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**Review Article**

# Drugs and hepatotoxicity: a comprehensive review

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## ABSTRACT

Hepatotoxicity is a leading cause of acute and chronic liver disease worldwide. It denotes liver damage resulting from exposure to pharmaceuticals, chemicals, herbal preparations, or other foreign compounds. It is a major concern in clinical practice and drug development, as liver injury is a frequent cause of treatment discontinuation and drug withdrawal. Owing to its central role in metabolism and detoxification, the liver is particularly susceptible to toxic injury. The spectrum of hepatotoxicity ranges from mild, transient elevations in liver enzymes to severe acute liver failure. This review discusses the role of the liver in xenobiotic metabolism, mechanisms of hepatotoxicity, types of liver injury, implicated drugs, diagnostic approaches, management strategies, and preventive measures. Emphasis is placed on integrating mechanistic insights with clinical applications to aid in early detection, better therapeutic strategies, and reduction of morbidity and mortality associated with hepatotoxicity.

**Keywords:** Drugs and hepatotoxicity, Xenobiotic metabolism, Advances

## INTRODUCTION

The liver serves as the principal organ for xenobiotic metabolism and detoxification because it is exposed to the majority of administered drugs and chemicals.[1,2] Drugs undergo biotransformation in the liver, which enables their conversion into hydrophilic metabolites suitable for elimination.[3]

Although these processes are generally protective, certain drugs generate reactive metabolites that can damage hepatocytes and other liver structures.[4,5] Hepatotoxicity is defined as chemical-driven liver damage and remains one of the most frequent adverse drug reactions leading to hospitalization and regulatory drug withdrawal.[6] It can manifest as asymptomatic elevations of liver enzymes, cholestasis, hepatitis, cirrhosis, or acute liver failure.[7]

Given its wide clinical spectrum and unpredictable nature, drug-induced hepatotoxicity represents a significant challenge for clinicians.[8,9]

### *Types of hepatotoxicity*

Hepatotoxicity can be broadly categorized into the following types mentioned in Table 1.

## ROLE OF THE LIVER IN XENOBIOTIC METABOLISM

For xenobiotic metabolism liver is the central organ due to its unique anatomical and functional position.[1,2] Around 75% of its blood supply comes from the portal vein, carrying absorbed drugs and toxins directly from the gastrointestinal tract.[3]

This high exposure necessitates efficient detoxification systems. The liver is also a metabolic hub, regulating carbohydrate, lipid, and protein metabolism alongside drug biotransformation.[4]

Drug metabolism is categorized into two phases.

***Phase I reactions***

These include oxidation, reduction, or hydrolysis, predominantly mediated by cytochrome P450 enzymes, introducing functional groups. Examples include hydroxylation of phenytoin, conversion of codeine into morphine, paracetamol → NAPQI.[5]

***Phase II reactions***

These include conjugation with glucuronic acid, sulfate, glutathione, or glycine, which increases water solubility and facilitates excretion. Examples include Paracetamol, Morphine, and Methyldopa.[7]

Drug metabolism processes may generate reactive intermediates contributing to hepatotoxicity.[10]

**Table 1: Types of hepatotoxicity.**

| Type | Intrinsic | Idiosyncratic |
|---|---|---|
| **Incidence** | Most common | Less common (approx. 1%)[1] |
| **Predictability** | Predictable | Unpredictable[1] |
| **Dose relationship** | Dose dependant | Dose independant[1,2] |
| **Latency** | Short latency | Variable latency (weeks - months)[3] |
| **Type of injury** | Usually necrosis | Necrosis or apoptosis[4] |
| **Associated** | Acute liver failure | Rash , fever, eosinophilia[5] |
| **Examples** | Acetaminophen | Isoniazid , Amoxicillin-clavulanate[6] |

## MECHANISMS OF HEPATOTOXICITY

The liver's central role in metabolism makes it especially vulnerable to injury from xenobiotics.[1,2] Mechanisms of hepatotoxicity are multifactorial and often overlapping. Key mechanisms include mitochondrial dysfunction, oxidative stress, immune-mediated reactions, and cholestasis.[11] Mitochondrial dysfunction involves impairment of β-oxidation, depletion of ATP, and micro-vesicular steatosis, as seen with valproate exposure.[4,5]

Oxidative stress arises from the generation of reactive oxygen species (ROS), lipid peroxidation, and DNA damage, typical in methotrexate-induced toxicity.[8]

Immune-mediated hepatotoxicity occurs when drug-protein adducts act as haptens, provoking adaptive immune responses, as in amoxicillin-clavulanate injury.[7]

Cholestasis develops when bile acid transporters are disrupted or bile duct epithelial cells are damaged, leading to impaired bile flow, as observed with chlorpromazine.[8]

The combination of these mechanisms explains the variability of drug-induced liver injury across patients.[12]

## PHARMACOKINETICS AND PHARMACO-DYNAMICS IN HEPATOTOXICITY

Pharmacokinetics (PK) and pharmacodynamics (PD) significantly influence the risk of hepatotoxicity.[1,2] The liver serves as the principle organ for xenobiotic metabolism and detoxification because it is exposed to the majority of administered drugs and chemicals. Changes in absorption, distribution, metabolism, and excretion can increase the concentration of toxic metabolites.[3]

***PK factors***

First-pass metabolism in the liver is especially important, as drugs with extensive metabolism can generate reactive intermediates that damage hepatocytes.[4]

For example, Methotrexate undergoes hepatic metabolism and enterohepatic recirculation, contributing to fibrosis and cirrhosis with prolonged use.[5]

Similarly, ketoconazole undergoes extensive metabolism and CYP3A4 inhibition, leading to elevated liver enzymes and cholestatic injury.[6]

Bioactivation is another PK factor, where non-toxic drugs are converted into reactive electrophilic metabolites capable of covalently binding to proteins, as in halothane metabolism producing trifluoroacetyl chloride, which triggers immune-mediated hepatitis.[7]

Drug-drug interactions are also critical; for example, isoniazid induces CYP2E1, enhancing conversion to hepatotoxic hydrazine derivatives, while ethanol further induces CYP2E1, increasing NAPQI formation from paracetamol.[7]

On the PD side, hepatotoxicity results from adverse biological interactions of drugs or metabolites with hepatic targets.[6]

Mitochondrial dysfunction, oxidative stress, immune-mediated toxicity, and cholestasis are major PD pathways.[12]

Valproic acid inhibits fatty acid β-oxidation, leading to ATP depletion and microvesicular steatosis.[10] Whereas methotrexate induces oxidative stress, causing DNA and protein damage with fibrosis during long-term therapy.[13]

Amoxicillin-clavulanate exemplifies immune-mediated PD toxicity, while chlorpromazine induces cholestasis by interfering with bile transporters.[14]

Thus, PK and PD determinants are central to understanding individual susceptibility to hepatotoxicity.

## RISK FACTORS FOR HEPATOTOXICITY

Multiple host and environmental factors modulate the risk and severity of hepatotoxicity.[1,2] Genetic polymorphisms in drug-metabolizing enzymes, such as NAT2 or CYP2E1, significantly affect susceptibility, with slow acetylators at higher risk for isoniazid-induced hepatitis.[3] Age is another determinant; elderly patients often have reduced hepatic reserve, predisposing them to severe outcomes.[5] Gender also plays a role, as women are more prone to cholestatic reactions, especially during pregnancy due to elevated estrogen.[6] Preexisting liver disease amplifies the risk of hepatotoxicity when additional drugs are administered.[7] Alcohol consumption induces CYP2E1 and enhances bioactivation of hepatotoxic metabolites such as NAPQI from paracetamol.[7] Nutritional deficiencies, obesity, and comorbidities such as diabetes or viral hepatitis further increase vulnerability.[8] Therefore, clinical risk stratification must consider both genetic and acquired risk factors.[10]

**Table 2: Risk factors for hepatotoxicity.1-7**

| Risk factors | Examples |
|---|---|
| **Genetic polymorphism** | Slow acetylators → higher risk of isoniazid induced hepatitis |
| **Age** | Older adults more susceptible due to reduced hepatic reserve |
| **Gender** | Women more prone to cholestasis; pregnancy increases risk |
| **Preexisting liver disease** | Underlying hepatitis or cirrhosis predisposes to severe outcomes |
| **Alcohol use** | Chronic etanol induces CYP2E1, enhancing toxic metabolite formation |
| **Comorbidities** | Obesity, diabetes, or viral hepatitis increase vulnerability |

## COMMON HEPATOTOXIC DRUGS

Numerous drugs are implicated in hepatotoxicity, with injury patterns ranging from hepatocellular necrosis to cholestasis and fibrosis.[1,2]

Paracetamol (acetaminophen) remains the most common cause of acute liver failure globally due to intrinsic dose-dependent toxicity.[15]

Isoniazid frequently causes idiosyncratic hepatocellular injury, requiring liver function monitoring during therapy.[4]

Amoxicillin–clavulanate is among the leading causes of cholestatic drug-induced liver injury, especially in elderly patients.[5]

Methotrexate is linked with cumulative dose-related hepatotoxicity, including fibrosis and cirrhosis.[6]

Valproic acid induces mitochondrial dysfunction, resulting in microvesicular steatosis, predominantly in pediatric populations.[4]

Azathioprine causes mixed hepatocellular and cholestatic injury through immune-mediated mechanisms.[7] Herbal remedies such as kava and green tea extract are increasingly reported as hepatotoxic, highlighting the risks of unregulated supplements.[8]

## DIAGNOSTIC APPROACHES TO HEPATOTOXICITY

Diagnosis of drug-induced liver injury (DILI) requires exclusion of alternative causes such as viral hepatitis, alcohol, or autoimmune liver disease.[1,2]

Initial laboratory tests include liver function tests (ALT, AST, ALP, bilirubin), coagulation profile (PT/INR), and renal function tests.[3]

Imaging modalities such as ultrasound, CT, or MRI rule out biliary obstruction.[4]

Liver biopsy is reserved for unresolved or chronic cases to assess fibrosis and confirm etiology.[16]

Causality assessment tools, such as the Roussel Uclaf causality assessment method (RUCAM), are widely used to determine the likelihood of DILI.[17]

The Council for International Organizations of Medical Sciences (CIOMS) criteria also provide standardized frameworks for diagnosis in clinical and regulatory settings.[7]

## MANAGEMENT OF HEPATOTOXICITY

The first and most important step in hepatotoxicity management is discontinuation of the offending agent, which often leads to recovery.[1,2] Specific antidotes include N-acetylcysteine (NAC) for paracetamol toxicity, silibinin or penicillin G for Amanita mushroom poisoning, and ursodeoxycholic acid for cholestasis.[18]

Carnitine is used in valproate-induced toxicity, while glutathione and natural hepatoprotective agents such as silymarin and curcumin are under clinical investigation.[3,4] Supportive care involves intravenous fluids, antiemetics, and close monitoring of liver and renal function.[19]

In severe cases, liver transplantation remains the definitive life-saving therapy. Preventive strategies include careful dose titration, baseline and regular liver function monitoring, avoidance of polypharmacy, and patient counseling on symptoms of liver injury.[20]

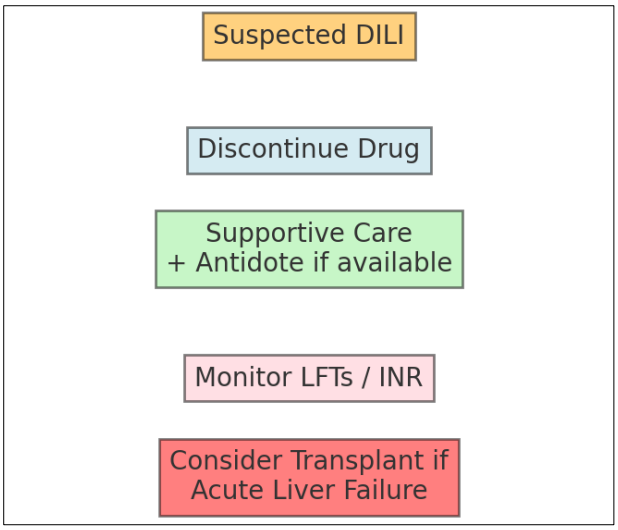


**Figure 1: Flowchart of management of hepatotoxicity.**

## REGULATORY AND PUBLIC HEALTH IMPLICATIONS

Major reason for drug withdrawals is a hepatotoxicity.[1,2] FDA and EMA closely monitor adverse drug events.[17] The NIH LiverTox database provides clinicians with updated drug hepatotoxicity.[4] Strengthened pharmacovigilance and early detection are essential globally.[5]

## AI AS TOOL FOR ANALYSIS OF DRUG INDUCED HEPATOTOXICITY

Drug-induced hepatotoxicity is a major cause of morbidity, clinical trial failure, and post-marketing drug withdrawal.[21] Artificial intelligence (AI) methods including classical machine learning (ML), deep learning (DL), and natural language processing (NLP) are increasingly used to identify, predict, and analyze hepatotoxic risk from preclinical and clinical data.[22] AI complements canonical toxicology approaches by integrating chemical structure, high-throughput assay data, toxicogenomics, clinical records, and spontaneous reporting systems to improve early detection, mechanistic understanding, and pharmacovigilance.[18]

## CONCLUSION

Drug-induced hepatotoxicity remains a significant clinical and regulatory challenge worldwide. The liver's central role in xenobiotic metabolism makes it particularly vulnerable to toxic insults from pharmaceuticals, herbal products, and environmental agents. The variability in mechanisms, ranging from mitochondrial dysfunction and oxidative stress to immune-mediated reactions and cholestasis, explains the heterogeneity of clinical presentations. Preventive measures, such as pre-treatment risk stratification, routine liver function monitoring, avoidance of polypharmacy, and patient education, are critical to mitigating the burden of hepatotoxicity. Advances in pharmacogenomics, improved *in vitro* and *in vivo* models, and strengthened pharmacovigilance systems hold promise for earlier detection and safer drug development. Ultimately, a multidisciplinary approach involving clinicians, pharmacologists, and regulatory authorities is required to reduce morbidity, mortality, and healthcare costs associated with drug-induced liver injury.

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