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THEORETICAL FOUNDATIONS FOR MATHEMATICAL MODELING OF LIVER STRUCTURE AND DAMAGE PROCESSES CAUSED BY DRUGS

Diloromxon Ubaydullayeva
Teacher of the Department of "Digital Educational Technologies"
Namangan State University
ubaydullayevadilorom378@gmail.com

Abstract
The liver is the largest gland in the human body, playing a central role in metabolism, detoxification, and various biological processes. In addition, drugs can affect liver cells (hepatocytes) and induce varying degrees of injury, known as Drug-Induced Liver Injury (DILI). This article provides a scientific overview of the pathophysiology, mechanisms, and clinical manifestations of DILI. The formation of reactive or toxic metabolites during drug metabolism, oxidative stress, organelle dysfunction, cholestasis, and immune responses play key roles in the development of DILI. Furthermore, the patient's genetic predisposition and pharmacogenetic factors influence these processes. Monitoring liver biomarkers (ALT, AST) is essential for DILI diagnosis. The article highlights modern scientific approaches, including mathematical modeling, for predicting drug safety and preventing liver injury.

Keywords: Drug-Induced Liver Injury (DILI), Hepatotoxicity, Hepatocyte, Cytochrome P450, Oxidative stress, Cholestasis, Immunological mechanism, Pharmacogenetics, Liver biomarkers (ALT, AST), Pathophysiology.

Introduction

The liver is the largest gland in the human body. Its average weight is approximately 1,500 grams. The liver is located in the upper part of the abdominal cavity, with its superior surface in contact with the diaphragm. The main portion

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of the organ is situated beneath the right rib cage. Anatomically, the liver is divided into two main lobes — the right (large) and the left (small) — by a falciform ligament located on the diaphragmatic surface. In a healthy state, the inferior border of the liver usually does not extend beyond the costal margin. The liver is one of the most important organs in the human body, playing a central role in metabolism, detoxification, and various biological processes. Blood rich in nutrients absorbed from the gastrointestinal tract reaches the liver through the portal vein. This blood contains carbohydrates, proteins, vitamins, and other metabolic breakdown products. These substances are processed by hepatocytes, with some stored as reserves and others transformed into different compounds through metabolic processes and released back into the bloodstream. Therefore, the liver is critically important as a center of metabolism in the body. Additionally, the liver plays a vital role in the processing and detoxification of various chemical substances entering the body, including drugs. After entering the body, the majority of drugs undergo metabolism by liver enzyme systems, particularly cytochrome P450 enzymes. During this process, drug molecules are chemically modified, making them ready for elimination from the body. However, in some cases, drug metabolism can produce reactive or toxic metabolites. These metabolites can damage liver cells, potentially leading to varying degrees of liver injury. In modern medicine, drug-induced liver injury is a significant clinical concern. This condition is referred to as Drug-Induced Liver Injury (DILI) and is widely studied as an adverse effect of drugs. In some patients, DILI manifests as an elevation in liver enzymes (e.g., ALT and AST), while in others, it may result in severe complications such as liver failure. Therefore, studying the effects of drugs on the liver is of substantial scientific importance in pharmacology, toxicology, and biomedical research. Mathematical modeling of these processes allows for a more precise analysis of changes in drug concentration over time, the rate of metabolism, and the degree of toxic impact on liver cells. This, in turn, plays a crucial role in predicting drug safety and preventing liver injury.

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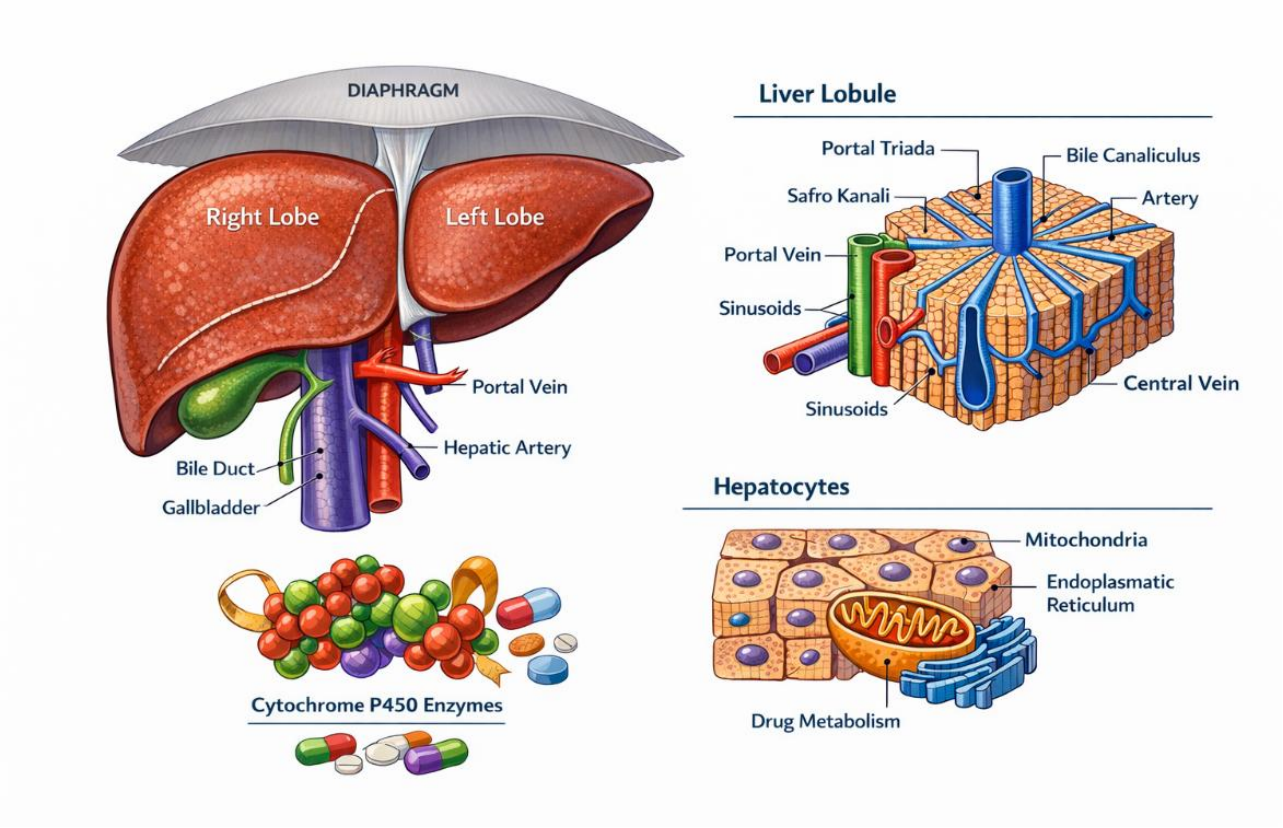

Liver Structure and Microscopic Composition

Effects of drugs on the liver: mechanisms and pathophysiology

"Drug-induced liver injury (DILI) caused by medications is a serious clinical problem for human health and can sometimes lead to severe complications, including death. DILI arises through various mechanisms depending on the chemical properties of the drug, its dose, duration of treatment, and the individual pharmacogenetic factors of the patient."

1. Hepatic Metabolism of Drugs and Formation of Reactive Metabolites: The liver is the primary organ for detoxification and metabolism in the body, and many drugs undergo metabolism primarily through it. Drug compounds are chemically modified in hepatocytes by cytochrome P450 enzymes, converting the parent molecules into more water-soluble and excretable forms. However, some drugs can generate reactive or toxic metabolites, which can bind to intracellular proteins, lipids, and DNA, exerting toxic effects.

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2. Oxidative Stress and Organelle Dysfunction: Toxic metabolites can induce oxidative stress within hepatocytes. This process is characterized by an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS), which impair the function of cell membranes, mitochondria, and the endoplasmic reticulum. Mitochondrial stress reduces ATP synthesis, leading to energy depletion in the cell, which contributes to hepatocyte degeneration and necrosis.

3. Cholangial Dysfunction and Cholestasis: Certain drugs can obstruct or impair the channels responsible for bilirubin and bile acid transport. This condition is known as cholestasis, which disrupts bile flow and causes bile salts to accumulate within the liver, resulting in cellular injury.

4. Immunological Mechanisms and Idiosyncratic DILI: A subset of DILI manifests through unpredictable idiosyncratic mechanisms. In these cases, metabolites may directly act as antigens to the immune system, or signals released from hepatocytes may trigger an immune response. This mechanism initiates immunological reactions, promoting inflammation and further hepatocyte injury.

5. Genetic Predisposition and Individual Variability: The risk of drug-induced liver injury varies significantly among patients. This variability is related to pharmacogenetic factors, particularly polymorphisms in cytochrome P450 and other conjugation enzymes. Certain genotypes are more prone to producing high amounts of toxic metabolites, increasing the likelihood of DILI development.

6. Clinical Features and Diagnosis: DILI represents a major limitation in clinical drug development, and many drugs are withdrawn during clinical trials or after market approval due to hepatotoxic effects. Diagnosis of DILI relies on monitoring liver enzymes, such as ALT and AST, which are primary biomarkers indicating hepatic injury.

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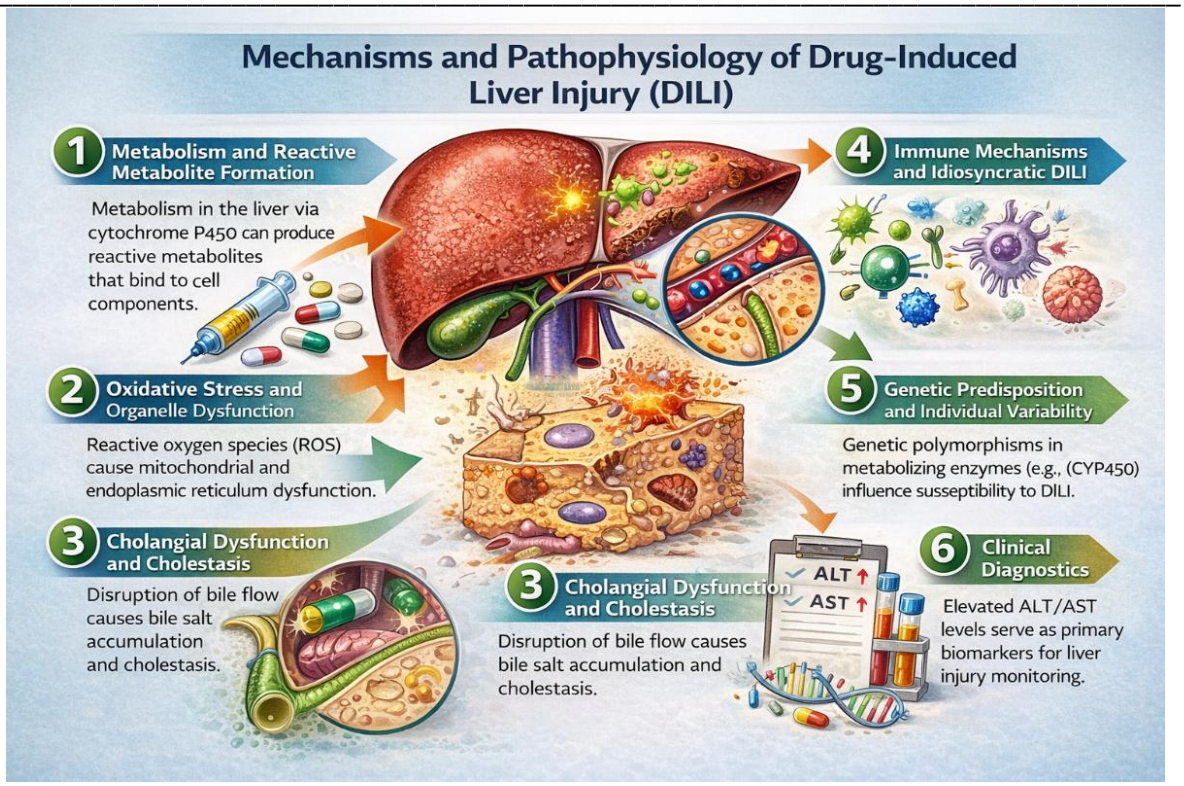

Mechanisms of Drug-Induced Liver Injury

In conclusion, drug-induced liver injury (DILI) represents a complex, multi-step, and multifactorial process. The formation of toxic metabolites during drug metabolism, oxidative stress, organelle dysfunction, immune responses, and individual genetic susceptibility all play central roles in its pathogenesis. The severity and clinical manifestations of these processes may vary depending on the patient's genetic factors and pharmacogenetic profile. Understanding these mechanisms is essential for predicting hepatotoxic risks, designing safer pharmaceuticals, and implementing personalized medicine approaches. Ongoing research, including in vitro studies, animal models, and mathematical modeling, continues to elucidate the molecular pathways underlying DILI, providing critical insights for both clinical management and drug development.

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