

DRUG-INDUCED LIVER TOXICITY: MECHANISMS AND THERAPEUTIC TARGETS

Sutrishna Manna¹, Suranjana Sarkar¹, Nimai Chandra Saha², Priyajit Banerjee*

¹Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, 700012, West Bengal, India.

²DPI, Education Directorate, Govt of West Bengal

*Corresponding Author. Priyajit Banerjee, Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, 700121, West Bengal, India.

Corresponding e-mail: priyajitb@svu.ac.in

ABSTRACT

Drug-induced liver injury (DILI) remains a critical challenge in clinical pharmacology, posing significant health risks and limiting the therapeutic potential of numerous drugs. This review explores the underlying mechanisms of DILI and highlights emerging therapeutic strategies aimed at mitigating hepatotoxicity. The pathogenesis of DILI involves intricate interactions between drugs and hepatic cellular structures, leading to oxidative stress, mitochondrial dysfunction, immune-mediated damage, and apoptotic pathways. Key molecular mediators, including cytochrome P450 enzymes, reactive oxygen species (ROS), and pro-inflammatory cytokines, are critically examined. Additionally, the limitations of current diagnostic biomarkers in predicting DILI are discussed. Emerging therapeutic approaches focus on modulating oxidative stress, enhancing mitochondrial protection, and regulating immune responses. Potential targets such as nuclear factor erythroid 2-related factor 2 (Nrf2), peroxisome proliferator-activated receptors (PPARs), and microRNAs (miRNAs) offer promising avenues for reducing hepatocellular injury. Furthermore, the role of personalized medicine and genetic predisposition in DILI

susceptibility is explored, emphasizing the need for tailored interventions. This review underscores the importance of advancing research to develop reliable biomarkers and innovative therapeutics, ultimately improving patient safety and drug efficacy.

Keywords: *Drug- induced liver injury, diagnosis, therapeutic*

INTRODUCTION

The liver, being the primary organ responsible for the metabolism and detoxification of drugs, is particularly susceptible to injury from various pharmaceutical agents, herbal products, and environmental toxins. Drug- induced liver injury (DILI) can manifest as a spectrum of liver abnormalities, ranging from mild, transient elevations in liver enzymes to severe, potentially life-threatening conditions such as acute liver failure. The mechanisms underlying DILI are diverse and complex, involving metabolic bioactivation leading to direct hepatocellular damage and immune-mediated responses resulting in liver inflammation. Despite advances in understanding the pathophysiology of DILI, diagnosing and managing this condition remains a challenge. Early detection and prompt cessation of the offending drug are crucial for preventing severe liver damage and improving patient outcomes[1-7].

The widespread use of medications and the continuous development of new pharmaceutical agents has raised growing concerns regarding their safety. One of the most frequent and severe adverse drug reactions (ADRs) is Drug-Induced Liver Injury (DILI) [8]. DILI can be triggered by various types of medications, including prescription and over-the-counter drugs, biological agents, traditional medicine (TM), natural medicines (NM), health products (HP), dietary supplements (DS), as well as their metabolites and excipients [9]. Despite extensive research, there are no specific diagnostic markers for DILI, making its diagnosis highly challenging. Globally, many countries and regions have developed empirical therapeutic strategies for DILI, supported by comprehensive guidelines. DILI is typically classified into three distinct clinical patterns—hepatocellular,

cholestatic, or mixed injury—based on the serum ALT and ALP ratio derived from the first available biochemical tests [10]. The therapeutic approaches for DILI, especially with regard to drug treatments, are often tailored to these three patterns of liver injury.

CLINICAL PRESENTATION AND DIAGNOSIS

Drug-induced liver injury (DILI) can present with a wide range of clinical manifestations, from asymptomatic elevations in liver enzymes to more severe conditions like jaundice, coagulopathy, and acute liver failure. Patients often exhibit symptoms such as fatigue, nausea, abdominal pain, and jaundice. Diagnosing DILI is particularly challenging due to its reliance on a combination of clinical history, exclusion of other potential causes of liver disease, and a temporal relationship with drug exposure. In certain cases, a liver biopsy may be performed to determine the extent of liver damage and to exclude other liver diseases. While ALT and AST are commonly used biomarkers to monitor liver function, there is a growing recommendation for the development of more specific biomarkers for predicting and early diagnosing DILI [11-13].

RISK FACTORS

The risk of developing DILI is influenced by both patient-related and drug-related factors. Patient-related factors include age, sex, genetic predisposition, pre-existing liver diseases, and comorbid conditions. For example, elderly individuals and those with pre-existing liver conditions such as hepatitis or non-alcoholic fatty liver disease (NAFLD) are at a higher risk. Genetic variations in drug-metabolizing enzymes and immune-related genes also play a role in determining susceptibility to DILI. Drug-related factors include the chemical structure of the drug, dosage, duration of therapy, and interactions with other medications. Certain drug classes, such as antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs), are more frequently associated with DILI [14-15].

DILI- INDUCED PHYSIOLOGICAL COMPLICATIONS

1. Cytochrome P450 Enzyme-Mediated Metabolism:One of the primary mechanisms underlying DILI is the metabolism of drugs by the liver's cytochrome P450 (CYP450) enzymes. These enzymes catalyze the biotransformation of drugs into metabolites, which, in some cases, can be highly reactive and toxic. The generation of reactive metabolites often leads to oxidative stress and cellular damage. For example, acetaminophen (paracetamol), a commonly used analgesic, undergoes CYP450-mediated metabolism to form a highly reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). In high doses, NAPQI depletes intracellular glutathione, resulting in hepatocellular damage and necrosis [17-18].

2. Oxidative Stress and Mitochondrial Dysfunction:Oxidative stress is a pivotal factor in the pathogenesis of DILI. Drugs that generate reactive oxygen species (ROS) can lead to lipid peroxidation, protein oxidation, and DNA damage. ROS accumulation disrupts cellular integrity, leading to mitochondrial dysfunction and hepatocellular apoptosis. Mitochondria play a crucial role in cellular energy metabolism, and their dysfunction is a hallmark of many forms of liver injury, including DILI. Disruption of the mitochondrial membrane potential and release of cytochrome c can trigger apoptotic pathways, exacerbating liver damage [19].

3. Immune-Mediated Mechanisms:In addition to direct hepatotoxicity, DILI may involve immune-mediated processes, where the immune system erroneously targets and destroys hepatocytes. The role of T lymphocytes and cytokines in DILI is gaining recognition, with studies indicating that certain drugs may induce immune responses that lead to liver damage. In some cases, this immune reaction can be attributed to a drug's ability to bind covalently to proteins in the liver, forming neoantigens that provoke an autoimmune-like response. The immune response can be both specific and nonspecific, with the activation of pro-inflammatory cytokines such as TNF- α and IL-1 contributing to the inflammatory cascade in DILI [20].

4. Apoptotic and Necrotic Pathways:The liver's response to toxic insults can trigger both apoptosis (programmed cell death) and necrosis. Apoptosis is typically mediated through the intrinsic pathway, involving mitochondrial dysfunction, and the extrinsic pathway, where death receptors on the hepatocyte surface trigger cell death. In cases of severe liver injury, necrosis can occur, leading to hepatocyte rupture and inflammation. These processes contribute to the clinical manifestation of liver injury, including jaundice, hepatomegaly, and elevated liver enzymes [21].

COMMON DRUGS ASSOCIATED WITH LIVER INJURY

TYPES OF DRUG	USED FOR	MODE OF ACTION	PHYSIOLOGICAL COMPLICATIONS
1. Uricosuric agent	Gout, hyperuricemia	Inhibits uric acid reabsorption in renal tubules, promoting uric acid excretion.	Hepatotoxicity, Kidney Stones, Liver toxicity, Headache, Gastrointestinal Symptoms [15-18]
2. Acetylcholinesterase inhibitor	Alzheimer's disease.	Inhibits acetylcholinesterase and also modulates nicotinic receptors, increasing acetylcholine release in the brain, enhancing cholinergic function.	Vomiting, Liver toxicity, Muscle weakness, Excessive salivation, Nausea, Diarrhea, [20-22]
3. Imidazopyridine	Anxiety disorders	Selectively binds to GABA-A receptors, increasing GABAergic activity, which helps induce sleep. It has a rapid onset and short duration of action.	Drowsiness, Dizziness, Headache, Memory Impairment, Daytime Sedation, Liver toxicity [19]

4. Antifungal	systemic and superficial fungal infections	Binds to ergosterol in fungal cell membranes, forming pores that disrupt membrane integrity, leading to leakage of cellular contents and fungal cell death.	Headache, Liver Toxicity, Skin Rash, Allergic Reactions [17-18]
5. Antibiotic	Infections	Inhibits DNA gyrase and topoisomerase IV, enzymes responsible for DNA replication and repair, leading to DNA strand breakage and bacterial death.	Allergic reactions, Liver toxicity [11]

Therapeutic Strategies to Combat Drug-Induced Liver Toxicity (DILT)

1. Antioxidants

Oxidative stress plays a crucial role in DILT, as many drugs generate reactive oxygen species (ROS) that damage liver cells. N-Acetylcysteine (NAC) is a widely used antioxidant, particularly in treating acetaminophen overdose, which depletes glutathione and results in hepatotoxicity. NAC replenishes glutathione levels, neutralizing ROS and preventing further liver damage. Beyond acetaminophen toxicity, NAC is being explored for other forms of DILT, with promising preliminary results [10, 17].

2. Immunosuppressive Agents

In certain DILT cases, liver injury is immune-mediated, such as in isoniazid-induced liver toxicity. In these cases, drugs such as corticosteroids (e.g., prednisone) are employed to suppress the immune response. Corticosteroids reduce inflammation and inhibit the activation of immune cells, offering protection against further liver damage. However, their use is limited by potential side effects, including immunosuppression and

metabolic disturbances [21].

3. Liver Support:

For patients who develop acute liver failure due to DILT, liver transplantation is the definitive treatment when the liver is no longer able to function. Although it is life-saving, liver transplantation comes with risks such as immune rejection and limited donor availability. Artificial liver support systems are also under investigation as temporary measures to support liver function while awaiting transplantation [22].

4. Enzyme Inhibitors

Some drugs undergo metabolic activation by cytochrome P450 enzymes (CYP450), leading to the formation of toxic metabolites. CYP450 inhibitors can block the enzymes responsible for metabolizing certain drugs, preventing the formation of harmful intermediates. This strategy holds promise in reducing DILT by limiting the bioactivation of toxic metabolites, though further research is required to establish its clinical effectiveness [22].

MANAGEMENT AND PREVENTION

Effective management of DILI involves early recognition, discontinuation of the offending drug, and providing supportive care. In cases of severe liver injury, hospitalization and close monitoring of the patient may be necessary. Preventive measures include the careful selection of medications, particularly in patients at risk, and regular monitoring of liver function during treatment with drugs known to have hepatotoxic potential. Ongoing research aims to develop safer drugs with reduced hepatotoxicity and to identify biomarkers for the early detection of DILI [19-20].

CONCLUSION

Drug-induced liver injury remains a significant challenge in clinical pharmacology. Understanding the complex mechanisms involved in DILI, improving diagnostic biomarkers, and developing targeted therapeutic strategies are crucial for minimizing hepatotoxicity and improving patient safety. Advancements in molecular biology, genetic

research, and personalized medicine hold great promise for the future management of DILI. As research continues to explore the underlying pathways and identify novel therapeutic targets, the hope is to develop more effective and personalized approaches to prevent or treat this potentially life-threatening condition.

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