

Hepatotoxicity: A Detailed Review of Its Types, Mechanisms, Drug Interactions, and Hepatoprotective Interventions

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Abstract—Hepatotoxicity, or drug-induced liver injury (DILI), is a significant clinical concern, often leading to acute liver failure and the withdrawal of drugs from the market. The liver plays a crucial role in drug metabolism, making it highly susceptible to toxic insults. This review provides a comprehensive analysis of hepatotoxicity, covering its types, underlying mechanisms, drug interactions, and potential hepatoprotective interventions. Hepatotoxicity can be classified into intrinsic (dose-dependent) and idiosyncratic (unpredictable) forms, with subtypes such as cholestatic, hepatocellular, and mixed-pattern injuries. Mechanistically, hepatotoxicity involves metabolic activation, oxidative stress, mitochondrial dysfunction, immune-mediated responses, and bile acid dysregulation. Various drugs, including acetaminophen, antibiotics, NSAIDs, and antitubercular agents, have been implicated in hepatotoxicity, along with herbal and dietary supplements. Understanding drug-drug interactions and their impact on hepatic function is crucial for minimizing liver toxicity.

Several hepatoprotective interventions have been explored to counteract hepatotoxicity, including pharmacological agents like N-acetylcysteine and silymarin, natural compounds such as curcumin and glycyrrhizin, and emerging approaches like stem cell therapy. Biomarkers for early detection of liver injury and regulatory guidelines for evaluating hepatotoxic potential play a vital role in clinical safety assessments. This review highlights the current knowledge on hepatotoxicity, existing challenges, and future directions in hepatoprotection and risk mitigation strategies. A deeper understanding of hepatotoxicity mechanisms and novel therapeutic interventions could improve drug safety and liver health management.

Index Terms—Hepatotoxicity, Drug-induced liver injury, Oxidative stress, Drug interactions, Hepatoprotective agents, Liver toxicity

I. INTRODUCTION

Definition of Hepatotoxicity

Hepatotoxicity refers to liver damage caused by exposure to chemical substances, including pharmaceutical drugs, environmental toxins, and herbal supplements. It manifests as liver enzyme elevation, hepatocellular injury, cholestasis, fibrosis, or liver failure. Drug-induced liver injury (DILI) is a major cause of hepatotoxicity and is a leading reason for drug withdrawals and regulatory warnings worldwide.

Importance of Liver Function in Drug Metabolism

The liver plays a pivotal role in drug metabolism, detoxification, and biotransformation. It is responsible for the metabolism of xenobiotics through Phase I (oxidation, reduction, hydrolysis) and Phase II (conjugation) reactions, primarily mediated by the cytochrome P450 enzyme system. While these processes aid in drug clearance, they can also lead to the formation of reactive metabolites that contribute to liver toxicity. Hepatic impairment can significantly alter drug metabolism, leading to toxicity or therapeutic failure.

Overview of Drug-Induced Liver Injury (DILI)

DILI is one of the most challenging forms of hepatotoxicity, as it is often unpredictable and presents with diverse clinical manifestations, including asymptomatic liver enzyme elevations, hepatitis, cholestasis, cirrhosis, or acute liver failure. DILI is broadly classified into:

- Intrinsic (dose-dependent) hepatotoxicity – predictable toxicity occurring at high doses (e.g., acetaminophen toxicity).

- Idiosyncratic hepatotoxicity – unpredictable, often immune-mediated, and independent of dose (e.g., certain antibiotics, antiepileptics).

Objective and Scope of the Review

This review aims to provide a comprehensive understanding of hepatotoxicity by:

1. Classifying different types of hepatotoxicity.
2. Exploring the underlying mechanisms contributing to liver injury.
3. Examining drug interactions that influence hepatotoxicity.
4. Discussing pharmacological and natural hepatoprotective interventions.
5. Addressing regulatory and clinical perspectives for detecting and managing hepatotoxicity.

II. TYPES OF HEPATOTOXICITY

1. Intrinsic (Dose-dependent) Hepatotoxicity

- Definition: This type of liver toxicity occurs in a predictable and dose-dependent manner, often due to direct toxic effects of a drug or its metabolites.
- Mechanism: It results from metabolic activation of the drug, leading to oxidative stress, mitochondrial dysfunction, and hepatocyte necrosis.
- Example: Acetaminophen-induced liver injury
 - Acetaminophen is metabolized in the liver, and excessive doses produce N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite.
 - NAPQI depletes glutathione (GSH), leading to oxidative stress, lipid peroxidation, and hepatocyte death.
 - Antidote: N-acetylcysteine (NAC) replenishes GSH and prevents severe liver injury.

2. Idiosyncratic (Unpredictable) Hepatotoxicity

- Definition: Occurs in a small subset of individuals and is not dose-dependent.
- Mechanism: May involve genetic susceptibility, immune responses, or unpredictable metabolic pathways.
- Subtypes:
 - Immune-mediated hepatotoxicity (e.g., Halothane hepatitis)
 - Drug metabolites act as haptens, triggering immune responses against hepatocytes.

- Non-immune-mediated hepatotoxicity (e.g., Isoniazid-induced liver injury)
 - Variability in N-acetyltransferase 2 (NAT2) enzyme leads to toxic metabolite accumulation.
- Example: Isoniazid hepatotoxicity
 - Slow acetylators accumulate toxic metabolites, increasing the risk of hepatotoxicity.

3. Cholestatic Hepatotoxicity

- Definition: Characterized by impaired bile flow due to hepatocyte or bile duct damage.
- Mechanism: Drug-induced inhibition of bile acid transporters, leading to bile acid accumulation and hepatocyte toxicity.
- Example: Chlorpromazine-induced cholestasis
 - Causes inflammation and obstruction of bile canaliculi.
 - Clinical Features: Elevated alkaline phosphatase (ALP) and bilirubin, pruritus, and jaundice.

4. Hepatocellular Injury

- Definition: Direct damage to hepatocytes, leading to inflammation and necrosis.
- Mechanism: Disruption of mitochondrial function, oxidative stress, and apoptosis.
- Example: Methotrexate-induced liver injury
 - Methotrexate accumulates in hepatocytes, causing fibrosis and cirrhosis.
 - Markers: Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

5. Mixed Pattern of Liver Injury

- Definition: A combination of hepatocellular and cholestatic injury.
- Mechanism: Drugs cause both direct hepatocyte damage and bile transport dysfunction.
- Example: Amoxicillin-clavulanate hepatotoxicity
 - Presents with elevated ALT, AST, ALP, and bilirubin.
 - Diagnostic Pattern: R-factor is used to classify mixed liver injury: $R = \frac{ALT/ULN}{ALP/ULN}$
 - If $R > 5$: Hepatocellular injury
 - If $R < 2$: Cholestatic injury
 - If $R = 2-5$: Mixed liver injury

III. MECHANISMS OF HEPATOTOXICITY

1. Metabolic Activation and Reactive Oxygen Species (ROS) Formation

- Mechanism:
 - Many drugs undergo phase I metabolism via cytochrome P450 enzymes (CYP450) in the liver.
 - Some drugs are converted into reactive metabolites, which bind to cellular macromolecules (proteins, lipids, and DNA), leading to oxidative stress and hepatocyte damage.
 - Overproduction of reactive oxygen species (ROS) causes lipid peroxidation, protein oxidation, and mitochondrial dysfunction.
- Example: Acetaminophen (Paracetamol) Hepatotoxicity
 - Metabolized by CYP2E1 to N-acetyl-p-benzoquinone imine (NAPQI).
 - In high doses, NAPQI depletes glutathione (GSH), leading to hepatocyte necrosis.
 - Antioxidant therapy with N-acetylcysteine (NAC) replenishes GSH and detoxifies NAPQI.

2. Mitochondrial Dysfunction and Apoptosis

- Mechanism:
 - Some drugs impair mitochondrial oxidative phosphorylation, leading to ATP depletion and hepatocyte injury.
 - ROS and toxic metabolites induce mitochondrial permeability transition (MPT), causing the release of cytochrome c, which activates caspase-mediated apoptosis.
 - In severe cases, necrosis occurs due to excessive mitochondrial damage.
- Example: Valproic Acid (VPA) Hepatotoxicity
 - Valproic acid inhibits β -oxidation in mitochondria, leading to fatty liver and hepatocellular apoptosis.

3. Cytokine and Immune-Mediated Injury

- Mechanism:
 - Certain drugs or their metabolites act as haptens, binding to liver proteins and triggering an immune response.
 - T-cell activation leads to the release of pro-inflammatory cytokines like TNF- α , IL-1, IL-6, causing hepatocyte apoptosis and necrosis.
 - Some reactions resemble autoimmune hepatitis, leading to chronic inflammation and fibrosis.
- Example: Halothane Hepatitis

- Halothane metabolites form trifluoroacetylated proteins, which induce an immune response against hepatocytes.

4. Bile Acid Dysregulation and Cholestatic Injury

- Mechanism:
 - Some drugs inhibit bile acid transporters like BSEP (Bile Salt Export Pump), leading to bile acid accumulation and cholestatic liver injury.
 - Bile acid toxicity results in membrane disruption, mitochondrial dysfunction, and hepatocyte apoptosis.
 - In severe cases, it leads to ductopenia (loss of bile ducts) and secondary biliary cirrhosis.
- Example: Chlorpromazine-induced Cholestatic Hepatitis
 - Chlorpromazine impairs bile secretion, causing intrahepatic cholestasis.

5. Genetic and Epigenetic Factors in Hepatotoxicity

- Mechanism:
 - Genetic polymorphisms in drug-metabolizing enzymes (e.g., CYP450, NAT2, UGT) influence susceptibility to hepatotoxicity.
 - Epigenetic modifications (DNA methylation, histone modifications, and microRNA regulation) can alter drug metabolism, inflammation, and liver regeneration.
- Example: Isoniazid (INH) Hepatotoxicity
 - Slow acetylators (due to NAT2 polymorphism) have higher risk of hepatotoxicity due to toxic metabolite accumulation.

IV. DRUG INTERACTIONS AND HEPATOTOXICITY

- Common Drugs Causing Hepatotoxicity
 - Acetaminophen, NSAIDs, Antibiotics, Antitubercular drugs, Antiepileptics
- Drug-Drug Interactions and Liver Toxicity
 - Role of Cytochrome P450 enzymes
- Herbal and Dietary Supplement-Induced Hepatotoxicity
 - Case studies and reported incidences

V. HEPATOPROTECTIVE INTERVENTIONS

Hepatotoxicity can be managed using various pharmacological, natural, and regenerative approaches. The goal is to mitigate liver damage,

enhance hepatocyte survival, and promote liver regeneration.

1. Pharmacological Interventions

Pharmacological agents help detoxify harmful metabolites, reduce oxidative stress, and restore liver function.

a) N-acetylcysteine (NAC)

- Mechanism: NAC replenishes glutathione (GSH) levels, neutralizing toxic metabolites like NAPQI (N-acetyl-p-benzoquinone imine) in acetaminophen-induced hepatotoxicity.
- Clinical Use: First-line antidote for paracetamol overdose.

b) Silymarin (Milk Thistle, *Silybum marianum*)

- Mechanism:
 - Acts as an antioxidant by scavenging free radicals.
 - Inhibits lipid peroxidation, stabilizes hepatocyte membranes, and enhances protein synthesis.
- Clinical Use: Used in alcoholic liver disease, drug-induced hepatotoxicity, and viral hepatitis.

c) Ursodeoxycholic Acid (UDCA)

- Mechanism:
 - Improves bile flow and reduces cholestatic liver injury by protecting hepatocytes from toxic bile acids.
 - Modulates mitochondrial function and reduces apoptosis.
- Clinical Use: Effective in primary biliary cholangitis (PBC) and drug-induced cholestasis.

d) Antioxidants (Vitamin E, Nrf2 Activators)

- Mechanism: Reduce oxidative stress, prevent mitochondrial dysfunction, and enhance liver regeneration.
- Clinical Use: Used in non-alcoholic fatty liver disease (NAFLD) and drug-induced liver injury (DILI).

2. Herbal and Natural Products

Natural compounds with hepatoprotective potential act through anti-inflammatory, antioxidant, and regenerative mechanisms.

a) Silymarin (*Silybum marianum*)

- Protects against drug-induced hepatotoxicity, alcoholic liver disease, and viral hepatitis.

b) Curcumin (*Curcuma longa*)

- Mechanism:
 - Suppresses NF-κB-mediated inflammation.

- Enhances bile acid metabolism and protects against oxidative stress.

- Clinical Use: Used in NAFLD, cholestatic liver disease, and fibrosis prevention.

c) Glycyrrhizin (*Glycyrrhiza glabra*)

- Mechanism:
 - Inhibits TNF-α and IL-6, reducing inflammation.
 - Prevents hepatocyte apoptosis and fibrosis.
- Clinical Use: Used in chronic hepatitis and liver fibrosis.

d) Andrographolide (*Andrographis paniculata*)

- Mechanism:
 - Protects hepatocytes by modulating Nrf2 signaling, reducing oxidative stress.
 - Inhibits liver fibrosis and inflammation.
- Clinical Use: Used in viral hepatitis and hepatoprotective formulations.

3. Nutraceutical and Dietary Approaches

Nutraceuticals, including vitamins and polyphenols, play a key role in liver health.

a) Role of Vitamins (Vitamin E, C, and D)

- Vitamin E: Reduces oxidative stress in NAFLD and hepatotoxicity.
- Vitamin C: Enhances glutathione levels and reduces lipid peroxidation.
- Vitamin D: Regulates immune responses in liver diseases.

b) Polyphenols (Resveratrol, Quercetin, Green Tea Catechins)

- Mechanism: Reduce oxidative stress, inflammation, and fibrosis.
- Clinical Use: Effective in NAFLD, drug-induced liver injury, and metabolic liver diseases.

c) Omega-3 Fatty Acids

- Mechanism:
 - Modulate lipid metabolism and reduce hepatic steatosis.
 - Inhibit TNF-α and pro-inflammatory cytokines.
- Clinical Use: Used in NAFLD and hepatic inflammation.

4. Liver Regeneration Strategies

Innovative therapies focus on enhancing hepatocyte proliferation and restoring liver function.

a) Stem Cell Therapy

- Mechanism:
 - Mesenchymal stem cells (MSCs) release hepatotropic factors, promoting hepatocyte regeneration.

- Reduces fibrosis and inflammation in chronic liver disease.
- Clinical Use: Being investigated for liver cirrhosis, NAFLD, and acute liver failure.

b) Hepatocyte Transplantation

- Mechanism:
 - Healthy hepatocytes are transplanted to replace damaged liver cells.
- Clinical Use: Potential therapy for acute liver failure and metabolic liver disorders.

c) Emerging Therapies (MicroRNA & Gene Therapy)

- MicroRNA-based therapy: Targets fibrotic genes to reverse liver damage.
- Gene editing (CRISPR-based approaches): Corrects genetic defects in inherited liver diseases.

VI. CLINICAL AND REGULATORY PERSPECTIVES

Hepatotoxicity remains a significant concern in drug development and clinical practice. Identifying liver injury early and adhering to regulatory guidelines is essential for patient safety. This section covers biomarkers for hepatotoxicity detection, regulatory frameworks, and preclinical/clinical evaluation methods.

1. Biomarkers for Hepatotoxicity Detection

Biomarkers play a crucial role in detecting drug-induced liver injury (DILI) and differentiating various types of liver damage.

a) Alanine Aminotransferase (ALT)

- Function: ALT is a cytosolic enzyme primarily found in hepatocytes.
- Significance:
 - Elevated ALT indicates hepatocellular injury (e.g., viral hepatitis, drug-induced liver injury).
 - More specific to liver damage than AST.

b) Aspartate Aminotransferase (AST)

- Function: AST is found in both liver and muscle tissues.
- Significance:
 - AST/ALT ratio >2 suggests alcoholic liver disease.
 - Isolated AST elevation may indicate muscle damage rather than liver injury.

c) Alkaline Phosphatase (ALP)

- Function: ALP is associated with bile duct function.
- Significance:
 - Elevated in cholestatic liver injury (e.g., drug-induced cholestasis, primary biliary cholangitis).
 - Used alongside GGT to confirm biliary involvement.

d) Bilirubin (Total & Direct)

- Function: Bilirubin is a breakdown product of hemoglobin.
- Significance:
 - Elevated direct (conjugated) bilirubin suggests cholestasis or liver dysfunction.
 - Elevated total bilirubin with ALT/AST abnormalities is a hallmark of severe hepatocellular injury.

e) Gamma-Glutamyl Transferase (GGT)

- Function: GGT is an enzyme involved in bile acid metabolism.
- Significance:
 - Elevated in drug-induced hepatotoxicity and alcoholic liver disease.
 - Used with ALP to assess cholestatic injury.

f) Emerging Biomarkers

- Keratin-18 (K18): Indicator of hepatocyte apoptosis.
- Glutamate Dehydrogenase (GLDH): Detects mitochondrial toxicity.
- High-Mobility Group Box 1 (HMGB1): Identifies immune-mediated liver injury.
- MicroRNAs (e.g., miR-122, miR-192): Potential early markers of liver toxicity.

2. Regulatory Guidelines for Hepatotoxic Drugs

Regulatory agencies have strict guidelines for monitoring drug-induced liver injury (DILI) to ensure patient safety.

a) U.S. Food and Drug Administration (FDA)

- Guidance for Industry – Drug-Induced Liver Injury (DILI) (2009)
- Key Points:
 - Any drug causing ALT $>3\times$ upper limit of normal (ULN) with total bilirubin $>2\times$ ULN is considered high risk for hepatotoxicity.
 - Requires preclinical and clinical hepatotoxicity assessment before drug approval.

b) European Medicines Agency (EMA)

- Guideline on the Evaluation of Hepatotoxicity in Human Medicines

- Key Points:
 - Mandatory liver function monitoring during clinical trials.
 - Requires risk management plans (RMPs) for hepatotoxic drugs.
- c) Indian Council of Medical Research (ICMR)
 - ICMR Guidelines for Drug Safety and Toxicology
 - Key Points:
 - Focus on traditional and herbal medicine safety.
 - Calls for standardized toxicity testing for Ayurvedic and herbal drugs.
- 3. Preclinical and Clinical Evaluation of Hepatotoxicity

New drugs must undergo extensive hepatotoxicity screening before approval.

 - a) Preclinical Evaluation
 - In Vitro Models:
 - Primary Human Hepatocytes (PHH): Gold standard for testing hepatotoxicity.
 - HepG2 Cells: Used for high-throughput drug screening.
 - Organoids and 3D Liver Cultures: Provide better physiological relevance.
 - In Vivo Models:
 - Rodent Studies (Rats, Mice): Standard for dose-dependent toxicity assessment.
 - Zebrafish Models: Used for high-throughput toxicology screening.
 - Genetically Engineered Models: Allow mechanistic studies of DILI.
 - b) Clinical Evaluation
 - Phase I Trials:
 - Assess ALT/AST changes in healthy volunteers.
 - Early detection of hepatotoxicity risk.
 - Phase II & III Trials:
 - Monitor liver function tests (LFTs) throughout the study.
 - Drugs showing hepatotoxicity are either modified or withdrawn.
 - Post-Marketing Surveillance (Phase IV):
 - Real-world data collection for long-term safety assessment.
 - Example: Troglitazone (anti-diabetic drug) was withdrawn due to severe idiosyncratic hepatotoxicity.

VII. CONCLUSION

Summary of Key Findings

Hepatotoxicity is a significant clinical and pharmacological concern, affecting both drug development and patient safety. This review highlights the following key aspects:

- Types of Hepatotoxicity: Intrinsic (dose-dependent), idiosyncratic (unpredictable), cholestatic, hepatocellular, and mixed-pattern injuries.
- Mechanisms of Hepatotoxicity: Involves metabolic activation, oxidative stress, mitochondrial dysfunction, immune-mediated injury, bile acid dysregulation, and genetic factors.
- Drug-Induced Liver Injury (DILI): Remains a leading cause of drug withdrawals, emphasizing the need for early detection and risk assessment.
- Hepatoprotective Interventions: Includes pharmacological agents (e.g., N-acetylcysteine, UDCA), herbal/natural products (e.g., silymarin, curcumin), dietary approaches (polyphenols, omega-3), and regenerative strategies (stem cell therapy).
- Clinical and Regulatory Perspectives: Biomarkers (ALT, AST, ALP, bilirubin, GGT) aid in early detection, while regulatory agencies (FDA, EMA, ICMR) enforce safety measures in preclinical and clinical drug evaluation.

Clinical Implications and Future Research Directions

- Precision Medicine Approach: Genetic and epigenetic studies may enable personalized risk assessment for drug-induced liver injury (DILI).
- Advanced Biomarkers & AI-based Prediction Models: Emerging technologies, including microRNAs, machine learning models, and omics-based approaches, may improve early hepatotoxicity detection and risk stratification.
- Safer Drug Development: Novel drug screening models, such as 3D liver organoids and bioengineered hepatocyte cultures, can reduce reliance on animal testing while improving predictive accuracy.
- Integration of Herbal and Pharmaceutical Approaches: The hepatoprotective potential of natural compounds should be further explored

through clinical trials to establish standardized, evidence-based treatments.

- Regulatory Framework Enhancements: Continuous updates to hepatotoxicity evaluation guidelines will help in the early withdrawal of high-risk drugs and promote patient safety.

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