INOSR APPLIED SCIENCES 13(2):49-52, 2025 ISSN: 2705-165X
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International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.4952

Drug-Induced Liver Injury (DILI): Advances in Predictive Biomarkers, In Vitro Models, and Risk Mitigation

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ABSTRACT

Drug-induced liver injury (DILI) remains one of the most challenging complications in drug development and clinical pharmacotherapy. It is a leading cause of drug attrition during preclinical development and a common reason for post-marketing drug withdrawals. DILI can manifest in a spectrum of hepatic injuries, from asymptomatic enzyme elevations to fulminant hepatic failure. This comprehensive review explores current advances in the identification of predictive biomarkers, development of novel in vitro models, and strategies for mitigating DILI risk. Emphasis is placed on the role of genomic, proteomic, and metabolomic markers in early detection, along with emerging technologies such as organoids, microphysiological systems, and 3D liver co-cultures. Risk mitigation strategies including improved drug screening protocols, patient stratification, regulatory frameworks, and pharmacovigilance systems are also discussed. The integration of predictive science and translational research is critical to reducing the burden of DILI and ensuring drug safety across the therapeutic lifecycle.

Keywords: Drug-induced liver injury, predictive biomarkers, liver organoids, hepatotoxicity screening, risk mitigation strategies

INTRODUCTION

Drug-induced liver injury (DILI) is a complex and potentially severe adverse event resulting from exposure to pharmaceutical agents [1]. It accounts for a substantial proportion of acute liver failure cases and poses significant challenges in both drug development and post-market surveillance. While DILI may be predictable and dose-dependent (intrinsic), as seen with acetaminophen overdose, it is more often idiosyncratic—occurring unpredictably and independent of dose in susceptible individuals [2]. The multifactorial nature of DILI involves direct hepatotoxicity, immune-mediated mechanisms, metabolic activation of drugs into reactive intermediates, and host genetic predisposition [3]. Because DILI is difficult to predict and diagnose, it remains a leading cause of late-stage drug attrition, drug withdrawals, and regulatory black box warnings [4]. Traditional biomarkers such as serum alanine aminotransferase (ALT) and bilirubin are neither specific nor sensitive enough to provide early or definitive diagnosis [5]. The growing complexity of drug metabolism, increased polypharmacy, and aging populations with underlying liver conditions have further underscored the urgency of improving DILI prediction. This review synthesizes emerging approaches to improving the prediction and management of DILI. It highlights key developments in predictive biomarkers, advancements in human-relevant in vitro models, and strategic approaches to risk reduction across the drug lifecycle. A more robust understanding of DILI pathophysiology and personalized patient profiles can significantly enhance therapeutic safety.

Predictive Biomarkers for DILI

The need for specific and sensitive biomarkers to detect early liver injury is paramount [5]. Current liver function tests (LFTs) such as ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin are widely used but have limited diagnostic utility in distinguishing DILI from other causes of liver damage [6]. Moreover, they do not reliably reflect the extent or type of liver injury. Emerging biomarkers aim to overcome these limitations by improving specificity, sensitivity, and temporal accuracy. Recent research has focused on the identification and validation of novel biomarkers with better predictive value. Key candidates include: Glutamate dehydrogenase (GLDH) is a mitochondrial enzyme released during hepatocyte necrosis [7]. Unlike ALT, GLDH is not present in skeletal muscle, making it more specific for hepatic injury. GLDH can be used to detect early

hepatocellular damage before the onset of clinical symptoms [8]. MicroRNA-122 (miR-122) is the most abundant liver-specific microRNA and has emerged as a sensitive early marker of hepatocyte injury [9]. It is released into the bloodstream in response to hepatocellular stress and is detectable prior to ALT elevation [10]. High mobility group box 1 (HMGB1) is a nuclear protein that is released by necrotic cells and secreted by activated immune cells. It provides insight into the mode of cell death and helps differentiate between apoptosis and necrosis, offering mechanistic information [11]. Keratin-18 (K18) and its caspase-cleaved fragment (ccK18) serve as complementary markers for apoptosis and necrosis [12]. Elevations in these biomarkers correlate with the severity of liver damage and may assist in stratifying patients based on injury type [12]. Bile acid profiles, particularly alterations in serum total bile acids and individual conjugated bile acids, can be used to detect cholestatic and mixed injury types. Shifts in bile acid homeostasis often precede conventional LFT changes and reflect early bile canalicular dysfunction [13]. Omics technologies have enabled the integration of genomic, proteomic, and metabolomic data to identify susceptibility markers and mechanistic signatures. For example, HLA genotyping has revealed associations between specific alleles such as HLA-B*57:01 and HLA-A*33:01 and increased risk of DILI from drugs like flucloxacillin and fenofibrate, respectively [14]. These findings underscore the potential of personalized genomics in guiding therapy.

In Vitro Models for DILI Assessment

Traditional in vitro liver models using primary human hepatocytes or immortalized cell lines have limited predictive capacity due to loss of hepatic phenotype and metabolic function over time [15]. Emerging in vitro platforms aim to replicate the physiological architecture and function of the human liver more accurately, providing greater translational value and ethical alternatives to animal models [16]. Three-dimensional (3D) spheroid cultures maintain hepatocyte polarity, bile canalicular networks, and liver-specific gene expression for several weeks [17]. HepaRG and primary hepatocyte spheroids respond to known hepatotoxins with clinically relevant dose responses, making them suitable for chronic toxicity assessments [18]. Liver organoids derived from pluripotent stem cells recapitulate aspects of hepatic development and can be genetically engineered to model patient-specific risk [19]. These self-organizing structures allow for long-term studies of DILI mechanisms, particularly when combined with CRISPR gene editing [20]. Microphysiological systems (MPS), also referred to as liver-on-chip devices, incorporate flow dynamics, extracellular matrix components, and co-cultures of hepatocytes with Kupffer, endothelial, and stellate cells [21]. These models simulate zonal differences in hepatic metabolism and inflammation, providing a powerful tool for evaluating immune-mediated and fibrotic DILI. Advanced co-culture systems that integrate multiple liver cell types in a spatially defined architecture enable the study of cell-cell interactions and paracrine signaling [22]. These platforms are particularly valuable for assessing drug-drug interactions and complex injury phenotypes. Taken together, these innovations provide enhanced systems for mechanistic investigation, safety screening, and regulatory decision-making. The adoption of standardized protocols and validation benchmarks is critical to ensure reproducibility and cross-platform comparability.

Risk Mitigation Strategies

Effective risk mitigation for DILI involves actions throughout the drug development pipeline and clinical use. At the preclinical stage, incorporation of hepatotoxicity assessments in lead optimization and candidate selection can identify compounds with favorable safety profiles. This includes use of high-content imaging, in silico modeling, and cytotoxicity assays in human-derived cells [23]. Clinical strategies include personalized dosing regimens based on pharmacokinetic modeling and early withdrawal of agents upon detection of liver enzyme elevations [24]. Genetic screening for high-risk alleles such as HLA-B*57:01 can guide drug choice and inform consent processes for patients [25]. Formulation optimization to reduce hepatic exposure, use of prodrugs, and co-administration with hepatoprotective agents are emerging strategies to mitigate liver injury [27]. For example, the co-formulation of isoniazid with pyridoxine has reduced hepatotoxicity in tuberculosis therapy [28]. Monitoring guidelines have evolved to include periodic liver function testing during drug administration, particularly for drugs with known hepatotoxic risk. Algorithms integrating dynamic biomarker thresholds and clinical features can support decision-making for drug discontinuation or re-challenge [29]. Post-marketing pharmacovigilance systems, including the FDA Adverse Event Reporting System (FAERS), EudraVigilance, and VigiBase, play an essential role in detecting emerging safety signals [30]. These systems rely on voluntary reporting and signal detection algorithms but require clinician awareness and patient cooperation to be effective [31]. Collaboration between regulatory agencies and industry stakeholders has led to the development of Drug-Induced Liver Injury Network (DILIN) and similar consortia that facilitate data sharing and mechanistic research [32]. Risk management plans and risk evaluation and mitigation strategies (REMS) are increasingly used to balance therapeutic benefit with potential hepatotoxicity.

Future Directions

The future of DILI prediction and prevention lies in integrating multi-dimensional data sources into predictive frameworks. Machine learning and artificial intelligence are being applied to mine electronic health records and clinical trial databases for DILI signatures, enabling dynamic risk assessment tools that evolve with accumulating evidence. Systems toxicology approaches combining in vitro, in vivo, and computational data allow for

comprehensive modeling of DILI pathways. This facilitates the development of adverse outcome pathways (AOPs) that can predict hepatotoxicity from molecular initiating events through clinical outcomes. Biobank-linked cohort studies offer opportunities to correlate genetic variants, metabolomic profiles, and real-world drug responses. These studies provide population-level insights into DILI susceptibility and support precision medicine initiatives. Development of point-of-care diagnostic platforms for DILI biomarkers could enable early detection in outpatient and primary care settings. Portable biosensors and multiplex assays are in development for rapid testing of biomarkers such as miR-122 and GLDH. Regulatory science is evolving to accommodate novel tools and approaches. The FDA and EMA have begun qualifying biomarkers and in vitro systems for specific DILI contexts, paving the way for their use in regulatory submissions. Continued harmonization of safety assessment standards across jurisdictions will facilitate global drug development.

CONCLUSION

Drug-induced liver injury represents a significant challenge in drug safety and patient care. Advances in predictive biomarkers, in vitro liver models, and comprehensive risk mitigation strategies are reshaping the approach to DILI management. From bench to bedside, the integration of mechanistic insights, human-relevant models, and robust regulatory frameworks holds promise for reducing DILI incidence and improving patient outcomes. Collaborative efforts among researchers, clinicians, regulators, and industry stakeholders are essential to translate these innovations into improved safety and outcomes for patients.

REFERENCES

1. Saleh AK, El-Masry TA, El-Kadem AH, Ashour NA, El-Mahdy NA. Exploring drug-induced liver injury: comprehensive insights into mechanisms and management of hepatotoxic agents. Future Journal of Pharmaceutical Sciences. 2025;11(1). doi:10.1186/s43094-025-00788-5
2. Nwadum, S.K., Ibiam, U.A., Uti, D.E., Umoru, G.U., Udoudoh, M.P., Aja, P.M., Alum, E.U.,Mordi, C.J., Ekpono, E.U., Obeten, U.N., Omang, W.A., Agada, S.A. (2023). *Cocos nucifera* Water Ameliorated Hepatic Complications and Attenuated Oxidative Stress in Cadmium-Induced Hepatotoxicity. *Asian J. Biol. Sci*, 16(4), 522-536. https://doi.org/10.17311/ajbs.2023.522.536.
3. Skat-Rørdam J, Lykkesfeldt J, Gluud LL, Tveden-Nyborg P. Mechanisms of drug induced liver injury. Cellular and Molecular Life Sciences. 2025;82(1). doi:10.1007/s00018-025-05744-3
4. Atienzar FA, Blomme EA, Chen M, Hewitt P, Kenna JG, Labbe G, et al. Key challenges and opportunities associated with the use of in vitro models to detect human DILI: integrated risk assessment and mitigation plans. BioMed Research International. 2016;2016:1–20. doi:10.1155/2016/9737920
5. Ukpabi-Ugo Jacinta Chigozie., Monanu, Michael Okechukwu., Patrick-Iwuanyanwu, Kingsley and Egbachukwu Simeon Ikechukwu. Potential hepatoprotective effect of different solvent fractions of *Ocimum gratissimum* (O G) in a paracetamol-induced hepatotoxicity in Wistar albino rats. *ScopeMed* 2016; 5(1): 10-16
6. Ogugua Victor Nwadiogbu., Uroko Robert Ikechukwu., Egba, Simeon Ikechukwu and Agu Obiora (2017) Hepatoprotective and Healthy Kidney Promoting Potentials of Methanol Extract of *Nauclea latifolia* in Alloxan Induced Diabetic Male Wistar Albino Rats. *Asian Journal of Biochemistry*,2017; 12: 71-78
7. Lee YT, Tan YJ, Mok PY, Subramaniam AV, Oon CE. The bifunctional roles of sirtuins and their therapeutic potential in cancer. In: Elsevier eBooks. 2021. p. 153–77. doi:10.1016/B978-0-12-822467-0.00009-7
8. Schomaker S, Potter D, Warner R, Larkindale J, King N, Porter AC, et al. Serum glutamate dehydrogenase activity enables early detection of liver injury in subjects with underlying muscle impairments. PLoS ONE. 2020;15(5):e0229753. doi:10.1371/journal.pone.0229753
9. Aja, P. M., Igwenyi, I. O., Ugwu, O. P. C., Orji, O. U., Alum, E. U. Evaluation of Anti-diabetic Effect and Liver Function Indices of Ethanol Extracts of *Moringa oleifera* and *Cajanus cajan* Leaves in Alloxan Induced Diabetic Albino Rats. Global Veterinaria 2015; 14(3): 439-447. DOI: 10.5829/idosi.gv.2015.14.03.93129.
10. Church RJ, Otieno M, McDuffie JE, Singh B, Sonee M, Hall L, et al. Beyond MIR-122: identification of microRNA alterations in blood during a time course of hepatobiliary injury and biliary hyperplasia in rats. Toxicological Sciences. 2015;150(1):3–14. doi:10.1093/toxsci/kfv260
11. Chen R, Kang R, Tang D. The mechanism of HMGB1 secretion and release. Experimental & Molecular Medicine. 2022;54(2):91–102. doi:10.1038/s12276-022-00736-w
12. Hempel F, Roderfeld M, Müntnich LJ, Albrecht J, Oruc Z, Arneth B, et al. Caspase-cleaved keratin 18 measurements identified ongoing liver injury after bariatric surgery. Journal of Clinical Medicine. 2021;10(6):1233. doi:10.3390/jcm10061233
13. Li T, Apte U. Bile acid metabolism and signaling in cholestasis, inflammation, and cancer. Advances in Pharmacology. 2015;263–302. doi:10.1016/bs.apha.2015.04.003

14. Clare KE, Miller MH, Dillon JF. Genetic factors influencing drug-induced liver injury: do they have a role in prevention and diagnosis? Current Hepatology Reports. 2017;16(3):258–64. doi:10.1007/s11901-017-0363-9
15. Collins SD, Yuen G, Tu T, Budzinska MA, Spring K, Bryant K, et al. In vitro models of the liver: disease modeling, drug discovery and clinical applications. In: Codon Publications eBooks. 2019. p. 47–67. doi:10.15586/hepatocellularcarcinoma.2019.ch3
16. Popovic M, De Sousa Lopes SMC. Emerging in vitro platforms and omics technologies for studying the endometrium and early embryo-maternal interface in humans. Placenta. 2022;125:36–46. doi:10.1016/j.placenta.2022.01.006
17. Kammerer S. Three-dimensional liver culture systems to maintain primary hepatic properties for toxicological analysis in vitro. International Journal of Molecular Sciences. 2021;22(19):10214. doi:10.3390/ijms221910214
18. Guo K, Van Den Beucken T. Advances in drug-induced liver injury research: in vitro models, mechanisms, omics and gene modulation techniques. Cell & Bioscience. 2024;14(1). doi:10.1186/s13578-024-01317-2
19. Nuciforo S, Heim MH. Organoids to model liver disease. JHEP Reports. 2020;3(1):100198. doi:10.1016/j.jhepr.2020.100198
20. Shinozawa T, Kimura M, Cai Y, Saiki N, Yoneyama Y, Ouchi R, et al. High-fidelity drug-induced liver injury screen using human pluripotent stem cell–derived organoids. Gastroenterology. 2020;160(3):831–846.e10. doi:10.1053/j.gastro.2020.10.002
21. Gough A, Soto-Gutierrez A, Vernetti L, Ebrahimkhani MR, Stern AM, Taylor DL. Human biomimetic liver microphysiology systems in drug development and precision medicine. Nature Reviews Gastroenterology & Hepatology. 2020;18(4):252–68. doi:10.1038/s41575-020-00386-1
22. Ishikawa S, Iijima K, Sasaki K, Kawabe M, Osawa S, Otsuka H. Three-dimensional co-culture model employing silica nonwoven fabrics to enhance cell-to-cell communication of paracrine signaling between hepatocytes and fibroblasts. Biotechnology and Bioengineering. 2023;120(7):1961–74. doi:10.1002/bit.28425
23. Persson M, Løye AF, Mow T, Hornberg JJ. A high content screening assay to predict human drug-induced liver injury during drug discovery. Journal of Pharmacological and Toxicological Methods. 2013;68(3):302–13. doi:10.1016/j.vascn.2013.08.001
24. Uroko, Robert I.., Adamude, Fatima A.., Egba, Simeon I., Ani, Chijioke C and 1 Ekpenyong, James E. Hepatoprotective Effects of Methanol Extract of *Acanthus montanus* (*acanthaceae*) Leaves on Acetaminophen Induced Liver Injury in Rats. *Pharmacologyonline*, 2020; 1: 248-260
25. Gilani B, Zubair M. HLA-B*57:01 testing. StatPearls – NCBI Bookshelf. 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560797/
26. Aja O. A., Egba S. I., Uhuo Emmanuel Nnaemeka, Alaebo Prince Ogocukwu, Mba Obinna Joseph, and Oriaku Chinwe Edith. Hepatoprotective potentials of aqueous chloroform and methanol leaf extracts Whitfieldia lateritia 2, 4-dinitrophenylhydrazine induced anaemia in rats. Bio-research and Biotechnology, 2022; 20(2) 1434-1445
27. Sankar J, Chauhan A, Singh R, Mahajan D. Isoniazid-historical development, metabolism associated toxicity and a perspective on its pharmacological improvement. Frontiers in Pharmacology. 2024;15. doi:10.3389/fphar.2024.1441147
28. Senior RJ. Evolution of the Food and Drug Administration approach to liver safety assessment for new drugs: current status and challenges. Drug Safety. 2014;37(S1):9–17. doi:10.1007/s40264-014-0182-7
29. Liu H, Ibrahim EIK, Centanni M, Sarr C, Venkatakrishnan K, Friberg LE. Integrated modeling of biomarkers, survival and safety in clinical oncology drug development. Advanced Drug Delivery Reviews. 2024;115476. doi:10.1016/j.addr.2024.115476
30. Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. Therapeutic Advances in Drug Safety. 2020;11. doi:10.1177/2042098620938595
31. Desai M. Pharmacovigilance and spontaneous adverse drug reaction reporting: challenges and opportunities. Perspectives in Clinical Research. 2022;13(4):177–9. doi:10.4103/PICR.PICR_169_22
32. Lucena MI, Villanueva-Paz M, Alvarez-Alvarez I, Aithal GP, Björnsson ES, Cakan-Akdogan G, et al. Roadmap to DILI research in Europe: a proposal from COST action ProEuroDILINet. Pharmacological Research. 2023;200:107046. doi:10.1016/j.phrs.2023.107046

CITE AS: Taliikwa Nicholas Ceaser (2025). Drug-Induced Liver Injury (DILI): Advances in Predictive Biomarkers, In Vitro Models, and Risk Mitigation. INOSR APPLIED SCIENCES 13(2):49-52. https://doi.org/10.59298/INOSRAS/2025/13.2.4952