(Bachmann *et al.,* 2018; Bhushan *et al.,* 2014; Mossanen and Tacke 2015c)
INH + RMP	BALB/c mice	INH 75 mg/kg + RMP 150 mg/kg orally every day for seven days.	(Hassan *et al.,* 2015; Li *et al.,* 2022; Song *et al.,* 2022)
MTZ (Metronidazole)	BALB/c mice	I.p. BSO (667 mg/kg) was used as a pretreatment; two hr later, MTZ (15 mg/kg) was gavaged. observed for a whole day.	(Akai *et al.,* 2016; Kobayashi *et al.,* 2012)
Tetracycline (Tc)	Wistar or SD rats	50-200 mg/kg given intraperitoneally (i.p.) once for six hr, or 250 mg/kg of 4% Tc HCl administered daily for seven days.	(Choi *et al.,* 2015; Korolova *et al.,* 2023; Yao *et al.,* 2015)

lower dose of DEN (30 mg/kg, twice weekly for 10 weeks, then once weekly) (Ghufran *et al.,* 2021).

Advantages and disadvantages

DEN offers a broad range of applications in liver disease modeling, particularly in studying liver fibrosis and hepatocellular carcinoma (Schulien and Hasselblatt 2021). Nevertheless, working with DEN poses significant risks, requires considerable time, and is associated with high mortality rates, highlighting the importance of prioritizing personnel safety and taking necessary precautions (Sakaida *et al.,* 2003).

Rodent model of immune liver damage

Concanavalin A model of induced liver damage

An effective method for researching human chronic hepatitis and liver fibrosis is Con A-induced liver damage, an immune-mediated model that is analogous to these diseases (Tamura, Uemoto, and Tabata 2016).

Mechanism

The liver damage caused by Con A is dependent on the interaction between T lymphocytes, macrophages, and CD4+ T cells, leading to an immunological inflammatory response. This response involves the activation of lymphocytes, monocytes, and Kupffer cells, and is mediated by cytokines, including IFN-γ, IL-6, and TNF-α, which contribute to liver cell necrosis, apoptosis, and proliferation (Figure 3) (Tu *et al.,* 2012).

Method of modelling

Con A-induced liver damage models can be created in C57BL/6 and BALB/c mice aged 6-8 weeks. Acute liver damage can be induced by a single tail vein injection of Con A (15-20 mg/kg), while chronic liver damage can be modeled by repeated injections of a lower dose (10 mg/kg) once weekly for 8 weeks (Hao, Sun, and Xu 2022; Yin *et al.,* 2012).

Advantages and disadvantages

This model offers advantages in its quick and easy establishment, with liver-specific damage, making it suitable for studying autoimmune hepatitis. Nevertheless, it has limitations, including the absence of viral replication and chronic damage, which may not accurately reflect the pathophysiology of human viral hepatitis (Guo *et al.,* 2009; Wang *et al.,* 2016).

Model of Liver Injury Induced by BCG + LPS

Mechanism

Through an allergic reaction marked by cellular immunity, BCG and LPS damage the liver. When BCG activates T lymphocytes, LPS activates macrophages and Kupffer cells, which releases cytotoxic chemicals such TNF-α, NO, IL-6, and IL-1β, causing damage to the liver (Covián *et al.,* 2019; Sato *et al.,* 2016).

Method

On day 1, male C57BL/6 or Kunming mice that are 6-8 weeks old get an injection of BCG (5 × 10^7 CFU) in their tail vein. When LPS (7.5-10 μg) is injected into the tail vein 16 hr after 10 days, the immunological hepatitis model is created (Hu *et al.,* 2020).

Advantages and Disadvantages

This model has limitations, such as the requirement for BCG pre-sensitization and possible batch-to-batch variability in activity that may necessitate adjusting BCG amounts, but it also has benefits, such as simplicity and a short modeling time, which make it helpful for researching viral hepatitis pathogenesis and screening liver protection (Jin *et al.,* 2010; Pan *et al.,* 2015).

D-GalN+LPS induced liver injury model

Mechanism

Liver Injury Model Induced by D-GalN + LPS. LPS stimulates Kupffer cells and macrophages to release TNF-α and IL-1β, which results in liver cell death and necrosis, while D-GalN depletes

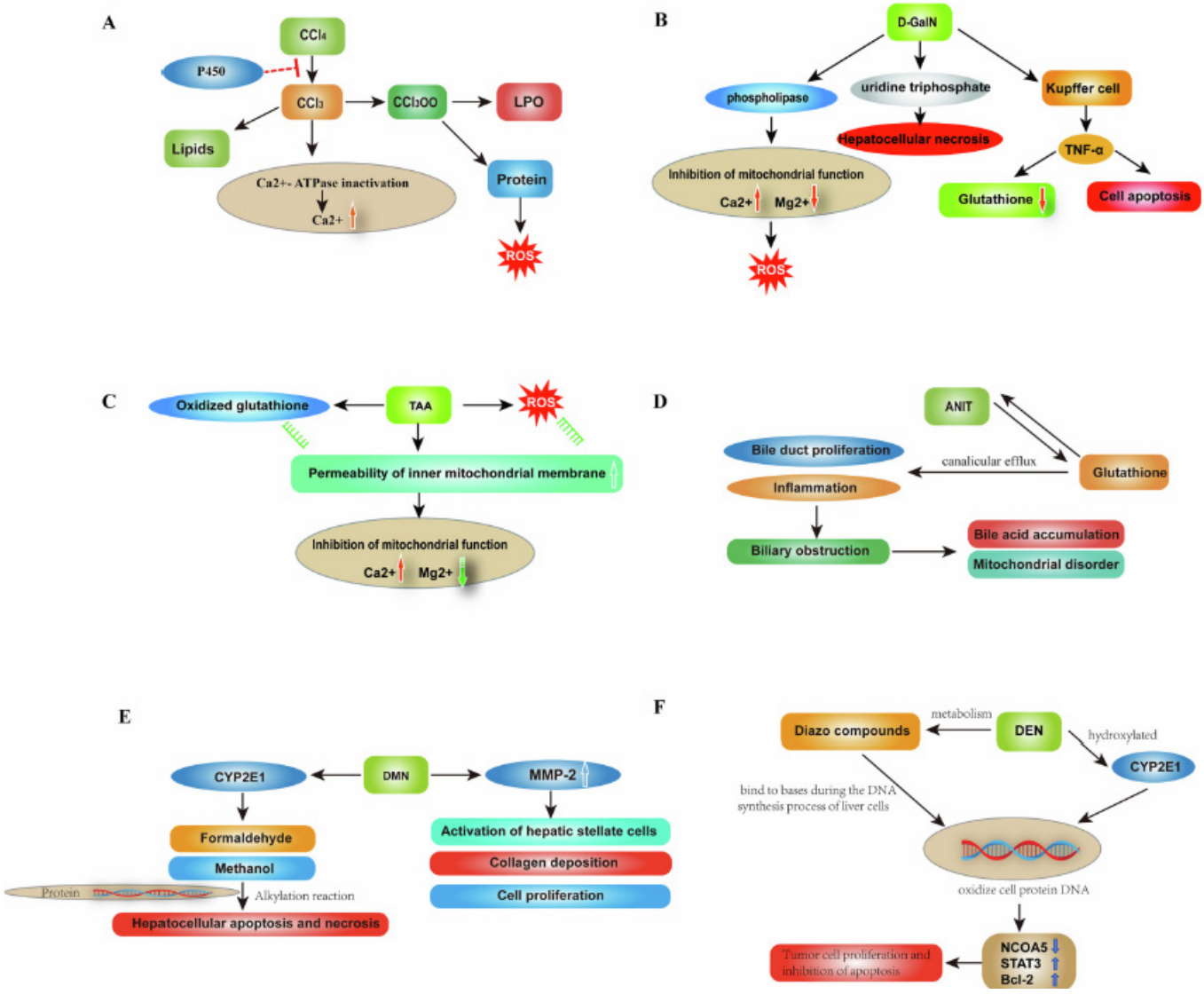

Figure 2: Mechanisms of (A) CCl_4, (B) D-GalN, (C) TAA, (D) ANIT, (E) DMN, (F) DEN hepatotoxicity in rodent model (Mao *et al.*, 2024).

UTP in liver cells, preventing RNA synthesis. Another role is oxidative stress (Bao *et al.*, 2017).

Method

Intraperitoneal injections of D-GalN (300-700 mg/kg) and LPS (50-100 µg/kg) are administered to 6- to 8-week-old Balb/c mice. A mouse immunological ALI model is created after 16 hr (Liu *et al.*, 2015). Alternatively, mice sensitized with HSA can get injections of D-GalN+LPS (Zhao, Liu, and Pu 2019).

Advantages and Disadvantages

This model's benefits include a brief modeling cycle, ease of use, and D-GalN's precise liver targeting, which makes it perfect for screening medications that protect the liver. Its requirement for pre-sensitization is a significant drawback, albeit (Zhang *et al.*, 2015).

Model of alcoholic liver damage in rodents

Alcohol-induced disruption to liver cell activity results in alcoholic liver injury, a dynamic pathological process. Alcoholic liver injury can progressively progress into alcoholic liver illnesses such alcoholic fatty liver, alcoholic hepatitis, alcoholic cirrhosis, and even hepatocellular cancer as its pathological alterations intensify, which can result in more severe clinical consequences (Lamas-Paz *et al.*, 2018).

Mechanism

Alcohol (ethanol) is a tiny, polar chemical that swiftly penetrates cell membranes and enters the bloodstream, where it travels to all bodily tissues and organs (Hyun *et al.*, 2021). This means that while the majority of alcohol is metabolized in the liver, many subtypes of Alcohol Dehydrogenase (ADH) that are produced in the stomach through their oxidative activity absorb and break down a relatively tiny percentage of alcohol (Palmer *et al.*, 2019; Zhang *et*

al., 2013). The liver cell peroxidase system, which oxidizes ethanol to acetaldehyde and reduces Nicotinamide Adenine Dinucleotide (NAD) to nicotinamide adenine dinucleotide (NADH), is catalyzed by ethanol molecules as they enter the liver cells (Yuan *et al.,* 2018). In a continuous oxidation-reduction process, acetaldehyde is mostly converted to acetate by the mitochondrial enzyme Aldehyde Dehydrogenase (ALDH). The acetate is then released from the cell after breaking down spontaneously into carbon dioxide and water (Yamashita, Kaneyuki, and Tagawa 2001). Through deoxyguanosine, acetaldehyde can attach to DNA and harm the DNA repair mechanism (Wang *et al.,* 2000). However, it can also trigger an oxidative stress response, activate the body's antioxidant system, and cause inflammation, necrosis, and liver cell damage (Hoek and Pastorino 2002). The body produces a lot of ROS and liver Cytochrome P4502E1 (CYP2E1) during the metabolism of ethanol, which raises the activity of the ethanol oxidation system and eventually causes liver damage (Massart *et al.,* 2022; Qiao *et al.,* 2019). Triglycerols (TG) build up as a result of mitochondrial activity-induced inhibition of fatty acid oxidation and oxidative phosphorylation (Free, Hazelwood, and Sibley 2009). Liver metabolic problems are caused by the intermediate product acetaldehyde, which binds to the protein molecules of liver cells (Figure 4).

Acute Alcoholic Liver Injury Model

Method

Ethanol is given intraperitoneally or by gavage to simulate Acute Alcoholic Liver Injury (AALI), orally for a short duration (4-6 g/kg body weight). Adding LPS or using overweight animal models can exacerbate severity (F. Zhang, Zhang, and Li 2012; Zhao *et al.,* 2022).

Features

Infiltration of inflammatory cells, moderate ballooning, and hepatocyte steatosis.

Advantages and Disadvantages

This technique is helpful for researching the pathophysiology and pathological process of ALD because it replicates the drinking patterns and pathophysiology of ALD patients, causing severe liver damage with high repeatability. Its drawbacks include its inability to create typical human ALD lesions, its limited capacity to cause minor liver damage, and its inability to sustain a constant high blood ethanol concentration (Keegan, Martini, and Batey 1995).

Model of chronic alcoholic liver damage

Chronic ethanol gavage method

Modeling technique

Rats who received ethanol (5 g/kg·body weight) orally every day for eight weeks also received drinking water containing ethanol, which over time caused liver damage. At the conclusion of four and eight weeks, respectively, mild Alcoholic Steatohepatitis (ASH) and mild steatosis were noted (Ikewuchi *et al.,* 2021; Xiaoxia Wang *et al.,* 2020). Rats given 10-40% ethanol solution in place of water for more than 25 weeks (Brandon-Warner *et al.,* 2012; Keegan *et al.,* 1995) or mice given 10-20% ethanol solution in place of water for longer than 8-40 weeks (Füllgrabe, Vengeliene, and Spanagel 2007; Liu, Du, and Zeng 2021) may develop liver damage, including steatosis, neutrophil infiltration, and fibrosis surrounding the central vein.

Advantages and disadvantages

A high success rate and simplicity of use are advantages. Cons: The experiment only resulted in mild to moderate steatohepatitis and steatosis, which are the most common forms of early-stage liver damage.

Lieber decarli liquid feed method (L/D model)

Modeling technique

There was no additional food or drink provided to the rats; they were simply fed an alcoholic liquid diet. Protein accounted for 18% of the calories, fat for 35%, and carbs for 47%, of which 36% were ethanol. A popular modeling technique in international labs, feeding over 4-12 weeks, might result in liver steatosis with unchanged or slightly raised serum transaminase levels (DeCarli and Lieber 1967; Ore *et al.,* 2020).

Advantages and disadvantages

Benefits: This liquid meal, which contains both ethanol and overall nutrients, ensures that the rats consume enough ethanol throughout time and maintain blood ethanol content. Additionally, it provides enough total nutrients to maintain the rats' nutritional health. Cons: This model does not completely remove the rats' alcohol aversion. Without concurrent therapy with liver toxic medicines like CCl or LPS, liver lesions such localized necrosis, inflammatory response, and fibrosis are difficult to acquire.

Chronic alcohol feeding combined with acute alcohol gavage model (Gao binge model)

Modeling technique

Experimental animals were given a liquid diet adaption phase for five days, a liquid feed period with five to six percent alcohol for ten days, and a high-dose alcohol gavage (5-6 g/kg·body weight ethanol) before to the eleventh day in order to generate the Gao binge model (Voigt *et al.,* 2018; Zhang *et al.,* 2023).

Benefits and drawbacks

Benefits: Based on a history of heavy drinking, this model accurately depicts the early development of alcoholic hepatitis brought on by alcoholism and intoxication. Drawbacks

include the brief modeling period and the possibility of severe inflammation and hepatic steatosis. Serum transaminases and BAC are noticeably higher. More severe liver damage could arise after an extended feeding duration of 8-12 weeks. However, the expense of the experiment is raised since a specially made feeding apparatus is needed to feed experimental animals in cages or individually during the modeling process (Carmiel-Haggai, Cederbaum, and Nieto 2003).

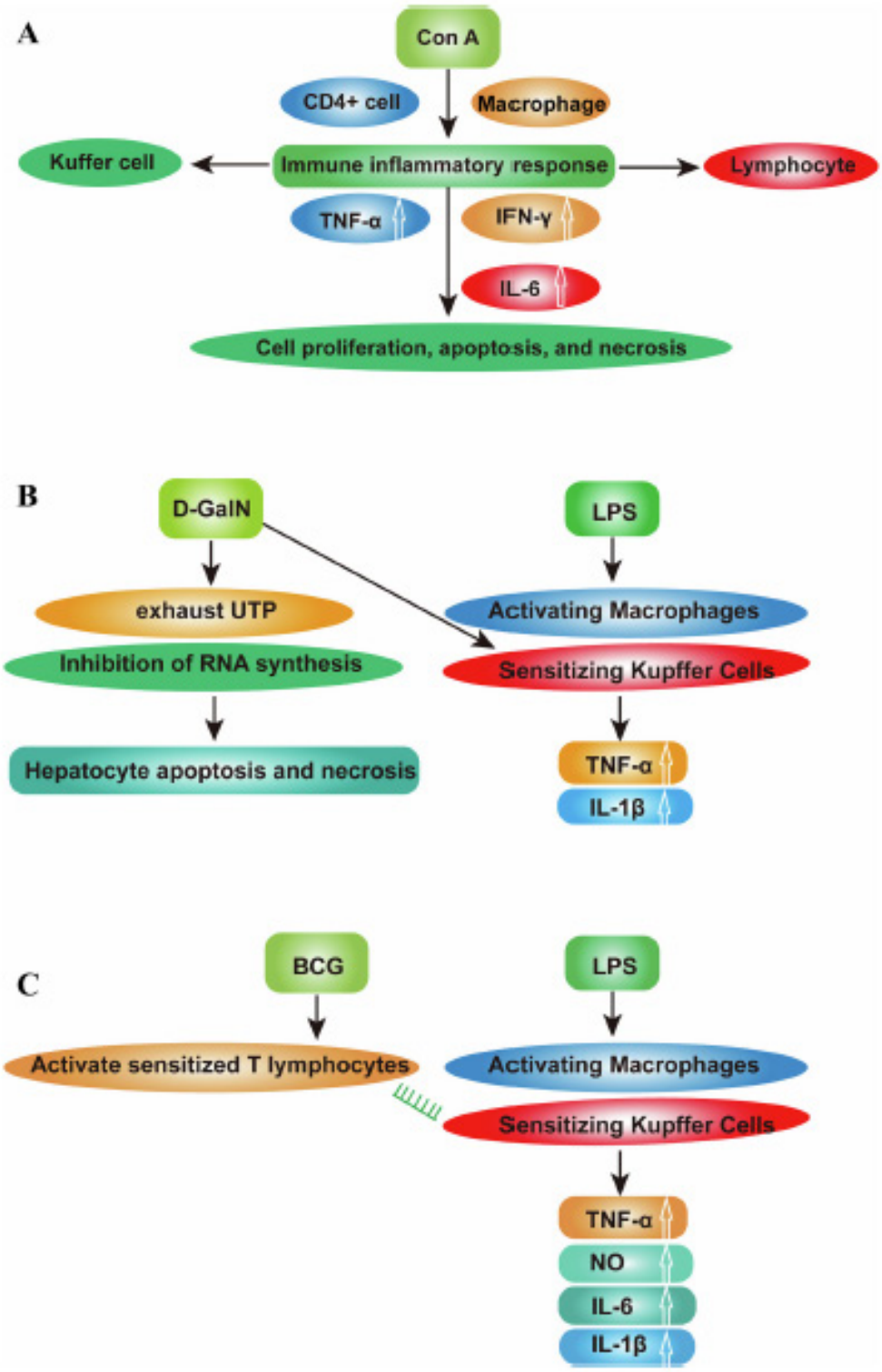

Figure 3: Mechanisms of (A) Con A, (B) BCG + LPS, (C) D-GalN +LPS hepatotoxicity in rodent model (Mao *et al.,* 2024).

Rodent model of drug-induced liver damage

Acetaminophen induced liver injury model

Mechanism

Although Acetaminophen (APAP) is a first-line antipyretic and analgesic medication in clinical practice, excessive usage of this medication might cause liver damage (Larsen and Wendon 2014). Glucuronic acid and sulfate conjugates are the primary APAP metabolites in the liver. At trace levels, CYP2E1 transforms these conjugates into the hazardous metabolite N-acetyl-p-benzoquinoimine (NAPQI). NAPQI is rapidly activated when the liver's GSH levels fall under normal circumstances. The bile and urine then remove the cysteine and thiol acids. When too much APAP is administered, the glucuronolactone and sulfate pathways become saturated. The liver utilizes a lot of NAPQI, which is produced when the CYP system breaks down too much APAP, to metabolize GSH. Acute liver necrosis, a reduction in the liver's antioxidant activity, and an increase in liver cell oxidation can result from NAPQI's covalent binding to cell protein thiols when it is not covalently coupled to GSH (Figure 5) (Mossanen and Tacke 2015a).

APAP-Induced Liver Injury Model

Method

Male C57BL/6 mice (10-12 weeks old) are given a single intraperitoneal injection of APAP (250 mg/kg) after it has been dissolved in physiological saline. After 12 hr, liver damage reaches its peak (Bachmann, Pfeilschifter, and Mühl 2018; Mossanen and Tacke 2015b). A Prominent Role of Interleukin-18 in Acetaminophen-Induced Liver Injury Advocates Its Blockage for Therapy of Hepatic Necroinflammation.

Characteristics

A sign of APAP toxicity is necrosis in the central lobular area (Bhushan *et al.,* 2014).

Advantages and Disadvantages

Because it is realistic, reasonably priced, and has a metabolic mechanism similar to clinical reality, this model can be used to evaluate therapeutic medications for acute liver injury (Patel *et al.,* 2017). Nevertheless, it has drawbacks, such as poor drug solubility and the requirement for more research to enhance the modeling technique.

Isoniazid combined with rifampicin induced liver injury model

Mechanism

INH is broken down to create the hazardous metabolites acetylhydrazine and hydrazine, which damage liver cells by depleting GSH, increasing oxidative stress, and upsetting mitochondrial structure. RMP increases INH metabolism and hepatotoxicity by inducing liver CYP450 (Cao *et al.,* 2018; X. Chen *et al.,* 2011; Chowdhury *et al.,* 2006; Enriquez-Cortina *et al.,* 2013; Perwitasari, Atthobari, and Wilffert 2015).

Method

RMP (150 mg/kg) and INH (75 mg/kg) are administered via gavage every day for one week to BALB/c mice (6-8 weeks old). Necrosis, inflammatory cell infiltration, and elevated liver enzymes are among the serious liver damage outcomes of this (Hassan *et al.,* 2015; Li *et al.,* 2022; Song *et al.,* 2022).

Advantages and Disadvantages

This model is appropriate for researching the causes of liver damage brought on by the combination of RMP and INH since it has a high repetition rate and strong stability. Its drawbacks, however, include limited translatability to people because of variations in drug metabolism and possible medication interactions that could compromise safety and efficacy (Wang *et al.,* 2012).

Methylimidazole (MTZ)-Induced Liver Injury Model

Mechanism

When MTZ is broken down, active metabolites are created that damage liver cells, interfere with the permeability of the mitochondrial membrane, and consume GSH (Heidari *et al.,* 2014; Woeber 2002).

Method

Six-week-old BALB/c mice are gavaged with MTZ (15 mg/kg) after receiving an injection of BSO (667 mg/kg) to deplete GSH. Significant liver damage, including elevated ALT levels and hepatic lobular degeneration and necrosis, is produced in an ALI model as a result (Akai *et al.,* 2016; Kobayashi *et al.,* 2012).

Advantages and Disadvantages

In addition to offering insights for forecasting biomarkers and creating medications, this model aids in clarifying the mechanism of liver damage (Qin *et al.,* 2023). Its drawbacks, however, include the requirement for optimization taking species differences into account and unstable model establishment brought on by variations in animal sensitivity.

Tetracycline (Tc)-Induced Liver Injury Model

Mechanism

Tc accumulation in mitochondria, disruption of fatty acid oxidation, suppression of lipoprotein secretion, and stimulation of fat storage in the liver cause microvesicular steatosis and liver injury (Hegarty *et al.,* 2018; Hunt and Washington 1994).

Method

To cause liver damage, mice or rats are given Tc via oral gavage (250 mg/kg for 7 days) or intraperitoneal injection (50-200 mg/kg) (Choi *et al.,* 2015; Korolova *et al.,* 2023; Yao *et al.,* 2015).

Characteristics

Elevated levels of oxidative stress, liver damage, and hepatic fat buildup.

Advantages and Disadvantages

This model, which mimics the "two-hit" concept of NAFLD, is appropriate for researching NAFLD processes and intervention strategies. Its drawbacks include a longer incubation period, a severity that varies with dosage and treatment length, and the possibility that high doses are required to cause appreciable liver damage (Ahmed and Siddiqi 2006; Devarbhavi and Andrade 2014; Nazmy *et al.*, 2017).

Sodium Valproate (VPA)-Induced Liver Injury Model

Mechanism

Toxic compounds produced by VPA impair mitochondrial activity, resulting in lipid peroxidation, oxidative stress, and damage to liver cells (Andrade *et al.*, 2019; Ezhilarasan and Mani 2022; Hadzagic-Catibusic *et al.*, 2017).

Method

VPA is given orally or intraperitoneally to rats (Wistar) or mice (Kunming or C57BL/6J) at doses of between 100 and 500 mg/kg for 7-14 days (Gao *et al.*, 2022; He *et al.*, 2017).

Characteristics

Mitochondrial damage, apoptosis of liver cells, and abnormalities of the liver enzymes AST and ALT.

Advantages and Disadvantages

This model has a negligible effect on animal health and is appropriate for researching liver damage in children. Its drawbacks, however, include the requirement for optimization and enhancement, inconsistent sensitivity across animal species, and unstable model establishment (Meseguer *et al.*, 2021).

The connection between liver damage and signaling pathways

Chemical Mechanism

Intermediate metabolites generated by cytochrome P450 processes are the main source of liver damage, which results in oxidative stress, membrane damage, and mitochondrial dysfunction (Paradies *et al.*, 2014).

Immune Mechanism

Immune responses, such as complement, NO, allergic reactions, and cytokines are the primary cause of liver injury (Adams *et al.*, 2010).

Key Signaling Pathways

Numerous signaling pathways are intimately linked to the development of liver damage, including:

1. NF-κB inflammatory pathway
2. LPS-TLR4-NF-κB pathway
3. Nrf2/Keap1 oxidative stress pathway
4. PI3K/AKT pathway
5. Apoptosis pathway
6. JAK/STAT pathway
7. SIRT1/AMPK pathway

Understanding these pathways can help identify potential therapeutic targets for liver injury (Tacke, Luedde, and Trautwein 2009; Xu *et al.*, 2022).

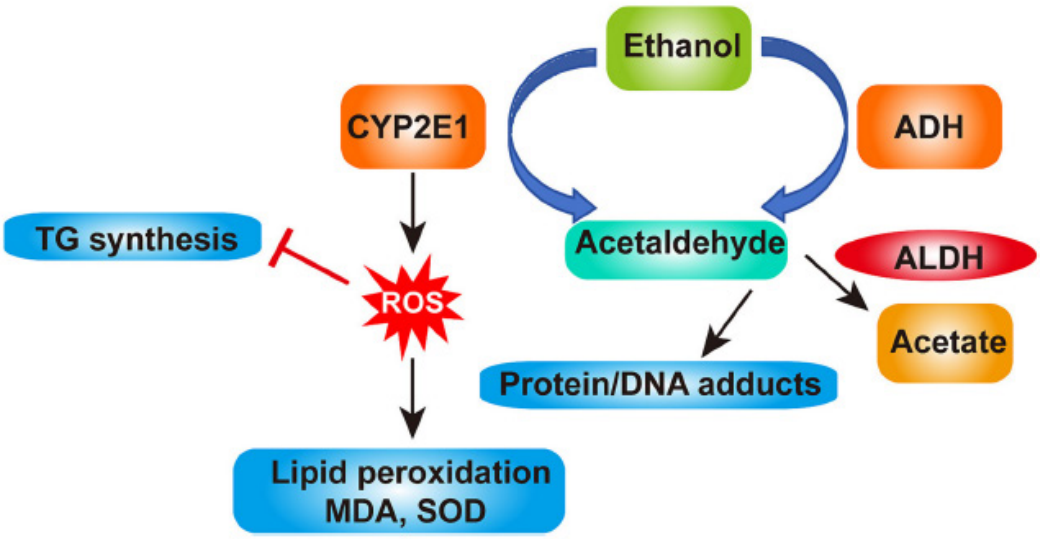

Figure 4: Mechanisms of ethanol hepatotoxicity in rodent models (Mao *et al.*, 2024).

Liver damage and the NF-κB inflammatory signaling pathway

In liver injury, the NF-κB signaling pathway is essential. Stimuli such as TNF-α, IL-1β, IL-6, and LPS activate NF-κB (p50 and p65), which causes IκB breakdown and NF-κB translocation to the nucleus. A positive feedback loop is started by this activation, which releases cytokines that intensify the inflammatory response even further. Important participants in liver inflammation, necrosis, and apoptosis include TNF-α, IL-1β, and IL-6. TNF-α activates NF-κB via the NIK/IKKα axis, IL-1β promotes inflammation, and IL-6 both promotes liver regeneration and exacerbates damage in chronic liver disorders.

Liver damage and the LPS-TLR4-MyD88 signaling pathway

In liver injury, the TLR4-mediated MyD88 signaling pathway is essential. TLR4 identifies PAMPs and LPS, which sets off a series of events that activate MyD88, IRAKs, and IKKs. The significance of this pathway in liver pathology is highlighted by the fact that this activation results in NF-κB activation, where NF-κB's p65 subunit enters the nucleus and induces pro-inflammatory factors like IL-6 and IL-1β. This ultimately causes liver injury through inflammation, damage, and oxidative stress, and may also lead to liver dysfunction, fibrosis, and the progression of the disease (Lei *et al.,* 2017; Li *et al.,* 2019).

Liver damage and the Nrf2/Keap-1 signaling pathway

In order to prevent oxidative stress and liver damage, Nrf2 is an essential transcription factor that controls detoxifying and antioxidant enzymes (Shih, Yeh, and Yen 2007). Oxidative stress triggers the Nrf2/ARE pathway, where Nrf2 separates from Keap-1 and moves into the nucleus, triggering the production of antioxidant enzymes such CAT, SOD, HO-1, and NQO-1. As antioxidants, these enzymes guard against harm from harmful chemicals and reactive oxygen species (Jadeja *et al.,* 2016; Klaassen and Reisman 2010). Research suggests that Nrf2 could be a therapeutic target for the management of inflammatory liver disease and liver injury. The pathway's function in liver damage is complicated; prooxidant doses at low levels may increase Nrf2 expression, while those at high levels may have the opposite effect (J. Das *et al.,* 2012).

The PI3K/AKT signaling pathway and damage to the liver

The PI3K/AKT signaling system, which controls cell survival, proliferation, and metabolism, is essential in liver damage. proliferation factors cause PI3K to create PIP3, which in turn triggers AKT and affects downstream effectors that support cell survival and proliferation (Liu *et al.,* 2008; Reif *et al.,* 2003; Wang *et al.,* 2008). Treatment for liver injury may target AKT because of its role in oxidative stress, inflammation, and cell proliferation (Pekgöz *et al.,* 2022; Shiau *et al.,* 2022; Zhong *et al.,* 2022). Inhibiting PI3K/AKT phosphorylation can lessen inflammation and tissue damage, and the pathway's connection with NF-κB signaling controls inflammatory responses and apoptosis (H. W. Chen *et al.,* 2011). Furthermore, the pathway's significance in liver damage pathogenesis is shown by its involvement in hepatic stellate cell activation and fibrosis (Nascè *et al.,* 2022).

Liver damage and the apoptosis signaling pathway

Programmed cell death, or apoptosis, is a major factor in liver damage. Hepatocyte apoptosis, which also feeds systemic inflammatory responses, is one of the primary causes of liver damage (Lelubre and Vincent 2018). The apoptotic process involves a number of signaling processes that culminate in cell death, including the activation of caspases such as caspase-8, caspase-9, and caspase-3 (Zhang *et al.,* 2017). Apoptosis is modulated by regulatory proteins such as Bcl-2 and Bax, where Bax promotes cell death and Bcl-2 inhibits it. One important marker of liver cell apoptosis is activated caspase-3 (Lee *et al.,* 2017). Preventing and treating liver injury requires an understanding of the mechanisms underlying apoptosis and the factors that influence it. According to certain research, cell apoptosis is suppressed by activating monocytes and tumor necrosis factor superfamily members. The amount of Bcl-2 protein rises while the amount of caspase-3 protein falls when compared to the unstimulated control group (McIlwain, Berger, and Mak 2013).

Injury to the liver and the JAK/STAT signaling cascade

Because it mediates inflammatory responses and cell signaling, the STAT pathway is essential in liver damage. When JAKs are activated by cytokine binding, they phosphorylate STAT proteins, causing dimerization and nuclear translocation that controls the transcription of target genes (Xiaoming Wang *et al.,* 2020). Important participants in this pathway are JAK2 and STAT3, with JAK2 causing the phosphorylation and activation of STAT3 (A. Das *et al.,* 2012). Gene transcription is regulated by activated STAT3, but JAK kinase activity is inhibited by SOCS3. In models of liver injury, research has demonstrated that blocking the JAK/STAT pathway can reduce inflammatory reactions and enhance liver function (Zheng *et al.,* 2009).

Liver damage and the SIRT1/MAPK signaling pathway

A NAD-dependent deacetylase, SIRT1 controls important gene transcription networks and is essential for lipid metabolism, oxidative balance, and anti-inflammatory responses (Poulose and Raju 2015). AMPK, the downstream target of SIRT1, regulates lipid synthesis and metabolism and reduces liver lipid accumulation by increasing fatty acid oxidation and lowering fatty acid synthesis (Chung *et al.,* 2010). Reduced SIRT1 and AMPK expression, as well as consequent liver lipid accumulation

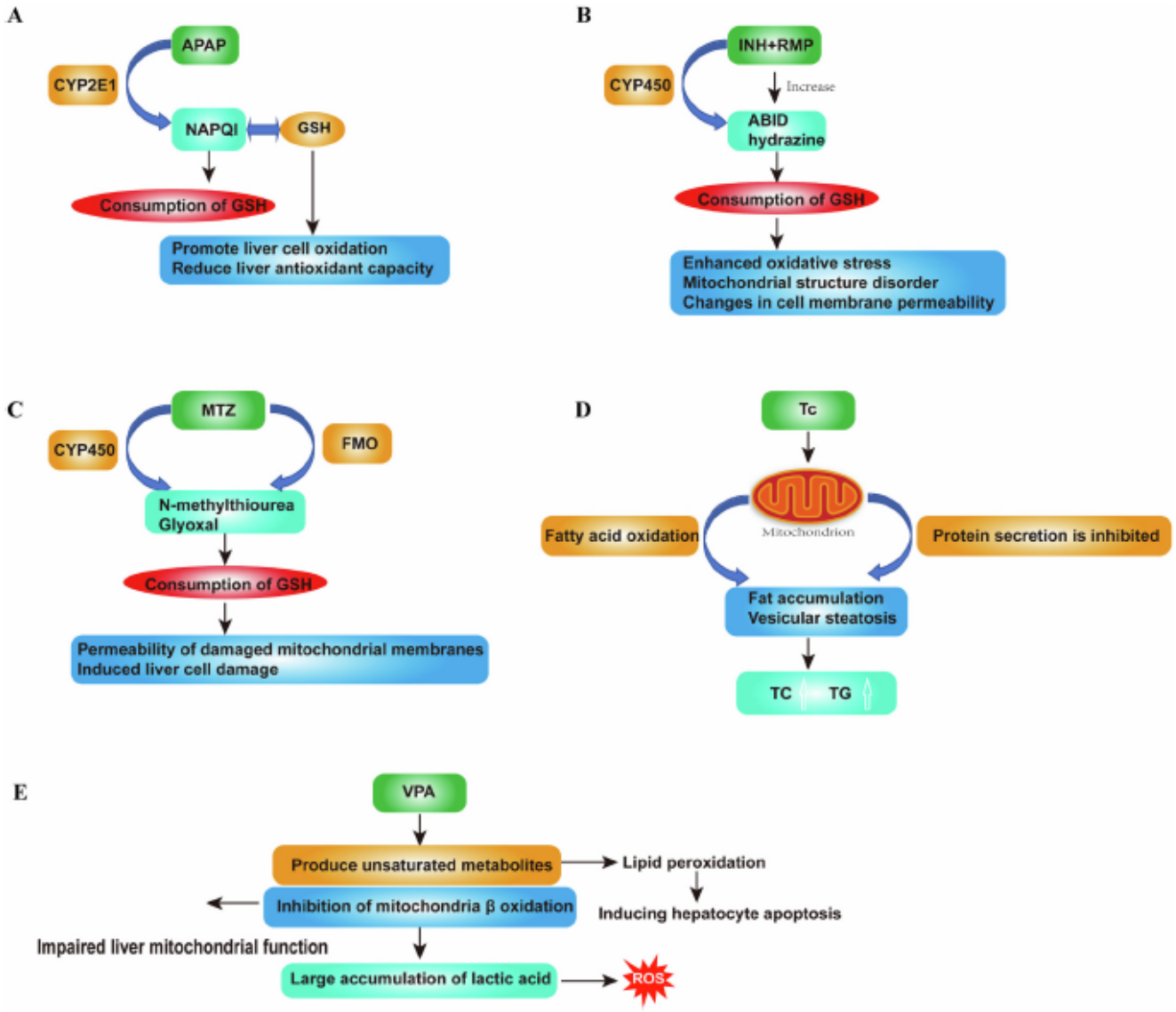

Figure 5: Mechanisms of (A) APAP, (B) INH + RMP, (C) MTZ, (D) Tc, (E) VPA hepatotoxicity in rodent models (Mao *et al.,* 2024).

and damage, are the results of the SIRT1-AMPK pathway being disturbed in Alcoholic Liver Disease (ALD) by an altered NAD+/NADH ratio. By increasing intracellular NAD+ and activating SIRT1, AMPK activation inhibits NF-κB activation and reduces pro-inflammatory gene expression (Tian *et al.,* 2019).

CONCLUSION

Environmental toxins, chemicals, and some medications can all cause liver injury, which is a complicated process. Commonly used drugs like DEN, DMN, TAA, CCl_4 and D-GalN, can harm the liver through mechanisms like lipid peroxidation, mitochondrial damage, and disturbance of bile acid metabolism (Badmus *et al.,* 2022). Drug-induced liver injury (DILI), alcoholic liver injury, chemical liver injury, and immunological liver injury all have distinct characteristics (Andrade *et al.,* 2019). Cell apoptosis, inflammatory activation, oxidative stress, disruption of metabolic pathways, and mitochondrial damage are frequent processes of liver injury that can result in cirrhosis, liver fibrosis, and even Hepatocellular Carcinoma (HCC). Animal models, such as those for liver fibrosis, cirrhosis, and HCC, are essential for comprehending these mechanisms and creating efficient treatments because they offer important insights into the intricate processes of liver injury and disease progression (Jilkova, Kurma, and Decaens 2019). Additionally, studies have demonstrated the critical roles that particular signaling pathways—like the PI3K/AKT and JAK/STAT pathways—play in liver regeneration and injury, pointing to possible therapeutic targets for the management of liver disease.

ABBREVIATIONS

CCl_4: Carbon tetrachloride; **ALI:** Acute liver injury; **VPA:** Valproic Acid; **D-GalN:** D-Galactosamine; **TAA:** Thioacetamide; **ANIT:** Alpha-Naphthyl isothiocyanate; **DMN:** Dimethyl nitrosamine; **DEN:** Diethyl nitrosamine; **Con A:** Concanavalin A; **APAP:** Acetaminophen; **MTZ:** Metronidazole; **CYP450:** cytochrome P450; **HCC:** Hepatocellular carcinoma; **IL-6:** Interleukin 6; **TNF-α:** Tumour Necrosis Factor α; **NAD:** nicotinamide adenine dinucleotide; **NF-κB Inflammatory Pathway:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **Nrf2/Keap1 Oxidative Stress Pathway:** Nuclear factor erythroid 2-related factor 2 / Kelch-like ECH-associated protein 1; **PI3K/AKT** Pathway: Phosphoinositide 3-Kinase / Protein Kinase B (also known as AKT); **JAK/STAT Pathway:** Janus Kinase / Signal Transducer and Activator of Transcription; **SIRT1/AMPK Pathway:** Sirtuin 1 / AMP-activated Protein Kinase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DECLARATION OF COMPETING INTEREST

All authors declare that there have no any commercial or associative interest that represents competing interests in connection with the work submitted.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Lokeshvar Ravikumar: Conceptualization, literature collection, methodology design, drafting of the initial manuscript, and critical revision of the content. **Ramaiyan Velmurugan:** Supervision, expert guidance, validation of scientific content, and final approval of the manuscript. **Grandhi Surendra:** Data curation, assistance in literature review, and preparation of figures and tables. **Sivasubramanian P:** Methodology support, analysis of preclinical models, and review of pharmacological sections. **Konatham Teja Kumar Reddy:** Writing – review & editing, verification of chemical-induced injury models, and contribution to manuscript refinement. **Kanaka Durga Hanumanthu:** Compilation of immunological liver injury mechanisms, data interpretation, and proofreading. **Venkateswararao R:** Contributions to pharmacological perspectives, technical inputs, and manuscript editing. **Dhanush Bellapu:** Literature survey on hepatotoxicity mechanisms, editing assistance, and checking for reference accuracy. **Ramenani Hari Babu:** Support in preparing graphical flow, cross-verification of experimental models, and formatting review. **Medishetti Swetha:** Drafting minor sections, cross-checking data consistency, and final polishing of the manuscript.

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