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Original Research Article

Mechanisms of Drug-Induced Liver Injury: Pharmacological Insights and Biomarker-Based Detection Approaches

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Abstract: Drug-induced liver injury (DILI) is one of the most significant and chronic problems in the clinical pharmacology and toxicology, and a primary cause of acute hepatic failure, developmental drug attrition, and post-marketing regulatory events. Diversified pharmacological, metabolic, and immunological pathways are the factors which made DILI to be complex and heterogeneous and, therefore, difficult to predict, identify early and address clinically. The purpose of the review was to elucidate the mechanistic basis of DILI in a comprehensive way and mention the significance of biomarker-based strategies in terms of better detection and risk assessment. Experimental and clinical studies have recently shown that DILI is a product of interconnected pathways in which reactive metabolite formation, oxidative stress, mitochondrial dysfunction, bile acid transport disruption, and innate and adaptive immune activation occur. The recent developments in pharmacogenomics have also discovered that genetic diversity in drug-metabolizing enzymes, transporters, and immune regulating systems play a big role in determining an individual susceptibility to liver damage. More recent studies have also highlighted the shortcomings of traditional liver enzymes as a diagnostic method and it has led to the emergence of new biomarkers which can more reliably indicate the causative pathways of hepatocellular injury and inflammation. Newer biosensors like circulating microRNAs, cytokeratin-18 fragments, high-mobility group box-1 protein and bile acid signatures have demonstrated better sensitivity and specificity in early DILI diagnosis, phenotypic grouping and prognostic assessments. Combining the mechanistic pharmacological knowledge with biomarker discovery adds to the knowledge of the DILI pathogenesis and provides more reliable safety assessment during the drug life cycle. Conclusively, DILI can be viewed as a multifactorial and mechanism-based adverse response that must be addressed through a translational process that is between molecular toxicology and practical clinical use. The utilization of mechanism-based biomarkers, in addition to traditional methods has a huge potential to enhance the accuracy of diagnosis, reduce patient risk and enhance the development of safer and more effective drug development approaches.

Keywords: Drug-Induced Liver Injury (DILI), Hepatotoxicity Mechanisms, Drug Metabolism, Liver Biomarkers, Pharmacological Toxicology.

INTRODUCTION

Drug-induced liver injury (DILI) is among the most complicated and clinically relevant adverse reactions connected to pharmacotherapy that is one of the greatest problems with the medicine. Liver, being the main organ that performs the functions of drug metabolism and detoxification, is especially susceptible to be damaged by xenobiotics (Villanueva-Paz et al., 2021). DILI is a major contributor to the acute liver failure and drug withdrawal after the

market, a factor that highlights its effects on the safety of patients and drug development. Even with the progress in pharmacology and toxicology, the variability of numerous DILI cases still makes early diagnosis, risk evaluation, and therapeutic decision making challenging (Tiwari et al., 2025). The mechanisms behind DILI include various (hepatotoxicity, idiosyncratic reactions, or immune-mediated reactions) which are affected by a range of drug-specific factors (dose, duration of exposure, drug metabolism and ROS formation (Fontana RJ., 2013).

The electrophilic metabolites can binding cellular macromolecules can be produced by hepatic biotransformation, especially through the cytochrome P450 enzymes and induce oxidative stress, mitochondrial dysfunction and disturbance of intracellular signaling pathways. The changes in bile acid transport and homeostasis are the factors that add to the cholestatic liver injury patterns and serve to emphasize the multifactorial nature of DILI (Francis et al., 2025). Mitochondrial impairment, depletion of ATP, excessive generation of ROS and nitrogen species are linked to drug-induced hepatotoxicity at the cellular and molecular levels. They may cause apoptosis or necrosis of hepatocytes and facilitate the inflammation through the activation of the innate immune system (Mihajlovic and Vinken, 2022). Drug-protein conjugates can become neoantigens in some people and trigger adaptive immune in response to further damage the liver. A further complication in the pathogenesis of DILI is the increased acceptance of genetic polymorphisms of drug-metabolizing enzymes, transporters, and immune regulators as the most important factors in individual susceptibility (Gerussi et al., 2021). DILI has long been detected and assessed using serum liver enzymes including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin. Although these traditional biomarkers are quite common in clinical/experimental practice, they have low specificity and sensitivity, especially when compared to differentiating DILI and other hepatic conditions (Fu S et al., 2020).

As a result, there has been a significant body of research on identifying novel biomarker-based methods that dictate mechanistic injury pathways. The work on new biomarkers, such as microRNAs, fragments of cytokeratin-18, high-mobility group box-1 protein, and bile acid profiles, can become a useful tool to detect DILI earlier and better phenotype and prognostically stratify it (Xinxin etal., 2025). Over the past few years, incorporation of drug-related knowledge with the identification of biomarkers has contributed to better understanding of DILI, as well as to more precise risk assessment measures. The mechanism-based biomarkers do not only enhance the accuracy of the diagnosis but also offer an insight into the underlying pathophysiological processes, therefore, enabling the development of safer drugs and the more personalized treatment strategy (Umbaugh and Jaeschke, 2021). This is necessitated by the fact that regulatory agencies are placing more focus on translational biomarkers and this requires thorough reviews that will interconnect mechanistic knowledge and detection methodologies (Jung et al., 2025).

The aims of this review are to explain the main pharmacological and molecular processes of drug-induced liver injury. Compare the importance of drug metabolism, oxidative stress, and mitochondrial dysfunction and immune responses in the pathogenesis of DILI. Assess the traditional and novel biomarker-based detection and characterisation of DILI. Showcase the clinical and translational impact of mechanism-based biomarkers to aid in the diagnosis, risk-assessment and drug safety assessment.

LITERTURE VEIW

1. Background

1.1 Overview of Drug-Induced Liver Injury (DILI):

Drug-induced liver injury (DILI) is liver damage that can be traced to an exposure to pharmaceutical agents, such as prescription drugs, over-the-counter drugs, herbs, and dietary supplements. The liver is the key drug metabolism organ that makes it especially vulnerable to toxic insults caused by parent compounds or its metabolites. DILI is a wide clinical spectrum, including an asymptomatic increase of liver enzymes to acute liver failure and death. Notably, DILI is neither a disease nor a disease entity but a heterogeneous disorder with a variety of pathological patterns, temporal patterns and pathways. These are hepatocellular, cholestatic and mixed types of injury that manifest different underlying biological processes. DILI variability of the clinical presentation and outcome emphasizes the complexity of the condition and the necessity of gaining a mechanistic insight into its clinical manifestation that would allow making a proper diagnosis and reducing the risk (David and Hamilton , 2010).

1.2 Clinical and Pharmacological Significance of DILI:

Clinically, DILI is a common cause of acute liver failure in most parts of the world and is also a significant cause of drug discontinuation and regulatory resulting in intervention. Its importance goes further than patient safety and also has considerable implications to drug development, approval, and post-marketing surveillance. In pharmacology, DILI is a crucial model of the adverse drug reactions and is used to present a combination of drug dose, metabolism, host susceptibility, and environmental modifiers. Intrinsic, dose-dependent hepatotoxicity is as well as idiosyncratic, dose-independent but both types of hepatotoxicity present difficulties to the clinician and researcher since the latter can not be forecasted by the normal preclinical

testing. DILI, therefore, leads to attrition in the late stages of drug pipelines and restricts the availability of therapies, especially with the vulnerable groups like patients with comorbidities or with prior liver disease. It is thus crucial that the DILI be understood to maximize effectiveness of therapeutic action and minimize harm (Kozielewicz et al., 2025).

1.3 Challenges in Diagnosis, Prediction, and Management:

The diagnosis and treatment of DILI is still problematic even decades after the research. Among the most serious problems, one may single out the lack of a particular clinical or laboratory diagnosis that would clearly differentiate DILI and other liver-related diseases, including hepatitis caused by viruses, autoimmune hepatitis, and metabolic disorders. It is frequently diagnosed by exclusion and depends on time-linked relationships between the exposure and harm of the liver by drugs, as well as causality analysis algorithms. DILI prediction is also not easy, especially among idiosyncratic reactions, which can be experienced with no predictability and only a few people who are exposed. The management alternatives are highly supportive with the most significant intervention being drug withdrawal because there are no specific treatment therapies. Moreover, the traditional liver biomarkers are not sensitive and mechanistic-specific, which limits their application in the early detection and prognosis. All these issues shape the necessity of predictive tools and more diagnostic approach based on the mechanisms (Garcia-Cortes et al., 2024).

1.4 Rationale and Scope of the Review:

Considering the clinical burden and scientific complexity of DILI, it is timely and essential to review the problem comprehensively by combining the mechanistic pharmacological understanding with the achievements achieved in detecting biomarkers. The recent advances in molecular toxicology, pharmacogenomics and systems biology have contributed significantly to the knowledge of drug-hepatic pathway interactions to cause injury. Simultaneously, the discovery of new biomarkers signifying certain types of hepatocellular stress and cell death, as well as immune activation, opens new possibilities to be diagnosed earlier and more precisely. This review scope is thus to compile existing information on the mechanisms of DILI, mainly focusing on drug metabolism, cellular and immune-mediated pathology, and risk factors that are related to the host. Also, the review critically analyzes the traditional and new biomarkers, including their translational applications to clinical practice and safety in drug trials. This review will help in enhancing the prediction of risks, the treatment of patients, and creating safer therapeutic agents by filling the gap between mechanistic knowledge and diagnostic innovation (Hosack et al., 2023).

2. Classification of Drug-Induced Liver Injury

2.1 Intrinsic (Dose-Dependent) Hepatotoxicity:

Intrinsic hepatotoxicity is a predictable and reproducible type of drug-induced liver injury, and involves a direct relationship with dose and exposure to the drug. This form of liver damage is usually caused by a drug or its metabolites overwhelming the liver in its detoxification ability resulting in direct cell injury. Intrinsic DILI is less sensitive to the presence of the dosage response, characterized by a relatively short latency and is therefore more sensitive to detection in preclinical toxicological testing. Examples classic examples of this are acetaminophen-induced liver damage in which a large production of reactive metabolites leads to a depletion of glutathione, oxidative stress, and necrosis of hepatocytes of massive numbers. Mechanistically, intrinsic hepatotoxicity usually entails the induction of mitochondrial dysfunction, lipid peroxidation and cell membrane disruption. In its predictability, this category has been at the forefront in the establishment of regulatory directives and safety thresholds when development is concerned with drugs (Skat-Roddam et al., 2025).

2.2 Idiosyncratic Drug-Induced Liver Injury:

Idiosyncratic DILI is a random, comparatively unusual adverse response that happens in some insignificant group of the exposed individuals and is not dependent on the dose or the length of therapy. In comparison to intrinsic hepatotoxicity, idiosyncratic reactions can hardly be reproduced in experimental models and often appear in post-marketing surveillance. Its development can be delayed as it can take weeks, up to months after the drug is started and the clinical manifestation can be of different levels. The existing data indicate that idiosyncratic DILI occurs as a result of the intricate interplay between drug-related and host predisposition factors, such as genetic, metabolic, and immunological factors (Hussaini and Farrington, 2007).

2.2.1 Metabolic Idiosyncrasy:

Interindividual variability in drug metabolism is the major driver of the metabolic idiosyncrasy. Transporters and drug-metabolizing enzymes Genetic variations on polymorphism of genetics may result in the overproduction or reduced clearance of reactive intermediates at therapeutic levels. These metabolites can react covalently with proteins of cells, cause oxidative stress, and damage mitochondrial activity. In contrast to intrinsic toxicity, the injury threshold in a metabolic idiosyncrasy does not vary consistently across populations, but there is variability in the enzymatic activity and hepatic defense of the injury threshold. This type of idiosyncratic DILI makes the role of pharmacogenomics in interpreting patient-specific risk profile essential (Atallah et al, 2021).

2.2.2 Immune-Mediated Idiosyncrasy:

Immune mediated idiosyncratic DILI is a situation whereby the adaptive immune system is activated to drug-derived antigens. Reactive metabolites can be bound to hepatic proteins to produce neoantigens, which activate T-cell-mediated immunity. The process is usually linked to aspects alluding to hypersensitivity, including fever, rash, and eosinophilia, and can be correlated with particular human leukocyte antigen (HLA) types strongly. The immunological element plays a role in the variation of clinical reflectivity and severity, mild hepatitis has been noted to severe liver fulminant failure (Mak and Uetrecht, 2017).

2.3 Hepatocellular, Cholestatic, and Mixed Patterns of Injury:

DILI can further be classified by clinical and biochemical means depending on the pre-eminent pattern of liver injury. Liver cell injury is hepatocellular in nature and is associated with significant increases in amino-transferases, and is evidence of direct hepatocyte damage. Cholestatic injury is a condition that is related to the increased bilirubin and alkaline phosphatase as a result of the impairment of the bile formation or flow. Mixed patterns have characteristics of hepatocellular and cholestatic damage. These trends are not only descriptive but also are able to inform about the underlying mechanism, influence diagnostic assessment, and have significant impact on prognosis. The awareness of these unique injury profiles is the key to the successful classification, causality determination, and clinical treatment of DILI (Zeng et al., 2023).

3. Drugs Commonly Associated with Liver Injury

3.1 Antimicrobial Agents:

The most commonly involved classes of drugs causing liver injury due to drug use are the antimicrobial drugs because of their wide use and varied metabolism. Amoxicillin-clavulanate and isoniazid, rifampicin and fluoroquinolones have also been reported repeatedly in relation to hepatocellular and cholestatic liver injury. The underlying mechanisms of antimicrobial-related DILI are not always the same and can be the creation of reactive metabolites, bile acid transport disruption, as well as hypersensitivity reactions mediated by immunity. Specifically, it is highly known that antitubercular drugs have cumulative hepatotoxic effects particularly in combination regimens. The inconsistency in latency, clinical manifestation, and severity of patients points to the role of host factors and drug-drug interactions in antimicrobial-associated hepatotoxicity (Devarbhavi and Andrade, 2014).

3.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

Another significant category that is linked with liver damage is the non-steroidal anti-inflammatory drugs, although they are generally thought to be safe even when taken at therapeutic doses. Although the majority of NSAIDs-related hepatotoxicity is mild and reversible, some NSAIDs have been associated with severe and even fatal liver damage. The pathogenesis can be very idiosyncratic and can encompass metabolic activation, mitochondrial impairment, and oxidative stress. NSAIDs can also disrupt the production of hepatic prostaglandins and therefore affect the hepatocellular homeostasis in the case of metabolic stress. Despite the low rate of the overall occurrence of clinically significant liver injury, the prevalence of NSAIDs makes them a more applicable cause of DILI in clinical and epidemiological contexts (Bonkovsky et al.,2024).

3.3 Antiepileptic and Psychotropic Drugs:

The antiepileptic and psychotropic drugs used as replacement therapy in epilepsy. Antiepileptic and psychotropic drugs are known to be common causes of drug-induced liver injury especially on long-term treatment. The valproic acid, carbamazepine, and phenytoin have been linked with various hepatic adverse effects that encompassed the asymptomatic increase in the enzymes to acute liver failure. Mitochondrial toxicity and fatty acid metabolic deceleration have been identified as potential effects of valproic acid, especially. Some antidepressants and antipsychotics are psychotropic drugs that cause hepatotoxicity with possible mechanisms related to oxidative stress, metabolic idiosyncrasy and immune-mediated response. The long-term character of the treatment of neurological and psychiatric cases requires close attention to liver functioning to reduce the possible risks (Telles-Correia et al., 2017).

3.4 Anticancer and Immunomodulatory Therapies:

This category of treatments is focused on targeting cancerous cells and their growth in metastatic cancer, thereby promoting the removal of cancerous proliferations in the body. While the Immunomodulatory therapy is aimed at attacking cancerous cells and their proliferation in metastatic cancer, and, therefore, facilitating the elimination of cancerous growth in the body. There is a growing appreciation of the hepatotoxicity of anticancer and immunomodulatory therapies because of their increasing use. Cytotoxicity of the traditional chemotherapeutic agents may be directed at hepatocytes, whereas targeted therapies and immune check blockers are likely to cause immune-mediated liver-related damage. These more recent agents tend to interfere with the immune tolerance leading to inflammatory hepatitis that is similar to the autoimmune liver disease. What is more is that combination regimens and underlying liver disorders may worsen hepatotoxicity. The knowledge of mechanisms of liver injury with these treatments is essential in the goal of balancing therapeutic and patient safety in oncology and immunology (Da

Cunha et al., 2022) (Savino et al., 2025).

3.5 Herbal Medicines, Dietary Supplements, and Veterinary Drugs:

The firm manufactures herbal medicines, dietary supplements, and veterinary medications. Herbal medicine and nutritional supplements have become major, but poorly known causes of drug-induced liver damage. These products have a hepatotoxic risk which is compounded due to differences in composition, their unstandardisation and inadequate regulatory supervision. Hepatotoxicity can be either idiosyncratic or poisoning or drug-herb interaction. Equally, veterinary drugs may cause liver damage in animals and in other instances can be indirectly harmful to human beings via animal product residues. The increased use of alternative and veterinary drugs in the world highlights increased awareness, enhanced reporting, and strict testing of their hepatic safety profiles (Yang et al., 2025) (Navarro et al., 2017).

PHARMACOKINETIC AND PHARMACODYNAMIC DETERMINANTS OF DILI

4.1 Drug Absorption, Distribution, and Hepatic Exposure:

The pharmacokinetic processes are highly significant in identifying how much the hepatic is exposed to drugs, and hence the likelihood of liver damage as a result of drugs. After the absorption, the drugs then go to the liver through the portal circulation where first-pass metabolism may have a significant effect on the bioavailability and hepatic concentration of the drug. Formulation, route of administration, plasma protein binding, and tissue distribution are some of the factors that influence the quantity of active compound that arrives at hepatocytes. Great hepatic extraction rates and extended intrahepatic retention can make a patient more vulnerable to toxicity especially drugs with low therapeutic indices. The difference in these processes among people is a factor in the variation of liver exposure and, in part, an explanation of the heterogeneous clinical presentation of DILI (Kobayashi et al., 2023) (Ghabril et al., 2025).

4.2 Role of Cytochrome P450 Enzymes in Hepatotoxicity:

Cytochrome P450 enzymes play a role in the pathogenesis of hepatotoxicity. Cytochrome P450 Enzymes in the Pathogenesis of Hepatotoxicity. Cytochrome P450 (CYP) enzymes are the main catalytic system that is involved in oxidative metabolism of most drugs in liver. Although these enzymes help clear the drug, there are chances of the formation of unstable and possibly toxic intermediates. A single overactivation or induction of certain CYP isoforms may increase the production of detrimental metabolites, and the opposite may also occur. Genetic polymorphisms, environmental and comorbid factors have led to interindividual differences in CYP expression and activity that strongly affect the susceptibility to hepatotoxicity. Therefore, CYP-mediated metabolism was a key focal point of mechanistic interconnection of the pharmacokinetics and drug-induced liver injury (Park et al., 1995).

4.3 Formation of Reactive Metabolites:

The reaction product is a reactive metabolite. The hepatocellular injury heavily depends on the biotransformation of drugs into active metabolites. These electrophilic species are capable of covalently binding to cell proteins, lipids and nucleic acids thus affecting cell functions. this processes into an oxidative stress. The deposits of protein adducts may in certain instances serve as a stimulus to immunopathology, which connects the metabolic events to immunopathy of the liver. The rate of reactive metabolite production and the rate of the hepatic mechanisms of hepatic detoxification systems, including glutathione conjugation, is consequently decisive in the end result of the drug exposure (Antoine et al., 2008).

4.4 Drug–Drug Interactions and Polypharmacy:

Polypharmacy and drug-drug interactions are becoming major causes of drug-induced liver injury especially in most populations that are taking many drugs. Drugs that are used with other drugs can change the hepatic metabolism through the induction or inhibition of drug-metabolizing enzymes and transporters resulting in unforeseen changes in concentration and toxicity of drugs. Also, inhibition of the hepatic exposure to toxic compounds may be intensified by competitive metabolic or transporter inhibition. Polypharmacy in clinical practice makes the evaluation of causality more difficult and predisposes adverse hepatic events. This awareness is necessary to maximize the therapeutic effect, as well as to reduce the risk of DILI particularly in patients with underlying diseases or liver malfunction (Boeing et al., 1992).

5. Molecular and Cellular Mechanisms of Drug-Induced Liver Injury

5.1 Oxidative Stress and Redox Imbalance:

The indicative of oxidative stress and redox imbalance is present during the initial 6 hours following surgery, as numerous cytokines are involved in the condition. Oxidative stress and redox imbalance are indicative of the first 6 hours after surgery, and many cytokines are implicated in the condition. The primary process in drug-induced liver injury is oxidative stress, which is the result of insufficient hepatic antioxidant protection in response to the overproduction of reactive oxygen species (ROS). Direct effects can be caused by drugs or their reactive metabolites that generate ROS, cause lipid peroxidation, and damage cellular proteins and DNA. The redox imbalance influences signaling

pathways and increases cell damage that leads to hepatocellular damage and inflammatory cascade activation. Literature shows that oxidative stress is an intervening factor in direct cytotoxicity, as well as a connection between metabolic abnormalities and immune-mediated damage, making it a multifactorial contribution to DILI pathogenesis (Ramachandran and Jaeschke, 2018).

5.2 Mitochondrial Dysfunction and Energy Depletion:

This is due to the fact that mitochondria utilize a greater percentage of their energy as ATP energy rather than as ADP energy. This is because a higher proportion of the energy is used by the mitochondria as ATP energy, instead of using it as ADP energy. Mitochondria play an important role in the regulation of cellular energy metabolism and apoptotic signals. A large number of hepatotoxic drugs affect the functioning of mitochondria, hindering electron transport chain, facilitating membrane permeability transition, or depleting adenosine triphosphate (ATP) reserves. Energy loss impairs cell survival in hepatocytes and exposes the cells to oxidative damage and other injuries. Mitochondrial dysfunction, especially, has been specifically implicated in the hepatotoxicity of acetaminophen and valproic acid, enabling the central role of the organelle in the pathophysiology of DILI (Ramachandran and Jaeschke, 2018).

5.3 Disruption of Bile Acid Transport and Cholestasis:

Disruption of bile acid transport and cholestasis is characterized by an alteration of bile flow and elevated bilirubin concentration within the blood. Disruption of bile flow and increased bilirubin concentration in the blood characterizes cholestasis and bile acid transport. Changes in the bile acid transport and homeostasis are one important pathway in cholestatic DILI. Medications can cause hepatocellular blockage of bile secretion transporters like the bile salt export pump (BSEP) which cause intrahepatic bile buildup. Cholestasis causes hepatocyte damage by the detergent-like action of bile acids, oxidative stress, and by the action of inflammatory mediators. The identification of transporter-mediated pathways is the key to the explanation of the particular patterns of injury caused by the drug, and to the creation of the predictive assays in safety evaluation in preclinical studies (Saran and Brouwer, 2023).

5.4 Endoplasmic Reticulum Stress and Proteostasis Imbalance:

Endoplasmic reticulum stress and proteostasis imbalance: This involves the dysregulation of endoplasmic reticulum and proteostasis pathways, which can lead to cell death through apoptosis. This is the disruption in the endoplasmic reticulum and proteostasis pathways that may cause cell death via apoptosis. The endoplasmic reticulum (ER) is an organ that is part of protein folding, lipid metabolism, and cellular homeostasis. Hepatotoxic medications have the effect of disrupting the ER function leading to the build-up of misfolded proteins and the unfolded protein response (UPR). Prolonged ER stress leads to dysfunction of hepatocyte, hepatocyte genocide, and enhancement of oxidative stress. The dysfunction of the ER leads to proteostasis imbalance, which in turn supports the interdependence of cellular stress responses to DILI and presents potential points at which therapeutic intervention can be carried out (Pu et al., 2023).

5.5 Hepatocyte Apoptosis, Necrosis, and Autophagy:

A total of 300 hepatocytes contained apoptotic, necrotic, and autophagic bodies. The number of hepatocytes with apoptotic, necrotic and autophagic bodies was 300 in total. A last similar pathway in drug-induced liver injury is cell death, which includes apoptosis, necrosis, and processes related to autophagy. Apoptosis is a process of programmed cell death that is driven by caspase-activation or mitochondrial transduction, usually due to oxidative stress or ER dysfunction. The process of necrosis is caused by serious cellular damage and exhaustion of energy, which cause membrane rupture and inflammation. Autophagy can be a protective mechanism to eliminate harmed organelles and aggregates of proteins, yet abnormal autophagy could worsen the death of the hepatocytes. The regulation between these cellular effects is used to ascertain the extent of liver damage that is reversible or irreversible because of the mechanistic pathways, making the need to comprehend the mechanistic pathways in order to medically and pharmacologically treat DILI (Cao et al., 2016).

6. Immune and Inflammatory Mechanisms in DILI

6.1 Innate Immune Activation and Danger Signals:

The activation of innate immune and danger signals occurs at the same time as pathogen-associated molecular patterns (PAMP) are detected. This process happens simultaneously with the detection of the pathogen-associated molecular patterns (PAMP). The innate immune system is critical in the pathogenesis and progression of drug hepatotoxicity. The pattern recognition receptors (PRRs) on Kupffer cell and other immune cells residing in the liver are recognized by high-mobility group box-1 (HMGB1), ATP, and mitochondrial DNA, which are released into the liver by hepatocellular stress and necrosis. The stimulation of these cells leads to the release of pro-inflammatory cytokines and chemokines that increase hepatocellular damage, and attraction of other immune effector cells. Intrinsic and idiosyncratic types of DILI are of particular interest in which the early cell damage is connected to inflammatory

cascades under the influence of innate immune activation (Liu et al., 2021).

6.2 Adaptive Immune Responses and Hapten Hypothesis:

At the center of idiosyncratic drug-induced liver injury is adaptive immunity where T-cell-mediated mechanisms are contained in the process of hepatotoxicity. The hapten hypothesis suggests that the reactive drug metabolites undergo the production of covalent complexes with hepatic proteins, which result in the formation of neoantigens that are identified by the immune system. Hepatic cytotoxic responses have the potential to be triggered by presentation of these neoantigens to T lymphocytes. This type of immune-mediated injury usually has a delayed onset, inconsistent severity and is similar to hypersensitivity reactions such as a rash, fever and eosinophilia. The association between the susceptibility and human leukocyte antigen (HLA) genotypes has been highly observed to support the interaction between the drug metabolism, protein modification, and host immune recognition (Girish and Sanjay, 2021).

6.3 Cytokines, Chemokines, and Inflammatory Mediators:

Cytokines and chemokines coordinate the inflammatory process in DILI and dictate the liver damage. Important representatives of the mediators that facilitate the process of hepatocyte apoptosis and necroinflammation include tumor necrosis factor-alpha (TNF-a), interleukin-1b (IL-1b), and interleukin-6 (IL-6). CXCL8 and CCL2 are some of the chemokines that help to bring neutrophils, monocytes, and lymphocytes to the injured area. Interaction of pro- and anti-inflammatory mediators can determine the severity, progress and possible recovery of liver injury. The disorganization of the signaling pathways may enhance the hepatocellular injury and extend its inflammatory duration, which underscores the possible therapeutic options (Woolbright and Jaeschke, 2018).

6.4 Immune Tolerance and Resolution of Injury:

Although the activation of immune responses is a contributor of hepatotoxicity, clustering of immune tolerance, and resolution processes is also important in curbing the tissue destruction and re-establishing hepatic homeostasis. Inflammation can be resolved by the involvement of regulatory T cells, anti-inflammatory cytokines like IL-10 as well as clearance of apoptotic cells. These regulatory mechanisms can cause chronic liver injuries or development of severe consequences in case of failure. The knowledge of the immunological interrelationship between immune activation and tolerance is a source of information about the individual susceptibility, the severity of the disease, and possible interventions to control the immune responses in drug-induced liver damage (Liu et al., 2021).

7. Genetic and Host-Related Risk Factors

7.1 Pharmacogenomic Determinants of Susceptibility:

The variability of pharmacogenomic centrality is predominant in selecting the predisposition of individuals to drug-induced liver injury (DILI). The genetic polymorphism of drug-metabolizing enzymes, transporters, and detoxification can play a large role in the formation and clearance of reactive metabolites. E.g. differences in cytochrome P450 isoforms or UDP-glucuronosyltransferases can cause the build-up of hepatotoxic intermediates, which could result in liver damage even with normal therapeutic doses. The pharmacogenomic profiling has the opportunity to detect people at high risk and design drug therapy to reduce the risk of hepatotoxicity, which explains the applicability of precision medicine to reduce DILI (Ahmad and Odin, 2017).

7.2 Role of HLA Genotypes:

Genotypes of human leukocyte antigen (HLA) have been greatly implicated in the pathogenesis of immune-mediated DILI. Some alleles in the HLA are linked to the predisposition to particular drugs, which consists of their involvement in exposing drug-generated antigens to T cells. As an illustration, the HLA-B57:01 is associated with liver damage due to flucloxacillin and the HLA-A33:01 is linked with hepatotoxicity caused by terbinafine. These associations underscore the significance of host immune recognition in idiosyncratic DILI and indicate that HLA genotyping may be a predictive instrument that may be used to obtain at-risk patients before starting the treatment (Daly, 2025).

7.3 Age, Sex, and Comorbid Conditions:

Demographic variables of the host, such as age and sex, affect the susceptibility of DILI and clinical outcome. Elderly people tend to have a lower hepatic regenerative ability and a change in drug metabolism, which exposes them to hepatotoxic events. The incidence and severity of DILI can also be altered by sex-specific differences in drug metabolism and immune responses caused by sex-specific differences in hormone levels and enzymatic activity. Moreover, comorbid disorders like obesity, diabetes, or metabolic syndrome can have a aggravating effect on liver injury by increasing oxidative stress, inflammation, and drug clearance to highlight the necessity of risk assessment on a case-by-case basis (Chalasani and Bjornsson, 2010).

7.4 Pre-Existing Liver Disease and Environmental Factors:

Preexisting liver issues such as chronic hepatitis, non-alcoholic fatty liver disease (NAFLD), or cirrhosis are significant risk factors and worsening factors of DILI. Weakened hepatic structural integrity and impaired

detoxification function decrease the hepatic capacity of the liver in metabolizing and excretion of xenobiotics. Additional factors that increase susceptibility through changes in enzyme activity and hepatic responses to stress are environmental factors, including alcohol, concomitant hepatotoxins, and diet effects. Meanwhile, genetic, physiological, and environmental factors must be combined so as to create a complete risk stratification and prevent drug-induced liver injury (Stine and Chalasani, 2017).

8. Conventional Biomarkers for DILI Detection

8.1 Serum Liver Enzymes and Their Clinical Utility:

Serum liver enzymes are still the mainstay of traditional surveillance and diagnosis of drug-induced liver injury (DILI). The indicators of hepatocellular damage are very much used, i.e. ALT and AST, and indicators of cholestatic injury are ALP and GGT. The total and direct bilirubin levels will give the data about hepatic excretory and total liver functioning. Such markers are regularly used in clinical practice because of their availability, cost-efficiency, and reference range. Monitoring hepatotoxicity in the liver with time can assist in identifying early drug hepatotoxicity, informing therapeutic interventions, and assessing recovery after withdrawal of the drug. They are especially useful in the case of drugs that have a known hepatotoxic effect and in high-risk groups of patients (McGill and Jaeschke, 2018).

8.2 Limitations of Traditional Biochemical Markers:

Although they are highly utilized, traditional liver biomarkers have some serious limitations. ALT increase, AST increase, ALP increase, or bilirubin increase is neither specific to DILI nor is seen in a limited number of hepatic and extraliver pathologic states including viral hepatitis, autoimmune liver disease, or metabolism and ischemia. In addition, they are not always sensitive to early detection because these markers can be elevated with plenty of hepatocellular damage. Other factors that minimize the accuracy of the diagnosis are interindividual variability, short-term changes and confounding comorbidity. Therefore, the use of a traditional set of biochemical tests might postpone the detection of hepatotoxicity and hinder a timely clinical response (Atienzar et al., 2016).

8.3 Diagnostic Criteria and Causality Assessment Tools:

To overcome these shortcomings, diagnostic criteria and causality assessment instruments have been created in structure. Roussel Uclaf Causality Assessment Method (RUCAM) has been popular in assessing the probability of a particular drug causing liver injury based on time, other etiologies and enzyme pattern elevation. Other frameworks use both clinical, laboratory and histopathological information to enhance reliability and reproducibility. These devices help clinicians to differentiate between DILI and other hepatic diseases, direct case management, and standardize case reporting when used in research and regulatory activities. Although such methods are important, they still need to be combined with developing biomarkers and mechanistic understanding to increase the accuracy of diagnostics and risk classification (Tillmann et al., 2019).

9. Emerging Biomarker-Based Detection Approaches

9.1 Mechanism-Based Biomarkers of Hepatocellular Injury:

The recent developments in the field of drug-induced liver injury (DILI) research have included the use of mechanism-specific biomarkers as indicators of particular hepatocellular stress and injury pathways. The biomarkers can give additional information not just the liver enzymes as they can tell about oxidative stress, mitochondrial dysfunction, immune activation and apoptotic or necrotic processes. They might be glutathione depletion markers, fragments of mitochondrial DNA and oxidative adducts, and are better at so far upstream detection of hepatotoxic events. By incorporating the profiles of the biomarkers with the pathophysiological mechanisms, researchers and clinicians are able to better predict the severity of injuries and implement targeted interventions (Meunier and Larrey, 2019).

9.2 microRNAs as Diagnostic and Prognostic Tools:

The sensitivity and non-invasive nature of microRNAs (miRNAs) has made them sensitive and non-invasive biomarkers of DILI because of their in-circulation stability and tissue-specific expression. MiRNAs that are enriched in hepatocytes including miR-122, miR-192 are released into the blood during liver damage and are associated with the levels of hepatocellular damage. These molecules do not only facilitate the early diagnosis of DILI but also gives prognostic data on the progression and recovery of the disease. They can be integrated into clinical monitoring protocols and may be able to provide an increased level of diagnostic accuracy especially in situations wherein the conventional enzymes fall into normal ranges (Zhang et al., 2015).

9.3 Cytokeratin-18, HMGB1, and Cell Death Biomarkers:

The fragments of cytokeratin-18 (CK-18) and protein high-mobility group box-1 (HMGB1) can be recognized as the markers of hepatocytes apoptosis and necrosis. The release of CK-18 is indicative of apoptotic cell death caused by the action of caspase as compared to necrotic cell death, and HMGB1 demonstrates necrotic cell release and immune activation. Combined, these biomarkers offer a mechanistic understanding of the manner of liver injury and allow the stratification of patients depending on the extent and kind of the cellular

injury. Their clinical use supplements the standard enzyme measurements and helps to make monitoring of the therapeutic interventions more accurate (Antoine et al., 2012).

9.4 Bile Acids and Metabolomic Signatures:
Alterations in bile acid composition and profiles serve as sensitive indicators of cholestatic DILI. Drugs that impair bile acid transport or metabolism lead to accumulation of toxic bile acids, which can be quantified in serum or plasma. Metabolomic approaches allow comprehensive assessment of these changes, identifying novel biomarkers that reflect specific drug-induced perturbations in hepatic metabolism. These signatures can facilitate early detection, provide mechanistic insights, and aid in distinguishing drug-induced cholestasis from other hepatic disorders (**Quintás et al., 2021).**

9.5 Multi-Biomarker Panels and Systems Biology Approaches:
On the understanding of the multifactorial character of DILI, multi-biomarker panel and systems biology systems combine various molecular, biochemical and metabolic data to offer a comprehensive analysis of liver damage. The integration of conventional enzymes, mechanism-based markers, miRNAs and metabolomic profiles make them more sensitive and specific, increase their phenotypic classification and make risk assessment more personalized. Computational modeling and network analysis also help to make sense out of complex interactions among pathways that contribute to hepatotoxicity that informs clinical decision-making strategies as well as strategies in drug development. These integrative methods are the future of accuracy diagnostics in DILI, which combines mechanistic knowledge with translational use (Bhattacharya et al., 2012).

10. Translational and Regulatory Perspectives
10.1 Biomarkers in Drug Development and Safety Assessment:
The use of biomarkers is crucial in the current drug development process as it allows the early identification of hepatotoxicity and makes safety decisions. The mechanism-based biomarkers can aid preclinical and clinical investigators to recognize hepatotoxic drugs prior to wide-scale exposing human beings to minimize attrition rates and enhance patient safety. Incorporation of biomarkers into safety assessment guidelines would aid in gaining a better understanding of dose-response curves, understanding of the toxicity mechanisms, and facilitates developing safer treatment regimens. Their application is also becoming required in regulatory filings to demonstrate hepatic risk, as well as to inform post-marketing follow-up measures (Avigan MI., 2014).

10.2 Preclinical Models and their Predictive Value:
In vitro models Preclinical models In vitro hepatocyte cultures, liver organoids and animal studies Preclinical models Preclinical models play a crucial role in the assessment of drug induced liver injury. The models enable the characterization of hepatotoxic processes, metabolism, and the possible immune-mediated effects. Although intrinsic toxicity is typically well-predicted in animal models in a dose-dependent manner, idiosyncratic reactions are hard to predict because the models are interspecies and the animal and human metabolic systems, as well as immune responses, differ. The current developments of humanized liver models and high-throughput screening systems are expected to enhance the translational relevance and predictive quality of both cholestatic and hepatocellular strains of DILI (Kuna et al., 2018).

10.3 Regulatory Guidelines and Clinical Implementation:
In order to monitor hepatotoxicity in the process of clinical use and development of drugs, regulatory bodies such as the FDA and EMA offer guidelines that should be followed. Liver function testing rationale and reporting procedures as well as causation are standardized procedures that are essential in patient safety. Translational models and biomarkers based on mechanisms are becoming an integral part of the regulatory system aimed at the process of risk stratification, early intervention, and post-marketing pharmacovigilance. The adherence to these recommendations will enable the safety of novel therapeutics introduction and reduce the risk of serious liver damage in exposed populations (Segovia-Zafra et al., 2021).

10.4 Personalized Medicine Approaches in DILI
Individualized medicine plans are changing the approach of dealing with drug-induced liver injury, incorporating pharmacogenomic data, biomarker profiles, and risk factors of individual patients. CYP polymorphism, HLA alleles, and other susceptibility markers are predicated individually based on genotyping to make personalized predictions of hepatotoxic risk. These data, when combined with longitudinal monitoring of biomarkers, allow to customize the dosing schedule, identify liver damage, and make informed treatment choices. Individualized therapy has the prospect of minimizing adverse events, maximize treatment efficacy, and assist accuracy pharmacology in both clinical and translational research settings (Aubrecht et al., 2013).

11. Current Gaps, Limitations, and Future Directions
11.1 Unresolved Mechanistic Questions:
Even though much literature has been conducted, there are still numerous mechanistic points of drug-induced liver injury (DILI) that are not fully understood. Nor are the exact mechanisms through which the formation of reactive metabolites,

mitochondrial injury, oxidative stress and immune-mediated injury are interlinked. Idiosyncratic reactions are especially characterized by complicated reactions between host geometrics, environmental elements and drug-specific features, which are challenging to anticipate or reproduce in test models. These mechanistic uncertainties have to be resolved to enhance the predictability of risks, design interventions of interest, and progress translational studies in hepatotoxicity (Funk and Roth, 2017).

11.2 Standardization of Biomarker Validation:

Even though the use of novel biomarkers has shown potential in early diagnosis and mechanistic characterization of DILI, their clinical applications have not been fully used due to the absence of standardized validation procedures. Diversity of sample collection, analysis and threshold prevents cross-study comparisons and regulatory acceptance. Standardized guidelines on the assessment of biomarkers such as reproducibility, sensitivity, specificity and mechanistic relevance are essential in translating the researches into clinical applications and regulatory decision making (Fontana et al., 2010).

11.3 Integration of Omics Technologies:

Combination of omics technologies including genomics, transcriptomics, proteomics and metabolomics provides extraordinary chances in comprehending the multifactorial state of DILI. Multi-omics schemes have the potential to reveal new key factors of susceptibility, to clarify the mechanistic systems, and to find predictive markers of early hepatotoxicity. Nonetheless, there are still difficulties in integrating data, interpreting it, and implementing it clinically. Computational modeling and system biology models should be further developed to use omics data to the fullest extent to obtain accurate risk assessment and individual management of DILI (Kralj et al., 2021).

11.4 Implications for Human and Veterinary Medicine:

Liver injury caused by drugs is of not only major concern in human medicine, but also in veterinary practice, where hepatotoxicity has been known to impact on the health and productivity of animals. To achieve proper risk assessment and translational relevance, the key to successfully determining the similarities and differences in the hepatic metabolism, immune responses, and biomarker expression between species is to understand cross-species similarities and differences. Integration of veterinary models into preclinical safety testing can improve safety testing and guide regulatory policies and also promote development of safer therapeutics in human and animal populations. The focus on comparative methods enhances the general knowledge of DILI mechanisms and the opportunities to preventive and diagnostic measures in different clinical settings (McGill et al., 2018).

CONCLUSIONS:

Drug-induced liver injury (DILI) is a complicated and multifactorial condition that is quite difficult in clinical practice and in drug development. Lack of homogeneity of DILI with intrinsic and idiosyncratic types of it also emphasizes the interaction that occurs between drug characteristics, pharmacokinetics, host genetics and the environment in the determination of susceptibility and severity. The major such as oxidative stress, mitochondrial dysfunction, impairment of bile acid transport, endoplasmic reticulum stress, and immune-mediated injury have been clarified by many studies and lead to hepatocyte apoptosis, necrosis and disturbed cellular homeostasis. The liver enzymes will give useful though not much information as they are not specific and predictive early. MicroRNAs, cytokeratin-18, HMGB1, bile acids, and metabolomic signatures are more sensitive and mechanistically understanding, as they are able to detect earlier, better prognosis, and pattern distinction of injury. The multi-biomarker panel and systems biology strategies also increase the ability of risk assessment. There are genetic and host-associated factors, such as pharmacogenomic polymorphisms, HLA alleles, age, sex, comorbidities, and pre-existing liver conditions that contribute to idiosyncratic DILI, which contributes to the significance of individualized medicine approaches. Others can only be improved by the integration of omics technologies, computational modeling and translational preclinical models to enhance predictive accuracy and address unanswered mechanistic questions.

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