Drug-induced liver injury (DILI) poses a significant challenge in drug development and patient safety assessment. Non-animal models offer promising alternatives for studying DILI mechanisms and drug toxicity in a controlled and ethically acceptable manner. However, the complexity of liver physiology and the intricate interactions between different hepatic cell types present challenges in recapitulating the dynamic microenvironment of the liver in vitro. We will discuss the current landscape of non-animal models for studying DILI, including 2D and 3D cell culture systems, organ-on-a-chip platforms, and computational models. We will explore the advantages and limitations of these models in simulating hepatotoxicity, metabolism, and immune responses, highlighting the need for multi-cellular and multi-organ interactions to accurately model DILI pathways. Additionally, we discuss recent advances in integrating liver models with other organ systems, such as the gut and immune system, to better mimic systemic drug effects and inter-organ crosstalk. Finally, we address future directions and challenges in refining non-animal models for DILI research, including standardization of protocols, incorporation of human-relevant endpoints, and validation against clinical data. Overall, non-animal models offer valuable tools for advancing our understanding of DILI mechanisms and improving drug safety assessment, but further efforts are needed to enhance their complexity and predictive capabilities.