ISSN- 0301-1216
Indian J. Prev. Soc. Med. Vol. 55, No.3, 2024

REVIEW ARTICLE

Impact of Drugs to Induce Liver Injury

Kasim[1], Kiran Dobhal[2], Rohit Kumar Trivedi[3], Sayantan Mukhopadhyay[4]

ABSTRACT

Drug-induced liver injury (DILI) is an unintended effect on the liver of medications and dietary supplements, which can be serious eventually leading to acute liver failure, transplantation, and death. DILI is an uncommon, but potentially fatal, cause of liver disease that is associated with prescription medications, OTC drugs, and herbal and dietary supplements (HDS). It can occur through direct toxicity from the drug or a reactive metabolite or redness of cells through immune or other idiosyncratic mechanisms. DILI has been categorized as direct or idiosyncratic but indirect liver injury has emerged as a third type of drug-induced liver injury. Alcohol consumption has been proposed as a risk factor for DILI from medications, but there is insufficient evidence to support this. Depending on the duration of injury and the histological location of damage, DILI is categorized as acute or chronic, and either as hepatitis, cholesterol, or a mixed pattern of injury. These changes can be due to liver disorders that are unique to pregnancy or as an acute or chronic liver disease occurring coincidentally in pregnancy. These fall into main depending on their associated with or without pre-eclampsia, such as hyperemesis gravidarum intra-hepaticcholestasis during pregnancy, and acute fatty liver of pregnancy.

Keywords: Drugs, Liver, Injury, Risk

Introduction

Drug Induced Liver Injury (DILI) is a common cause of hepatic impairment, which presents with a broad spectrum of exhibitions, the most serious of which is hepatocellular death primary to acute liver failure (ALF) following drug ingestion.[1,2] DILI is one of the leading causes of acute liver failure in the US, accounting for 25% of effects of acute liver failure; these events pose a major experiment for drug improvement and safety of 76 medicines withdrawn after the market between 1969 and 2002 were attributable to liver injury.[3] In Korea and us the yearly extrapolated frequency of hospitalized cases at academy hospital was intended to be14/100,000 persons/year.[4] The age distribution was varied, with the age groups <15, 21-29, 40-50, 51-59, and ≥60 representing 3.3%, 9.4%, 18.7%, 28.9%, 22.7% and 26.7% of cases, individually. DILI has been associated to over thousands of drugs and is one of the most cited reasons for drug non-approval, withdrawal, rejection and post-marketing monitoring actions.

1. College of Pharmacy, Shivalik campus, Dehradun, Uttarakhand, India
2. College of Pharmacy, Shivalik campus, Dehradun, Uttarakhand, India
3. College of Pharmacy, Shivalik campus, Dehradun, Uttarakhand, India
4. Associate Professor, College of Pharmacy, Shivalik campus, Dehradun, **Email:** mksp0407@gmail.com; **Mob..** 8630248652

Corresponding Author: Mrs. Kiran Dobhal, Associate Professor, College of Pharmacy, Shivalik campus, Dehradun, Uttarakhand, **Email:** mksp0407@gmail.com; Mob.. 8630248652; Orcid id:0000-0002-2797-9875

Submission	16.07.2024	Revision	15.08.2024	Accepted	10.09.2024	Printing	30.09.2024

Prior Publication*: Nil*; Source of Funding:* Nil; *Conflicts of Interest*: None, *Article #139/248

In China, the annual report incidence in the overall population is 25.80/100,000, which is higher than Western countries. Modern Chinese medicine and dietary trimmings (27.81%), anti-tuberculosis drugs (24.99%) and cholestasis injury (20.31%) are the prominent classes of drugs causing DILI.[5]

Among the 1288 patients in the Indian Network of DILI (INDILI), the top six consequences were found due to consumption of anti-TB drugs (46%), traditional and alternative medicines (14%), first-generation drugs antiepileptic agents (8%), non-TB antimicrobials (6.5%), antiretroviral agents (3.5%), and non-steroidal anti-inflammatory drugs (NSAIDs) (2.6%). India had a projected 2.7 million case of tuberculosis (TB) in 2019 as per the WHO (World Health Organization) report and other than 50% of Hansen's disease problem in the world.[6] The Roussel Uclaf Causality Assessment Method (RUCAM) system is a method to allocate the numeric results for clinical, investigation, serologic and radiologic characteristics of hepatic impairment which calculate the total valuation score which highlights the probability of the hepatic injury is due to specific drug consumption.[7, 8] Table-1 is the depiction of drug causing acute liver toxicity along with their therapeutic category.

Table-1: List of drugs inducing liver injury[9]

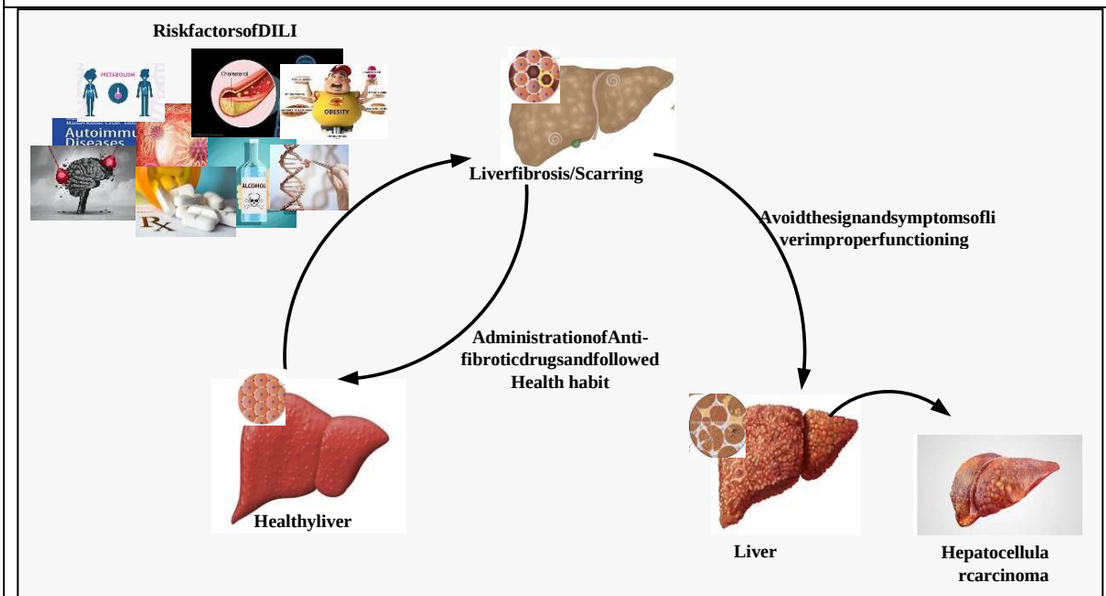
Name of drug	Category	Name of drug	Category
Amoxicillin-clavulanate	Antibiotic	Disulfiram	Carbamate derivative
Isoniazid	Antituberculosis	Anabolicsteroids	Body building
Nitrofurantoin	Antibiotic	Erythromycin	Antimicrobial
Sulfamethoxazole	Antibiotic	Ibuprofen	NSAID
Minocycline	Antibiotic	Ketoconazole	Antifungals
Cefazolin	Antibiotic	Nimesulide	NSAID
Azithromycin	Antibiotic	Rifampin	Antituberculosis
Ciprofloxacin	Antibiotic	Simvastatin	Lipid lowering agent
Levofloxacin	Antibiotic	Sulindac	NSAID
Diclofenac	NSAID	Telithromycin	Antibiotic
Methyldopa	Antihypertensive	Valproate	Antiepileptic
Azathioprin	Immuno-suppressive agent	Carbamazepine	Antiepileptic
Phenytoin	Antiepileptic	Hydralazine	Antihypertensive
Terbinafine	Antifungals	Methyldopa	Antihypertensive
Lamotrigine	Anticonvulsants	Propylthiouracil	Antithyroid
Atrovastatin	Lipidloweringagent	Sulfonamides	Antibiotic
Moxifloxacin	Antibiotic	Chlorpromazine	Psychosis
Thioguanine	Antineoplastic	Allopurinol	Xanthine oxidase inhibitor
Busulfan	Malignancy	Amiodarone	Arrhythmia
Halothane	Anaesthetic	Infliximab	Immunosuppressive agent
Didanosine	Antimicrobial	Floxuridin	Antineoplastic
Efavirenz	Antimicrobial	Flucloxacillin	Antimicrobia
Contraceptives	Birthcontrol	Flutamide	Antineoplastic

Increased blood level of liver enzymes such as alanine amino transferase (ALT), aspartate amino transferase (AST), ALP (Alkaline Phosphatase), and TBIL (Total Bilirubin), damage-associated molecular pattern molecules (DAMPS), heat shock proteins, adenosine triphosphate (ATP), high-mobility group box-1 (HMGB1) or markers of

mitochondrial damage e.g., glutamate dehydrogenase (GLDH), nuclear deoxyribonucleic acid (DNA) fragments or micro-RNA (miR) are the key biochemical indicators of DILI. It is difficult to predict the degree of DILI in humans since it depends on several clinical, biochemical, and genetic variables. The severity of DILI can be predicted in part by machine learning models; however, since DILI is a complicated and multifaceted disorder, any predictive model must be used in conjunction with professional medical judgment. This is a general overview of how to create a DILI severity prediction model.[10, 13]

Drug use during pregnancy can cause liver damage, which is quite concerning because it can harm the developing fetus as well as the mother. When a pregnant woman consumes drugs or other substances that are harmful to the liver, she may suffer from DILI. Because the liver is essential for the body's detoxification and medication metabolism, injury to the liver can have serious health repercussions. A study using a nationwide in patient sample in the United States revealed that the rate of liver disease among hospitalized pregnant women ranged from 0.3% for chronic and alcohol-related liver disease to 7.18 % for liver disorder of pregnancy, despite the fact that accurate estimates of liver disease incidence and prevalence during pregnancy are not available.[16-18]

Figure-1: Deteriorating of hepatic functioning [14-15]



Materials and Methods

This comprehensive review was done in September 2023 to extract the published work related to DILI for last five years. The published work relevant to the topic was gathered from numerous databases including PubMed, Science Direct, Frontiers, Scopus, Research Gate and AHA journals in the previous years. This period displayed incline of the prevalence of DILI in the population globally. The keywords used for searching included Drug induced, Hepatic injury, Toxicity, Mortality etc.

Insertion standards

- Literature published on DILI for last ten years.
- Applicable only for standard semantic Elimination standards

- Literature reported before 2012.
- Only abstract available and Media reports.

All authors were the part of reviewing the published literature data. Selected studies lie on chronic and acute liver injury due to drug consumption. During the initial search for articles in the databases, forty studies were extracted. Out of forty articles twenty were discussed after applying the exclusion standards. The study opted for comprehensive review consisted of various study patterns, such as review articles, systematic reviews, meta-analytic studies, cross-sectional studies, instrumental evaluation, and experimental studies. The information obtained from each publication was abstracted.

Discussion

Although practically any clinical pathological acute or chronic patterns of liver disease may occur, DILI can present clinically with a variety of symptoms such as acute hepatitis, cholestasis and jaundice, nodular regenerative hyperplasia, or sinusoidal obstruction syndrome. The medicine ortoxin, the severity of liver damage, and the subroutine implicated all play a significant role in the mechanisms of cell death and direct toxicity and intracellular organelle stress (ER stress or mitochondrial toxicity) in hepatocytes can trigger the intrinsic mechanism of apoptosis through the permeabilization of the mitochondrial outer membrane (MOMP) or result in necrosis through the mitochondrial permeability transition (MPT). DILI can also present as a silent subclinical disease, detected during routine blood tests, male gender and age are factors of pattern and cruelty of injury; female gender is a risk factor for emerging hepatocellular DILI and acute liver failure while age greater than 60 predisposes to the development of cholestatic DILI with a more indolent course.[22]

DILI refers to the unanticipated liver damage caused by prescription and non-prescription medicines, as well as herbal and dietary supplements (HDS).Conditional on the extent of increase in individuals' enzymes and the R-ratio of ALT/ALP or AST/ALP action at DILI appearance, DILI is incompletely confidential as hepatocellular when ALT or AST ≥5 × ULN alone or when R-ratio is ≥5, cholestasis when ALP ≥2 × ULN unaccompanied or if R-ratio is ≤ 2, and mixed if the ratio is 2–5. Age is a clear driver of DILI phenotype, with older age demonstrating the cholestatic phenotype more commonly across changed DILI associates. The RUCAM/Council for International Organizations of Medical Sciences (CIOMS) scale is commonly used to measure DILI.[23]

Patients who take more than 7.5 g of acetaminophen (APAP) in a single dose have acute liver damage, especially if plasma concentrations exceed 200 or 100 g/L 4 or 8 hours after ingestion, respectively. In one-third of individuals, taking APAP at the permitted dose of 4 g/day for two weeks results in ALT elevations above three times the upper limit of normal (ULN).The frequency of adverse hepatic responses caused by newer molecular targeted therapies (MTAs) in oncology is a serious challenge in medication development.[24]

DILI happens when drugs or other chemical agents cause liver damage or malfunction. It can appear in a variety of ways, ranging from modest, reversible liver enzyme increases to severe, life -threatening acute liver failure. The numbers you cited, indicating that DILI accounts for 13% of instances of acute liver failure in the United States, underscore its importance as a cause of severe liver injury. This has been evolved cause a number of difficulties for medication development, safety monitoring, and regulatory supervision. Antimicrobials and central nervous system agents are the most common causes of DILI, and health foods or dietary supplements account for 7% of DILI cases in the United States. The projected yearly incidence of cases hospitalized at university hospitals is 12/100,000 people per year. Most DILI instances are caused by erratic metabolic responses or unanticipated drug effects.[25]

In pharmacology and medicine, DILI is a major concern. It describes liver injury or malfunction brought on by using different drugs, herbal supplements, or other chemicals. DILI can appear in a variety of ways, from slight increases in liver enzymes to severe liver failure. Numerous natural substances have demonstrated a possible hepatoprotective property, which suggests that theymight aid in defending the liver against harm brought on by a variety of conditions, including medications. The following are a few examples of natural substances and the ways by which they protect the liver: Natural substances with strong antioxidant capabilities include curcumin (found in turmeric) and silymarin (found in milk thistle).They can aid in lowering liver inflammation and oxidative stress. Anti-Inflammatory substances like quercetin and resveratrol can control the liver's inflammatory response, minimizing the harm brought on by immune-mediated DILI.[26]

DILI is a severe issue that affects populations and geographic areas all over the world. According to the information you gave, India is expected to have a larger incidence of DILI than Western nations, and the idiosyncratic type of DILI predominates. According to the statement, Idiosyncratic DILI Predominance, almost 99% of DILI cases in India are of the idiosyncratic type. Rare in India: Less than 1% of DILI cases in India are intrinsic DILI, which is caused by acetaminophen/ paracetamol hepatotoxicity. This shows that, compared to the idiosyncratic variety, incidences of DILI caused by medications like acetaminophen (paracetamol) are rather uncommon. These trends in India may be caused by a variety of variables, including variances in the population's genetic susceptibility to DILI, changes in prescription and use patterns, and variations in drug safety monitoring and regulation.[27]

A crucial subject called pharmacovigilance is concerned with monitoring and evaluating the security of pharmaceutical medicines after they are placed on the market. A crucial component of pharmacovigilance is highlighted in the quote you provided, especially in relation to DILI. In the fields of medicine and herpetology, DILI is a serious concern. It happens when the usage of specific pharmaceuticals or medications causes hepatotoxicity or damage to the liver. Numerous Causative Agents like mentioned that almost1, 100 medications have been linked to DILI. These medicines range from OTC medicines to prescription treatments, nutritional, supplements, and herbal cures. Jaundice (a yellowing of the skin a dyes), abdominal discomfort, gaseousness, vomiting, exhaustion, and dark urine are typical symptoms and indicators. The exact medicine implicated, and the person's vulnerability has a significant impact on the clinical presentation.[28]

A rare adverse response to amoxicillin-clavulanate can result in liver damage in some people. Amoxicillin-clavulanate use can, in rare circumstances, result in liver impairment or damage because the liver oversees the body's medication metabolism and elimination. The term DILI is frequently used to describe this illness. Within six months of the onset of DILI, eligible patients must meet minimal laboratory or histology requirements and have any competing causes of liver injury ruled out. Patients in the general community context who have abnormal baseline liver biochemistry and/or pre-existing HIV, hepatitis B, or hepatitis C infections are eligible for enrollment.[29]

Inflammatory Reaction: Acetaminophen (paracetamol) is metabolized in the liver, and N-acetyl-p-benzoquinone imine (NAPQI), one of its metabolic byproducts, can be extremely dangerous. Oxidative stress, liver cell injury, and the generation of damage-associated molecular patterns (DAMPs) from injured hepatocytes are all possible outcomes of NAPQI. One of the extensively researched inflammasomes, the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome is thought to be responsible for the liver damage brought on by acetaminophen. By encouraging the maturation and production of pro-inflammatory cytokines, the inflamma some activation leads to the amplifying of the inflammatory cascade. These cytokines draw immune cells to the liver, including neutrophils and macrophages, aggravating tissue injury and inflammation.[30]

A drug called disulfiram is primarily used to treat alcohol consumption disorders. In order to deter alcohol use, it operates by creating unpleasant side effects, such as nausea, vomiting, and headache. Disulfiram is known to have potential side effects, such as liver toxicity, which can result in acute liver injury brought on by disulfiram. Disulfiram-induced acute liver injury is a rare but seriousadverse reaction to disulfiram. It can manifest with symptoms such as jaundice (yellowing of the skin and eyes), dark urine, abdominal pain, and fatigue. The exact mechanism by which disulfiram can cause liver injury is not fully understood, but it may involve the accumulation of toxic metabolites in the liver. It is critical to stop taking disulfiram and get help right once if a patient using it exhibits symptoms that could indicate liver damage. To evaluate the severity of liver damage and choose the best course of action, liver function tests and other diagnostic procedures may be carried out.[31]

Athletes and body builders occasionally use androgenic-anabolic steroids, which are synthetic forms of the male sex hormone testosterone, to increase muscle growth and performance. These drugs, however, have the potential to negatively impact the liver as well as other organ systems in the body. This research topic likely investigates the use of androgenic-anabolic steroids, their prevalence in the context of fitness and bodybuilding culture (hence, "From the Gym"), and howtheir use may contribute to drug-induced liver injury. The study may involve assessing the risks and mechanisms through which anabolic steroids impact liver function, potentially leading to liver damage or injury. [32]

Understanding the mechanisms underlying flucloxacillin-induced liver injury requires the identification of proteins that have undergone flucloxacillin modification. A β-lactam antibiotic flucloxacillin is frequently used to treat bacterial infections, however in a tiny percentage of people, it has been known to cause idiosyncratic DILI. The immune system appears to be the main player in flucloxacillin-induced liver injury, according to the isolation and characterization of flucloxacillin reactive IgE as well as CD4+ and CD8+ T-cells from individuals with DILI. Flucloxacillin-DILI's protagonist is the immune system: The immune system is implied to be the main "protagonist" in the emergence of DILI linked to flucloxacillin in this statement. In other words, it implies that a major contributing element to liver damage is the immune system's reaction to the medicine.[33]

An important field of research and clinical exploration is the identification of anti-isoniazid and anti-CYP antibodies in patients with isoniazid-induced liver failure. An antibiotic called isoniazid (INH) is frequently used to treat tuberculosis; nevertheless, in a small number of individuals, it carries the risk of liver damage, including liver failure. Although the exact mechanism underlying isoniazid-induced liver injury is not entirely understood, the hepatic cytochrome P450 (CYP) enzyme system is thought to play a role in the generation of hazardous metabolites. It has been suggested that the immune system may develop antibodies against isoniazid or its metabolites in some cases of isoniazid-induced liver damage. These antibodies might contribute to the damageto the liver. In the liver, cytochrome P450 enzymes, particularly CYP2E1, metabolize isoniazid. According to certain research, the liver failure brought on by isoniazid may be attributed toantibodies directed against these enzymes. Healthcare professionals regularly check the liver function of patients on isoniazid to reduce the risk of isoniazid-induced liver failure and may stop the drug if symptoms of liver damageoccur.[34]

Although paracetamol is safe and effective when taken as directed, an overdose can result in hepatotoxicity and acute liver failure (ALF). After attaching to liver proteins, the residual portion of NAPQI causes oxidative stress, mitochondrial malfunction, and necrotic cell death. According to recent reports, oxidative stress is a crucial factor in the hepatotoxicity of Paracetamol. Paracetamol is largely metabolized in the liver after ingestion. The enzyme cytochrome P450 is involved in the major metabolic pathway, where by Paracetamol is transformed into two non-toxic compounds: Paracetamol sulfate and NAPQI.[35]

When treating tuberculosis, pyrazinamide, an antimycobacterial medication, is frequently used in conjunction with other antibiotics. Like many drugs, it is generally well tolerated but can have side effects, including in some cases liver damage. When pyrazinamide-related DILI occurs, the blood levels of liver enzymes such ALT and AST rise. A variety of symptoms, such as jaundice (yellowing of the skin and eyes), exhaustion, abdominal pain, and dark urine, can indicate pyrazinamide-induced liver damage. On the other hand, some instances might not show any symptoms and be identified only by regular liver enzyme testing.[36]

Alcohol- induced liver injury; Alcohol consumption can cause hepatocytes to accumulate damaged organelles and proteins, which can cause oxidative stress and inflammation. By assisting in the removal of these harmed elements, autophagy lowers cellular stress levels generally and liver damage. Patients with ALD might choose between liver transplantation and alcohol cessation as their primary treatments. Due to the good results of patients obtaining early liver transplantation, many transplant programs have eliminated the earlier condition that ALD patients be so for six months prior to getting liver transplantation. [37]

Confronts in DILI investigations

It is unfortunate that neither laboratory markers nor prediction marker is unable to identify the patient when DILI is suspected, but also markers for DILI prediction especially in drug development are highly sought after. It is important to make distinctiveness between patient and drug risk factors.

- Hyperactive inflammatory cascade due to drug exposure can trigger the risk for DILI. IL-22BP acts by inhibiting the physiological effects of IL-22, which is one of causative factor accounts for exaggerated inflammation. Additionally, IL-22BP has also been exhibited to inhibit the harmful effects initiated by IL-22in patients suffering for hepatic.
- Numerous symptoms address on the chief pathophysiology behind DILI expansion: viz. reactive metabolites generation, development of reactive oxygen species (ROS), mitochondrial injuriousness, dysfunction of bile export salt pumps (BSEP) developing in accumulation of toxic bile acids and activate the non-specific immunity.
- Furthermore, BSEP suppression causes the release of DAMPs which account for the acquired immunity directly triggers the hepatotoxic effect.
- Mitochondria is considered as powerhouse of cell. Its damage plays a significant role in the DILI development via. destruction of the mitochondrial respiratory chain and ß-oxidation of fatty acids, escalated mitochondrial permeability and reduction of mitochondrial DNA.
- DILI involvement i.e., drugs with black boxed warning were accompanying with dual inhibition of mitochondrial function and BSEP.[38-40]

Predictive Human Models—Future of DILI Detection

To the till date, numerous research having been done to predict the DILI through developing DILI models and encounter the DILI. Severity of DILI in the present time need the more reliable *in-situ* model to investigate the DILI pathophysiology which provide the sophisticated solution towards DILI priortoits entrance in clinical trials and/or in the post-marketing surveillance.

- DILI causality assessment tool (DILI-CAT) an innovative data-driven algorithm for the diagnosing DILI early during drug development, has been framed. It was revealed that the DILI-CAT Score could distinguish DILI caused by ximelagatran, an oral pro-drug of melagatran, and warfarin. Such kind of innovation strategies could serve as better drug development by avoiding risk factor.[41-42]

- Conventionally, primary human hepatocytes (PHHs) have been employed to predict the liver functioning. It expresses the in-situ biotransformation along with synthetic reaction and conjugation reaction, maintain CYP action and can therefore indicate injuriousness. Human hepatic cell lines, such as the human-liver-derived HepaRG cell line, have the advantage of advanced functional stability while retaining various liver-specific functions, comprising major CYPs as well as having a limitless accessibility and propagation potential. Significant variation in the PHHs and liver cell line was observed that PHHs exhibit specific phenotypic variability and in stability regarding phenotypic characteristics in *in vitro* medium, but hepatocyte celllines lack physiological drug-metabolizing enzymes and transporters limiting the representativeness of normal cellular toxic responses. Likewise, PHH and hepatocyte cell lines establish merely simplified models without *in vivo* physiological culture viz.bile flow and continuous perfusion.[43-44]

- Besides hepatocyte cellline, human pluripotent stem cells along with both human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSCs) could be employed as progenitors for hepatocyte-like cells (HLCs). hESC, human iPSCs derived from reprogrammed somatic cells are mainly developed but ethical restrictions offer the limited accessibility. Moreover, these iPSC-generated hepatocyte-like cells can maintain hepatocytic function viz. serum protein secretion, enzymatic reaction, drug biotransformation. One caveat in the iPSCs DILI model, slow in compare of the natural physiologic mechanisms.[45-46]

- Furthermore, Organoids developing iPSC derived HLCs can assist as 3D cellular models for DILI prediction or *in vitro* modeling of disease mechanisms. However, limitation of iPSC-based liver models is the absence of biliary and vascular structures. To overcome this limitation, efforts have been made to develop three-dimensional culture systems with vascular- and bile-canaliculi-like structures.

- Human liver organoid model from human PSCs was developed possessing liver function, viz. the secretion of complement factors and albumin and showed a bile-duct-comparable micro-architecture with reproducible bile acid transportation. Utilization of such models, DILI prediction outcomes is accurate, specificity and sensitive through repeatability and reproducibility.

- "Liver-on-chip" is sophisticated bioengineering projects can be capable to predict drug toxicity before DILI would show as a relevant problem in clinical studies or post-marketing safety evaluations. These bioengineered liver models is more resembling to the physiological relations of hepatocytes and stroma cells which can improve liver cellfunction.[47-48]

Conclusion

To the till date, DILI still be coming a difficult for diagnosis and curing, even in accurately alleged DILI can have foremost influences on the individual victim as well as on drug development procedures. Numerous human predictive models, in vitro causality assessment tools and serum biomarkers have been identified to address the DILI. This review represents the numerous drugs caused DILI and the major development to predict the DILI has been previously done made, further investigation is needed to grip the confronts in DILI diagnosis and prediction. Unfortunately, liver models are tedious and complex, but developing compatibility with high throughput screening, and resolve the major confronts due to cellular interactions. Moreover, predictive human models depend on drug concentration and biochemical parameter leads DILI toward DILI restricting their application in the clinical investigation and DILI diagnosis.

References

1. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, Devarbhavi H, Merz M, Lucena MI, Kaplowitz N, Aithal GP. Drug-induced liver injury. Nature Reviews Disease Primers. 2019 Aug 22;5 (1) :58.
2. Fisher K, Vuppalanchi R, Saxena R. Drug-induced liver injury. Archives of Pathology and Laboratory Medicine. 2015 Jul 1; 139 (7):876-87.
3. Sarges P, Steinberg JM, Lewis JH. Drug-induced liver injury: highlights from a review of the 2015 literature. Drug safety. 2016 Sep; 39 (9):801-21.
4. Suk KT, Kim DJ, Kim CH, Park SH, Yoon JH, Kim YS, Baik GH, Kim JB, Kweon YO, Kim BI, Kim SH. A prospective nationwide study of drug-induced liver injury in Korea. Official journal of the American College of Gastroenterology| ACG. 2012 Sep 1; 107 (9):1380-7.
5. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. InMayo clinic proceedings 2014 Jan 1 (Vol. 89, No. 1, pp. 95-106). Elsevier.
6. Devarbhavi H, Joseph T, Kumar NS, Rathi C, Thomas V, Singh SP, Sawant P, Goel A, Eapen CE, Rai P, Arora A. The Indian network of drug-induced liver injury: etiology, clinical features, outcome and prognostic markers in 1288 patients. Journal of clinical and experimental Hepatology. 2021 May 1; 11 (3):288-98.
7. Danan G, Teschke R. Drug-induced liver injury: Why is the Roussel Uclaf Causality Assessment Method (RUCAM) still used 25 years after its launch?. Drug safety. 2018 Aug; 41 (8):735-43.
8. Ye L, Feng Z, Huang L, Guo C, Wu X, He L, Tan W, Wang Y, Wu X, Hu B, Li T. Causality evaluation of drug-induced liver injury in newborns and children in the intensive care unit using the updated Roussel Uclaf Causality Assessment Method. Frontiers in Pharmacology. 2021 Dec 20; 12: 790108.
9. t Io FP. National Library Of Medicine I.
10. Robles-Díaz M, Medina-Caliz I, Stephens C, Andrade RJ, Lucena MI. Biomarkers in DILI: one more step forward. Frontiers in pharmacology. 2016 Aug 22; 7: 267.
11. Villanueva-Paz M, Morán L, López-Alcántara N, Freixo C, Andrade RJ, Lucena MI, Cubero FJ. Oxidative stress in drug-induced liver injury (DILI): from mechanisms to biomarkers for use in clinical practice. Antioxidants. 2021 Mar 5; 10 (3): 390.
12. Danjuma MI, Sajid J, Fatima H, Elzouki AN. Novel biomarkers for potential risk stratification of drug induced liver injury (DILI): A narrative perspective on current trends. Medicine. 2019 Dec;98(50).
13. Church RJ, Kullak Ublick GA, Aubrecht J, Bonkovsky HL, Chalasani N, Fontana RJ, Goepfert JC, Hackman F, King NM, Kirby S, Kirby P. Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: an international collaborative effort. Hepatology. 2019 Feb; 69 (2):760-73.
14. Thapa BR, Walia A. Liver function tests and their interpretation. The Indian Journal of Pediatrics. 2007 Jul;74 : 663-71.
15. Jakhmola V, Dobhal K, Singh A, Kumar D, Ansori AN, Saklani T. Hepatoprotective effect of the Hexane extract of Luffa echinata root and Stem bark against Tetrachloromethane Induced Hepatic Disorder in rats. Research Journal of Pharmacy and Technology. 2023 Apr 1; 16 (4):1976-80.
16. Hay EJ. Liver disease in pregnancy. Hepatology. 2008 Mar 1; 47 (3):1067-76.
17. Jamjute P, Ahmad A, Ghosh T, Banfield P. Liver function test and pregnancy. The Journal of Maternal-Fetal & Neonatal Medicine. 2009 Jan 1; 22 (3):274-83.
18. Subramaniyan V, Jegasothy R. Update on ethanol induced oxidative stress in liver toxicity and the effects of pregnancy. Indian Journal of Public Health. 2019 Aug 1; 10 (8):1800-4.

19. Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, Roerecke M. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug and alcohol review. 2010 Jul; 29 (4):437-45.
20. Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. Obesity reviews. 2016 Jun; 17 (6): 510-9.
21. Naveau SY, Giraud V, Borotto E, Aubert A, Capron F, Chaput J. Excess weight risk factor for alcoholic liver disease. Hepatology. 1997 Jan; 25 (1):108-11.
22. Iorga A, Dara L, Kaplowitz N. Drug-induced liver injury: cascade of events leading to cell death, apoptosis or necrosis. International journal of molecular sciences. 2017 May 9;18 (5):1018.
23. Segovia-Zafra A, Di Zeo-Sánchez DE, López-Gómez C, Pérez-Valdés Z, Garcia-Fuentes E, Andrade RJ, Lucena MI, Villanueva-Paz M. Preclinical models of idiosyncratic drug-induced liver injury (iDILI): Moving towards prediction. Acta Pharmaceutica Sinica B. 2021 Dec 1; 11(12):3685-726.
24. Kullak-Ublick GA, Andrade RJ, Merz M, End P, Benesic A, Gerbes AL, Aithal GP. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut. 2017 Jun 1; 66 (6):1154-64.
25. Suk KT, & Kim DJ. Drug-induced liver injury: present and future. Clinical and molecular hepatology, 2012, 18(3), 249.
26. Zhou Y, Wang J, Zhang D, Liu J, Wu Q, Chen J, Tan P, Xing B, Han Y, Zhang P, Xiao X. Mechanism of drug-induced liver injury and hepatoprotective effects of natural drugs. Chinese Medicine. 2021 Dec 11;16 (1):135
27. Devarbhavi H. Drug-induced liver injury unique to India. Clinical Liver Disease, 2021, 18(3), 108.
28. Bessone F., Hernandez N., Tagle M., Arrese, M., Parana, R., Mendez-Sánchez, N., ... & Silva, M. (2021). Drug-induced liver injury: A management position paper from the Latin American Association for Study of the liver. Annals of hepatology, 24, 100321.
29. Delemos, Andrew S, et al. "Amoxicillin–clavulanate-induced liver injury." Digestive diseases and sciences 61 (2016): 2406-2416.
30. Woolbright, BL, & Jaeschke, H. Role of the inflammasome in acetaminophen-induced liver injury and acute liver failure. Journal of hepatology, 2017; 66 (4), 836-848.
31. Ramer, L., Tihy, M., Goossens, N., Frossard, J. L., Rubbia-Brandt, L., & Spahr, L. Disulfiram-induced acute liver injury. Case Reports in Hepatology, 2020.
32. Alves AS, Perdigão S, Morais S, Sousa C & Salvador, F. Androgenic-Anabolic Steroids: From the Gym to Drug-Induced Liver Injury. Cureus, 2022; 14 (9).
33. Ali SE, Waddington JC, Lister A, Sison-Young R, Jones RP, Rehman AH, ... & Meng, X. Identification of flucloxacillin-modified hepatocellular proteins: implications in flucloxacillin-induced liver injury. Toxicological Sciences, 2023, 192 (1), 106-116.
34. Metushi IG, Sanders C. Acute Liver Study Group, Lee WM, & Uetrecht J. Detection of anti-isoniazid and anti–cytochrome P450 antibodies in patients with isoniazid-induced liver failure. Hepatology, 2014, 59 (3), 1084-1093.
35. Ahmed HM, Shehata HH, Mohamed GS, Abo-Gabal HH, & El-Daly SM. Paracetamol Overdose Induces Acute Liver Injury accompanied by oxidative stress and inflammation. Egyptian Journal of Chemistry, 2023, 66(3), 399-408.
36. Wang YC, Chen KH, Chen YL, Lin SW, Liu WD, Wang JT, & Hung CC. Pyrazinamide related prolonged drug-induced liver injury: A Case Report. Medicine, 2022, 101(39).
37. Williams JA, & Ding WX. Role of autophagy in alcohol and drug-induced liver injury. Food and Chemical Toxicology, 2020, 136, 111075.
38. Weber S, Gerbes AL. Challenges and Future of Drug-Induced Liver Injury Research—Laboratory Tests. International Journal of Molecular Sciences. 2022 May 27; 23 (11): 6049.

39. Corsini A, Ganey P, Ju C, Kaplowitz N, Pessayre D, Roth R, Watkins PB, Albassam M, Liu B, Stancic S, Suter L. Current challenges and controversies in drug-induced liver injury. Drug safety. 2012 Dec; 35: 1099-117.
40. Liu W, Zeng X, Liu Y, Liu J, Li C, Chen L, Chen H, Ouyang D. The immunological mechanisms and immune-based biomarkers of drug-induced liver injury. Frontiers in Pharmacology. 2021 Oct 15; 12: 723940.
41. Danan G, Teschke R. Drug-induced liver injury: Why is the Roussel Uclaf Causality Assessment Method (RUCAM) still used 25 years after its launch?. Drug safety. 2018 Aug; 41 (8):735-43.
42. Hayashi PH, Lucena MI, Fontana RJ. RECAM: a new and improved, computerized causality assessment tool for DILI diagnosis. Official Journal of the American College of Gastroenterology ACG. 2022 Sep 1; 117 (9):1387-9.
43. Mizoi K, Arakawa H, Yano K, Koyama S, Kojima H, Ogihara T. Utility of three-dimensional cultures of primary human hepatocytes (spheroids) as pharmacokinetic models. Biomedicines. 2020 Sep 23; 8 (10):374.
44. Li F, Cao L, Parikh S, Zuo R. Three-dimensional spheroids with primary human liver cells and differential roles of Kupffer cells in drug-induced liver injury. Journal of pharmaceutical sciences. 2020 Jun 1; 109 (6):1912-23.
45. Gutierrez-Aranda I, Ramos-Mejia V, Bueno C, Munoz-Lopez M, Real PJ, Mácia A, Sanchez L, Ligero G, Garcia-Parez JL, Menendez P. Human induced pluripotent stem cells develop teratoma more efficiently and faster than human embryonic stem cells regardless the site of injection. Stem cells. 2010 Sep 1; 28 (9):1568-70.
46. Jozefczuk J, Prigione A, Chavez L, Adjaye J. Comparative analysis of human embryonic stem cell and induced pluripotent stem cell-derived hepatocyte-like cells reveals current drawbacks and possible strategies for improved differentiation. Stem cells and development. 2011 Jul 1; 20(7):1259-75.
47. Ehrlich A, Duche D, Ouedraogo G, Nahmias Y. Challenges and opportunities in the design of liver-on-chip microdevices. Annual Review of Biomedical Engineering. 2019 Jun 4; 21: 219-39.
48. Du K, Li S, Li C, Li P, Miao C, Luo T, Qiu B, Ding W. Modeling non-alcoholic fatty liver disease on a liver lobule chip with dual blood supply. Acta Biomaterialia. 2021 Oct 15; 134: 228-39.

Citation: Kasim, Dobhal K., Trivedi RK, Mukhopadhyay S. Impact of Drugs to Induce Liver Injury**.** Indian J Prev Soc Med, 2024; 55 (3): **237-247.**