

Mechanisms of Drug-induced Hepatotoxicity and Medicinal Chemistry Approaches for Prevention

Cristian Iwona*

Department of Pharmacology and Toxicology, Warsaw University of Life Sciences, Warsaw, Poland

Introduction

Hepatotoxicity, or liver toxicity, is a significant concern in the development and clinical use of pharmaceutical drugs. The liver is the primary organ involved in drug metabolism and its intricate network of enzymes and receptors makes it both a target for drug action and a site vulnerable to drug-induced damage. Understanding the underlying biochemical and molecular mechanisms that contribute to hepatotoxicity, along with developing medicinal chemistry approaches to mitigate these effects, is essential for improving the safety profile of drugs and minimizing adverse liver-related events. The liver plays a central role in the detoxification and clearance of drugs, but this process can also lead to the formation of toxic metabolites that cause damage to liver cells. The severity of hepatotoxicity depends on various factors, including the drug's pharmacokinetics, the liver's ability to detoxify harmful substances, genetic predispositions and pre-existing liver conditions. While many drugs are metabolized without causing harm, others can generate reactive metabolites that covalently bind to cellular macromolecules, leading to oxidative stress, inflammation and cell death. In some cases, Drug-Induced Liver Injury (DILI) can be idiosyncratic, meaning it occurs unpredictably in certain individuals, making it particularly challenging to anticipate and prevent [1].

Description

Several key mechanisms contribute to drug-induced hepatotoxicity and understanding these pathways is essential for developing preventive strategies. One of the most common mechanisms of liver injury involves the formation of reactive metabolites during drug metabolism. As drugs are processed by liver enzymes, such as cytochrome P450 (CYP450) enzymes, they can undergo oxidation, resulting in the production of highly reactive intermediates. These reactive metabolites can interact with cellular proteins, lipids and DNA, causing covalent binding and oxidative damage. The resulting oxidative stress activates inflammatory pathways, leading to hepatocellular damage, necrosis, or apoptosis. This process is particularly problematic for drugs with a high potential for bioactivation, as the accumulation of these toxic metabolites overwhelms the liver's detoxification capacity, ultimately resulting in liver injury. Another important mechanism is the activation of immune-mediated reactions. This leads to autoimmune-like responses and inflammation in the liver. Immune-mediated toxicity can manifest as hepatitis, liver fibrosis, or cirrhosis and may occur through direct activation of immune cells or the formation of drug-specific immune complexes. This form of toxicity is often unpredictable and may be influenced by genetic factors, such as HLA (human leukocyte antigen) polymorphisms, which predispose certain individuals to these adverse reactions [2].

The mitochondrial dysfunction pathway also plays a significant role in

hepatotoxicity. Many drugs, especially antiretroviral agents, antifungals and chemotherapeutic agents, can interfere with mitochondrial function, leading to the depletion of cellular energy and the generation of toxic metabolites. Mitochondrial dysfunction impairs ATP production, disrupts calcium homeostasis and induces the release of pro-apoptotic factors, culminating in hepatocyte injury and cell death. In some cases, mitochondrial toxicity can lead to more severe forms of liver injury, such as hepatocellular apoptosis and necrosis, which contribute to chronic liver disease. In addition to the previously mentioned mechanisms, cholestatic liver injury is another important form of hepatotoxicity that occurs due to the inhibition of bile flow. Some drugs can interfere with bile acid transporters, disrupting the normal flow of bile and leading to the accumulation of bile acids within liver cells. This buildup results in biliary stasis and cholestasis, causing damage to hepatocytes and the bile duct epithelium. Cholestatic liver injury can manifest as jaundice, itching and elevated liver enzymes and can progress to more severe forms of liver disease, such as cirrhosis or liver failure [3].

Addressing drug-induced hepatotoxicity requires a multi-faceted approach that integrates improved drug design, biomarker identification and therapeutic interventions. Medicinal chemistry offers several strategies to mitigate the risk of hepatotoxicity, particularly through the modification of drug structures to reduce the formation of toxic metabolites and improve liver safety profiles. One promising strategy is the use of selective and isoform-specific cytochrome P450 (CYP450) inhibitors. This approach involves designing drugs that are metabolized by enzymes with lower bioactivation potential, thereby minimizing the formation of toxic intermediates. Another approach is the development of prodrugs that are metabolized into non-toxic compounds. Prodrugs are inactive compounds that undergo metabolic conversion to release the active drug. By designing prodrugs that are less likely to generate reactive intermediates during their metabolism, medicinal chemists can reduce the risk of hepatotoxicity. The use of targeted drug delivery systems can also play a crucial role in reducing hepatotoxicity by ensuring that drugs are directed to their site of action, thereby limiting exposure to the liver. Liposomes, nanoparticles and other drug delivery systems can be engineered to enhance the bioavailability of drugs while minimizing the potential for liver injury by controlling the release of active drug compounds in a controlled manner [4].

A complementary strategy involves the identification and development of hepatoprotective agents that can be co-administered with potentially hepatotoxic drugs. These agents act as protectants by neutralizing oxidative stress, enhancing the liver's detoxification capacity and modulating inflammatory responses. Antioxidants, such as N-Acetylcysteine (NAC) and anti-inflammatory agents, such as corticosteroids, are examples of hepatoprotective agents that have been explored in preclinical and clinical settings. By co-administering these agents with hepatotoxic drugs, the overall risk of liver injury can be reduced. Another key area of focus in the prevention of hepatotoxicity is the use of biomarkers for early detection and monitoring. Advances in proteomics, genomics and metabolomics have led to the identification of potential biomarkers that can predict liver damage before clinical symptoms become apparent. For example, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly used biomarkers to monitor liver function, but they may not always detect early stages of hepatotoxicity. New biomarkers, such as microRNAs, liver-specific proteins and mitochondrial markers, may offer more sensitive indicators of liver damage and allow for the early detection of hepatotoxicity. Early identification of at-risk patients could enable timely intervention to prevent irreversible liver damage [5].

*Address for Correspondence: Cristian Iwona, Department of Pharmacology and Toxicology, Warsaw University of Life Sciences, Warsaw, Poland, E-mail: iwona.chris@warsaw.edu

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Conclusion

Drug-induced hepatotoxicity remains a significant challenge in the development and clinical use of pharmaceutical drugs. Understanding the complex mechanisms underlying liver injury, such as reactive metabolite formation, immune-mediated reactions, mitochondrial dysfunction and cholestatic injury, is essential for mitigating the risks associated with drug therapy. Advances in medicinal chemistry provide promising strategies for the prevention of hepatotoxicity, including the design of drugs with lower metabolic activation, the use of prodrugs and the development of hepatoprotective agents. Additionally, the identification of biomarkers for early detection of hepatotoxicity holds promise for improving patient safety and reducing the burden of liver-related adverse drug events. As research in this field continues, more effective approaches to preventing and managing drug-induced hepatotoxicity will emerge, leading to safer and more effective therapeutic options for patients.

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Conflict of Interest

None.

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