

## DRUG INDUCED LIVER INJURY: A SYSTEMATIC REVIEW

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**Abstract**– Drug-induced liver injury (DILI), which has a variety of pathophysiological characteristics, is an important clinical problem. This review offers a thorough analysis of DILI, covering its pathophysiological mechanisms, the interaction between the microbiota and liver disease, the potential benefit of probiotics in preventing or treating DILI, diagnostic and prognostic methods, risk factors for DILI, current prevalence rates, and available treatments. The emergence of liver damage is influenced by the complex interplay of drug metabolism, immunological responses, and hereditary variables. An extensive list of medications, nutritional supplements, herbal products, and chemotherapeutic medicines that have been linked to DILI is provided based on the various research papers. The impact of the gut microbiota on healthy liver function and liver disease has been clarified by recent studies. Drug metabolism, immunological responses, and hepatic inflammation can all be affected by changes in gut microbial makeup and function, thereby worsening DILI. Probiotics' impact on the gut-liver axis and their potential therapeutic advantages in the prevention and treatment of DILI are investigated. For effective management of DILI, a precise diagnosis and prognosis are essential. The outcomes of patients are predicted and treatment choices are guided by prognostic variables, such as liver function tests and drug causality evaluation tools. Inherited liver illnesses, genetic differences, patient characteristics, concurrent medication use, and other risk factors all have a role in the development of DILI. Identification of those at higher risk and the facilitation of specialized preventative interventions and patient monitoring is made possible by the recognition of these risk factors. DILI prevalence rates differ between populations and geographical areas. Planning for public health and allocating resources depend on tracking the incidence and prevalence of DILI. Although supportive care and medication withdrawal are the mainstays of DILI treatment, severe cases may call for a liver transplant. As a result, DILI is a multifactorial disorder that necessitates a thorough understanding of its processes, risk factors, diagnosis, and therapy. New insights into the gut microbiota and the possible impact of probiotics present intriguing directions for further study and treatment approaches to reduce liver damage caused by DILI.

### INTRODUCTION

Drug-induced liver injury (DILI) is a rare and unpredictable condition affecting a small proportion of individuals exposed to a drug. It is typically not dose-related but requires a dose threshold of 50-100 mg/day. Both types share common features and major differences, with the chemical characteristics of the drug being important. Screening for stress in cell systems and isolated mitochondria is predictive of the risk associated with idiosyncratic DILI. Acetaminophen

hepatotoxicity is a common cause of acute liver failure (ALF) in the US and parts of Europe. It accounts for over 50% of cases, with half due to single overdoses and half unintentional. Factors such as concomitant drugs, fasting, systemic illnesses, and chronic alcoholic abuse modulate the threshold toxic dose by influencing CYP2E1 and glutathione status. If glutathione is severely depleted, the toxic metabolite binds to mitochondrial proteins, causing increased reactive oxygen species (ROS) production and mitochondrial damage (Raúl *et al.*, 2019).

### Several factors can contribute to the development of drug-induced liver injury

1. Drug-related factors: Some drugs are more likely to cause liver injury than others. Certain medications, such as acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), statins, antiepileptic drugs, and certain antibiotics and antifungals, have been associated with a higher risk of DILI (Einar *et al.*, 2016).

2. Individual susceptibility: Some individuals may be more susceptible to drug-induced liver injury due to genetic factors or pre-existing liver conditions. Certain genetic variations can affect the metabolism and detoxification of drugs in the liver, increasing the risk of liver injury.

3. Dose-dependent toxicity: The risk of DILI can be dose-dependent, meaning higher doses or prolonged use of a drug may increase the likelihood of liver injury. However, DILI can also occur at therapeutic doses or even with a single dose in susceptible individual (Bissell *et al.*, 2001).

4. Immune system response: In some cases, the immune system plays a role in DILI. The drug or its metabolites can trigger an immune response in the liver, leading to inflammation and liver cell damage.

Adverse hepatic events caused by drugs can be predictable (high incidence) or unpredictable (low incidence). Predictable events, like paracetamol, usually occur within a few days and are caused by direct liver toxicity of the parent drug or its metabolites. Unpredictable events manifest as overt or symptomatic disease, with intermediate or long periods of latency. Most adverse drug-induced hepatic events are unpredictable and immune-mediated hypersensitivity reactions. The pathogenesis of drug-induced liver injury involves

the participation of toxic drugs or metabolites that either elicit an immune response or directly affect cell biochemistry (Bissell *et al.*, 2001).

The symptoms of drug-induced liver injury can vary widely and may include fatigue, nausea, and vomiting, abdominal pain, loss of appetite, jaundice (yellowing of the skin and eyes), dark urine, pale stools, and itching.

Note: This table is for illustrative purposes and should not be used as a diagnostic tool. The presence of these symptoms does not necessarily indicate liver disease, as they can occur in various other conditions as well. If you suspect liver disease or have concerning symptoms, it is important to consult a healthcare professional for a proper evaluation and diagnosis.

Many herbal and dietary supplements are involved in hepatotoxicity. These include Pyrrolizidine alkaloids, Teucriumchamaedrys, Atractylisgummifera, Heliotrpium, Teucriumpolium, Atractylisgummifera, Hedeomapulegioides, Heliotrpium, Piper methysticum, Camellia sinensis, Actaearacemosa, Morindacitrifolia, Serenoa, Azadirachtaindica, and other plants. Dietary supplements include usnic acid with other ingredients, lipoKinetix, UCP-1, oxylite, hydrocut, linoleic acid, plethoryl, and illicit anabolic androgenic steroids (Raúl *et al.*, 2019).

### History of drug-induced liver injury (DILI)

The study conducted by Aithlal, *et al.* (1999) focuses on patients with idiosyncratic drug-induced liver injury, which is believed to be largely reversible even when the histological pattern of injury is chronic active hepatitis. The results show that a third of patients (11/33) had either biochemical,

**Table 1.** General symptoms and signs of liver disease (Dennis *et al.*, 2022).

Category	Symptoms and Signs
Nonspecific	Fatigue
	Weakness
	Vague abdominal pain
	Loss of appetite
Specific	Yellowing of the skin (jaundice)
	Itching associated with liver disease
Cirrhosis	Easy bruising
	Fluid accumulation in the legs (edema)
	Fluid accumulation in the abdomen (ascites)
	Mental confusion or coma (hepatic encephalopathy)
	Kidney failure
	Vulnerability to bacterial infections
Gastrointestinal bleeding (from varices)	

radiological, or histological evidence of liver disease a median of five years following their index liver biopsy, including 9/15 patients with chronic hepatitis, two of whom had persistent necro inflammation on biopsy. The most common factor for adverse outcomes in patients with liver injury is continued drug intake for over six months after the index biopsy. Prompt recognition of drugs as the cause of liver injury is crucial for effective management. Factors contributing to this failure include changing drug patterns, histological patterns, and new drugs not widely known for hepatotoxicity. Maintaining a high index of suspicion for any drug taken with liver injury is essential, as failure to discontinue the ordering agent increases the risk of liver damage persisting even after the drug is stopped (Aithal *et al.*, 1999).

### Pathophysiological processes

Drug-induced liver injury (DILI) involves complex pathophysiological processes that can vary depending on the specific drug involved and individual susceptibility. While the exact mechanisms of DILI are not fully understood, several key pathophysiological aspects have been identified. Here are some important factors contributing to the pathophysiology of DILI:

- **Direct Hepatotoxicity:** The liver has a significant impact on therapeutic efficacy and adverse drug reactions (ADRs). Drug oxidation and reduction reactions depend on cytochrome P450s (CYP), which are critical components. As a result, medications can be metabolized and produce ions, oxygen-free radicals, and other active ingredients. Drug-induced liver damage (DILI)

**Table 2.** Representing the milestones in the history of DILI

Milestone	Description	References
1. Early Recognition.	First documented cases of DILI traced back to the 1940s and 1950s. Link between liver damage and medications like isoniazid observed.	Terziroli <i>et al.</i> , 2022
2. Development of Drug Safety Regulations	Thalidomide use in the 1960s was linked to severe birth defects and liver injury. Stricter drug safety regulations established. Pre-marketing testing requirements implemented to assess drug toxicity.	Jack <i>et al.</i> , 1986
3. Identification of Drug-Induced Hepatitis	Term “drug-induced hepatitis” was coined in the 1970s. Liver inflammation caused by medications recognized. World Health Organization (WHO) establishes the International Drug Monitoring Program to collect data on adverse drug reactions.	Garibaldi <i>et al.</i> , 1972
4. Recognition of Idiosyncratic DILI	Differentiation between predictable, dose-dependent liver toxicity and idiosyncratic DILI. Idiosyncratic DILI refers to liver injury in a small subset of individuals without an obvious dose relationship. Immune-mediated mechanisms thought to be involved in idiosyncratic DILI	Fontana <i>et al.</i> , 2014
5. Collaboration and Research	Efforts by organizations like NIH and FDA to understand and address DILI. Establishment of collaborative research initiatives like DILIN to study causes, risk factors, and mechanisms of DILI.	Alempijevic <i>et al.</i> , 2017
6. Advancements in Testing and Diagnosis	Medical technology and diagnostics advancements aid in the identification and diagnosis of DILI. Biomarkers (liver enzyme tests) and imaging techniques (ultrasound, MRI) assist in evaluating liver function and detecting injury.	Kullak <i>et al.</i> , 2017
7. Ongoing Monitoring and Pharmacovigilance	Regulatory agencies (FDA, EMA) worldwide monitor drug safety through post-marketing surveillance systems. Data collection and analysis of adverse drug reactions, including DILI reports. Informing regulatory decisions and providing safety information to healthcare professionals and the public.	Raschi <i>et al.</i> , 2014

requires a balance between toxic production and detoxification. A frequently investigated medicine called paracetamol (APAP) produces intrinsic DILI because of increased N-acetyl-p-benzoquinone imine (NAPQI) production from CYP metabolism. Overdosage causes the sulfation and glucuronidation pathways to become saturated, which results in mitochondrial malfunction and the creation of protein adducts. In addition, an overdose can impair hepatobiliary transporter systems including the bile salt export pump (BSEP), and clog the bile duct. Significant biliary effects can result from inhibiting BSEP expression (Ye *et al.*, 2018).

- **Immune-Mediated Injury:** Immune checkpoint inhibitors (ICIs) boost T-cell responses and revive cancer-suppressed antitumor immune responses. CTLA-4, PD-1, and programmed cell death ligand 1 are among the targets. These medications, however, can cause hepatotoxicity and other immune-related adverse events. Hepatotoxicity rates with CTLA-4 inhibitors were found to be greater than those with PD-1 inhibitors in a meta-analysis. Acute liver failure to hepatitis and fulminant liver failure are all possible outcomes of hepatitis caused by ICIs. The classification scheme for ICI-related hepatotoxicity and its treatment are described in the 2018 American Society of Clinical Oncology Clinical Practice Guideline (Sandhu *et al.*, 2020).
- **Oxidative Stress and Reactive Metabolites:** Numerous liver illnesses are influenced by ROS-induced oxidative stress, and excessive ROS formation depletes endogenous antioxidants. The development of liver damage is influenced by several number of variables, including alcohol usage, high-calorie meals, drug overdoses, environmental contaminants, and heavy metals. Antioxidants are widely utilized to treat oxidative liver injury since the principal sites for ROS formation are the endoplasmic reticulum and hepatocyte mitochondria. Clinical research on the mechanism of ROS-mediated hepatocyte damage and the protective function of antioxidants, however, is still lacking. Studies have revealed that cholesterol plays a crucial role in liver damage, with high cholesterol-fed rats demonstrating increased oxidative stress and apoptosis, decreased hepatocyte proliferation, and higher mortality after BDL surgery. By altering the expression patterns of hepatic

proteins, exercise may benefit old rats (Ravirajsinh *et al.*, 2017).

The creation of mitochondrial proteins can be inhibited by oxidative stress, which can also enhance the transition of mitochondrial permeability. The mitochondrial membrane potential (MMP) collapses as a result of the production of MPT, which increases mitochondrial membrane permeability. The inner mitochondrial membrane of the mitochondria then bursts, ruptures, and releases proteins that block electron transport, increase ROS production, and cause more mitochondrial damage (Ye *et al.*, 2018).

- **Hepatocellular necrosis** is caused by mitochondrial dysfunction, which leads to increased oxidative stress, reduced protein synthesis, and increased permeability transition. This leads to depolarization, collapse of the mitochondrial membrane potential, swelling, rupture, and protein release, causing apoptosis, DNA damage, compromised  $\beta$ -oxidation, and disrupted ATP production (Ye *et al.*, 2018).
- **Impaired Bile Flow and Cholestasis:** There are two types of acute cholestasis caused by DILI: bland cholestasis and cholestatic hepatitis. While cholestatic hepatitis is brought on by immunological responses of the immuno-allergic or hypersensitivity type, bland cholestasis is associated with anabolic steroids and estrogens. Cholestatic hepatitis can be brought on by penicillins, sulfonyleureas, methimazole, and cephalosporins. In cholestatic DILI, disappearing bile duct syndrome (VBDS) is a frequent finding, and 94% of patients with VBDS have chronic DILI compared to 47% of individuals without it (Sandhu *et al.*, 2020)
- **Endoplasmic reticulum stress:** Protein folding can be hampered by cellular stresses like ROS and calcium fluctuations, which can cause endoplasmic reticulum stress (ER stress), which is essential for APAP-induced hepatotoxicity. After APAP intoxication, ER stress does not develop until 12 hours later and then becomes substantial. Although the exact causes of ER stress are unknown, some theories include binding to microsomal proteins, changes in microsomes, and ER oxidoreductases' oxidative shift. In addition, ROS overproduction and mitochondrial malfunction, including MMP loss and elevated intracellular calcium, may lead to ER stress (Ye *et al.*, 2018).
- **Immune tolerance:** Most people who are



exposed to insulting medications have hepatocyte stress show ever, this is only true for a small percentage of them. Due to immunological deviation, immune active suppression, and death of activated T cells, the liver, an immune-tolerant organ, is vulnerable to stress reactions. Through certain signals, hepatocytes draw apoptotic T lymphocytes, and immunological deviation happens during hepatic immune responses. The liver contains tolerogenic APCs, such as LSECs, KCs, and hepatic dendritic cells, which interact with dormant T cells and encourage tolerance. These cells can't activate T cells that are specific to an antigen, but they can trap and engage dormant T cells, fostering tolerance (Ye *et al.*, 2018).

- **Genetic Factors:** The risk of developing diabetic lipidemia (DILI) is increased by single nucleotide polymorphisms in genes and HLA areas. Influential roles in the susceptibility to flucloxacillin, amoxicillin-clavulanate, and minocycline DILI are played by HLA genotypes like HLA-B\*5701 and HLA DRB1\*15:01. The ability to accurately and confidently diagnose DILI may be enhanced by HLA genotyping (Sandhu *et al.*, 2020).

Pharmacogenetics studies have focused on identifying single-nucleotide polymorphisms (SNPs) in drug-metabolizing enzymes and drug transporters to identify genetic markers of DILI. CGAS and GWAS are used to identify key genes and SNPs, but GWAS is hypothesis-free and can lead to false positives. However, GWAS is limited due to genetic variations and may not detect genes with low frequency. A strong mechanistic understanding of DILI is needed to assess the potential importance of identified polymorphisms

in the appropriate context. Target genes are identified based on the drug's initial pathway of causing dialysis-induced liver injury (DILI). GSTs, N-acetyltransferase (NAT), and allele variants within UGT2B7, CYP2C8, and ABCC2 are associated with hepatotoxicity. HLA class II variants have been linked to cholestatic/mixed patterns of hepatocellular injury. HLA-B\*5701 is the strongest genetic association reported, with flucloxacillin toxicity being the strongest. Three CGAS studies have identified a correlation between HLA-DRB1\*15 and amoxicillin-clavulanic acid-induced DILI (Au *et al.*, 2011). APAP-induced liver damage is characterized by hemorrhagic centrilobular necrosis and high plasma transaminase levels. Overdose saturates liver pathways, leading to the highly reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI). This toxic byproduct is rapidly conjugated with glutathione, causing mitochondrial dysfunction and cell death. Understanding the underlying mechanisms of APAP hepatotoxicity is incomplete, and developing realistic human models is crucial for accurate prediction and effective therapeutic interventions (Jose *et al.*, 2014).

#### Clinical Presentation of DILI (Ortega-Alonso *et al.*, 2016)

- Acute DILI Presentation
- Hepatocellular Injury
- Cholestatic Injury
- Mixed Injury
- Chronic DILI
- Autoimmune Features
- Steatosis
- Sinusoidal Obstruction Syndrome (SOS)
- Hypersensitivity and Extrahepatic Manifestations

**Table 3.** Pathological Features of DILI (Iluz *et al.*, 2020).

Type of Liver Injury	Description	Clinical Presentation
Hepatocellular Injury	Predominant damage to hepatocytes, the liver's main functional cells.	-Hepatocellular necrosis, Inflammation, Ballooning degeneration of hepatocytes
Cholestatic Injury	Liver injury primarily affects the bile ducts and impairs bile flow.	- Bile duct inflammation (cholangitis), Bile duct obstruction, Alterations in bile composition
Mixed Injury	Drugs cause a mixed pattern of hepatocellular and cholestatic injury. Features of both observed on liver histology.	- More severe clinical presentation, Combination of hepatocellular and cholestatic injury observed on liver biopsy

### Microbiota and Liver disease

Clinicians use nonabsorbable disaccharides like lactulose to modulate the gut microbial environment, promoting the growth of certain bacteria like Bifidobacterium and Lactobacillus. This approach, known as selective gut decontamination, is also used with prebiotics, probiotics, and synbiotics. Probiotics are live microorganisms supplied from outside the body but must tolerate acidic gastric juices and survive the journey. Prebiotics are fermented substrates, while synbiotics are combinations of prebiotics and probiotics. Probiotics should only be used in clinical situations

with proven benefits and safe strains and dosages. Hepatic encephalopathy (MHE) is a condition characterized by abnormal neuropsychometric or neurobiologic test results. Traditional therapy for MHE has been antibiotics or nonabsorbable polysaccharides. Probiotic preparations have been shown to have a role in various stages of MHE, with a meta-analysis showing a beneficial effect in MHE patients (Jennison *et al.*, 2020).

### Role of probiotics in drug-induced liver injury (DILI)

However, there is less clear evidence for overt

**Table 4.** Effect on gut microbiota in different Liver diseases (Minemura *et al.*, 2015).

Liver Disease	Changes in Gut Microbiota
Nonalcoholic fatty liver disease (NAFLD)	Decreased Bacteroidetes, increased Prevotella and Porphyromonas species
Liver cirrhosis	Increased Enterobacteriaceae and Streptococcaceae, decreased Bifidobacteria and Lachnospiraceae
Alcoholic liver disease	Decreased Bacteroidaceae, increased Prevotellaceae
Cirrhosis with encephalopathy	Increased Porphyromonadaceae and Alcaligenaceae
Hepatocellular carcinoma (HCC)	Gut bacterial metabolites (e.g., deoxycholic acid) promote HCC development; TLR4 activation and propionate inhibit hepatocarcinogenesis; gut microbiota influences the generation of Th17 cells associated with poor prognosis in HCC patients.

**Table 5.** Role of probiotics in drug-induced liver injury (DILI)(Patel, *et al.*, 2017).

Effects of Probiotics on DILI	Examples/Details
Gut-Liver Axis	Disruptions in gut microbiota composition and function can influence liver health and contribute to liver diseases, including DILI. - Probiotics can modulate the gut microbiota and potentially impact liver function
Anti-inflammatory and Immunomodulatory Effects	Probiotics have anti-inflammatory and immunomodulatory properties. - They can reduce gut permeability, inhibit pro-inflammatory cytokines, and promote the production of anti-inflammatory molecules.
Protection Against Oxidative Stress	Probiotics have antioxidant effects and help protect against oxidative stress implicated in liver injury. - They reduce reactive oxygen species production and enhance antioxidant defenses.
Modulation of Bile Acid Metabolism	Probiotics can influence bile acid metabolism, which is closely tied to liver health. - They promote the conversion of primary bile acids to secondary bile acids, which can have protective effects on the liver.
Drug Metabolism and Detoxification	Probiotics can modulate liver enzymes involved in drug metabolism, potentially impacting the bioavailability and toxicity of drugs.
Prevention of Gut Dysbiosis	Some drugs disrupt the gut microbiota and lead to gut dysbiosis, which can contribute to liver injury. - Probiotics restore the balance of gut microbiota and prevent or mitigate drug-induced gut dysbiosis.
Positive Effects on Alcohol-induced Rat Experimental Models	Probiotics, such as Lactobacillus caseiShirota and Lactobacillus rhamnosus GG, have shown beneficial effects in alcohol-induced liver injury models.
Pharmaceutical Preparations with Multiple Bacterial Strains	New therapeutic approaches involve pharmaceutical preparations using multiple strains of bacteria for treating DILI.

hepatic encephalopathy, and further trials are needed to determine their effectiveness. Probiotics have been shown to modulate gut microbiota in animal experiments, but it is premature to recommend probiotics for the treatment of NAFLD (Sharma *et al.*, 2013).

### Diagnosis of DILI

Identification of risk variables and clinical course prediction could both benefit from a diagnostic method for acute hepatotoxicity injury (IDILI). Before giving potentially hepatotoxic chemicals, there was no predicted safety assessment, which highlights the necessity of early detection and increased surveillance. Novel biomarkers have acquired regulatory support for systematic adoption, such as those examined in the SAFE-T Consortium. Current diagnosis relies on subjective assessment and expert judgment, but consensus approaches can lessen these drawbacks. Hepatotoxicity assessment is made more difficult by liver damage brought on by herbal and nutritional supplements, and there is no scientific way to determine if a drug is to blame for a particular case of liver damage other than to rely on expert opinion (Kullak *et al.*, 2017).

**Medical History:** Obtaining a detailed medical history is crucial in identifying potential causative drugs. Information about the timing of drug initiation, dosage, duration of use, and concomitant medications can help establish a temporal relationship between drug exposure and liver injury.

**Clinical Evaluation:** Physical examination may reveal signs of liver injury, such as jaundice, hepatomegaly, or abdominal tenderness. Evaluation of other organ systems may help exclude alternative causes of liver injury (Lala *et al.*, 2023).

### Laboratory Tests

**Liver Function Tests:** Serum ALT/AST, ALP, and TBL levels have been used as the pillars for DILI case detection and qualification due to the lack of diagnostic DILI biomarkers; however, minor and reversible increases in ALT/AST should not be classified as DILI as they can be related to other organ damages, such as muscle injury. Testing for creatine phosphokinase can help distinguish between liver- and muscle-driven ALT elevations (Andrade *et al.*, 2020).

**Serological Testing:** Due to the lack of precise biomarkers, the diagnosis of drug-induced liver injury (DILI) depends on ruling out alternate causes

of liver damage. To rule out frequent causes of hepatitis and cholestasis, the initial diagnostic approach can be aided by the classification of injury types. To rule out alcohol misuse, comorbidities, and viral hepatitis risk factors, the patient's age, and thorough medical history should be gathered. Particularly in patients with hepatic disease and hepatotoxicity, serology testing for viral hepatitis A, B, C, and E should be carried out. In addition to being a prevalent cause of viral hepatitis in Eastern nations, anti-hepatitis E (HEV) is also an increasing cause in Western nations and can thus be a DILI confounder (Andrade *et al.*, 2020).

**Imaging Studies:** To rule out other possible causes, diffuse ileal infarction (DILI) is diagnosed by liver imaging. For all DILI suspicions, abdominal ultrasonography is advised, independent of the biochemical pattern of damage. To rule out gallstone disease and other competing aetiologies, magnetic resonance cholangiography (MRCP) and computerized tomography may be required. Chemotherapy medications have been characterized as causing toxic damage to the biliary tract in rare instances, which manifests as sclerosing cholangitis. Methimazole and docetaxel have also been linked to secondary sclerosing cholangitis in some cases (Andrade *et al.*, 2020).

**Liver Biopsy:** In acute and chronic liver illnesses, histological examination is less frequently recommended than non-invasive testing, especially for stage fibrosis. But liver biopsy has long been regarded as an additional diagnostic technique to support and strengthen the diagnostic procedure. According to an examination of liver biopsies from 249 DILI patients, hepatocellular patterns were linked to more severe inflammation and cell death than bile plugs and ductal paucity, which were more common in cholestasis patients. However, because it cannot make a definitive diagnosis, liver biopsy is not frequently carried out in suspected DILI cases. Hepatocellular damage must be present to diagnose AIH, which can still be confused with AIH even after thorough examinations. The streamlined diagnostic scale for AIH diagnosis incorporates histological abnormalities, making liver biopsy necessary (Andrade *et al.*, 2020).

**Genetic testing:** HLA genotypes and haplotypes linked to diabetic liver damage (DILI) linked to particular medicines have been discovered through genome-wide association studies. HLA genotyping is accessible and reasonably priced, supporting the

clinical diagnosis. High negative predictive values can exclude DILI when not a carrier, despite the poor pre-treatment value of genetic testing. Having an HLA risk allele linked to a particular medicine would favor a DILI diagnosis, whereas the absence or presence of the typical HLA alleles linked to AIH would support an AIH diagnosis. HLA testing could also help distinguish between DILI and AIH (Andrade *et al.*, 2020).

### Prognosis of DILI

The prognosis for most patients with drug-induced liver injury (DILI) is favorable, with full recovery expected during the dechallenge process. Patients with jaundice may take up to 30 to 40 days to recover, and severe cholestasis cases may require up to a year. Hepatocellular injury phenotype in DILI carries a worse prognosis compared to cholestatic or mixed presentations. Hyman Zimmerman, a renowned hepatologist, developed a rule stating that a bilirubin level of 3 or more times the upper limit of normal (ULN) in hepatocellular-type DILI indicates a risk of death of approximately 10%. The FDA has modified Zimmerman's rule to consider a bilirubin level of >2x ULN as an indicator of DILI severity in clinical trials. Acetaminophen-induced acute liver failure (ALF) has a better prognosis compared to idiosyncratic DILI as a cause of ALF. DILI can progress to a chronic form of liver disease, with varying rates reported in different epidemiologic studies. Death rates from idiosyncratic DILI range from 1% to 8%, with 1% to 2% of cases requiring liver transplantation. Advances have been made in predicting outcomes in non-idiosyncratic acetaminophen DILI, including the use of the Rumack.

Matthew nomogram and miR-122 as early marker. The Model for Acetaminophen-induced Liver Damage has been developed to predict mortality based on specific laboratory values, showing promise but not yet ready for clinical use.

### Top of Form

**Severity Assessment:** The severity of DILI is evaluated based on the pattern and degree of liver injury, clinical presentation, and laboratory findings. Various scoring systems, such as the R-value or the Roussel Uclaf Causality Assessment Method (RUCAM), may be used to assess the likelihood and severity of DILI.

**Clinical Course:** DILI can have a wide range of outcomes, from complete recovery upon drug

withdrawal to acute liver failure or chronic liver disease. Factors associated with a poorer prognosis include older age, severe initial liver injury, the presence of jaundice, co-existing liver disease, and delayed recognition or withdrawal of the offending drug.

**Monitoring and Follow-up:** Regular monitoring of liver function tests is necessary to assess the progression of liver injury and monitor recovery. Follow-up visits allow for evaluation of symptoms, physical examination, and adjustments to treatment plans as necessary.

**Prognostic Factors:** Certain prognostic factors, such as the severity of the liver injury, presence of jaundice, coagulopathy, and encephalopathy, can help predict the clinical course and determine the need for advanced interventions, such as liver transplantation.

### Age

**Older Age:** Advanced age is often considered a risk factor for DILI. This may be due to age-related changes in liver function, decreased drug clearance, and increased vulnerability to liver injury. Older individuals may also have multiple comorbidities and may be taking multiple medications, increasing the potential for drug interactions and liver injury. DILI can also occur in children, but the pattern and types of drugs implicated may differ compared to adults. Children may be at increased risk due to factors such as immature liver function, differences in drug metabolism, and specific drug therapies used in pediatric populations (Chalasani *et al.*, 2010).

**Female:** Some studies have suggested that females may have a higher risk of developing DILI compared to males. This could be related to hormonal factors, differences in drug metabolism, or variations in drug utilization patterns. For example, certain drugs like anti-tuberculosis medications and some antibiotics have been associated with a higher risk of DILI in women. Hormonal factors, such as pregnancy or the use of oral contraceptives, may also play a role in the susceptibility to DILI in women. Pregnancy-associated liver injury, such as acute fatty liver pregnancy, can occur with specific drugs and is more common in pregnant women (Chalasani *et al.*, 2010).

Age is a potential risk factor for severe adverse drug reactions (ADRs) in older people, possibly due to impaired drug clearance. However, data from large prospective DILI registries do not support this



as older age is generally older. Age may affect the risk of DILI induced by specific causative agents. Advanced age is a risk factor for isoniazid hepatotoxicity, with cases more frequent in patients aged 35-49 and  $\geq 50$ . Younger age is associated with dialysis-induced liver injury (DILI) induced by valproic acid, with children under 10 years old having a higher risk. Older age is associated with an increased risk of DILI with persistent liver biochemical abnormalities (Raúl *et al.*, 2019).

The frequency of diabetic liver damage (DILI) is higher in people over the age of 70 and is correlated with advanced age. However, neither the American nor the Spanish networks identified growing older as a risk factor for all-cause DILI. Age may also play a role in the liver damage caused by drugs such as nitrofurantoin, isoniazid, and amoxicillin/clavulanate. Older people are more likely to have cholestatic DILI (Sandhu *et al.*, 2020).

### Sex

Women are at higher risk for idiosyncratic liver injury (DILI) than men due to the higher prevalence of women in published studies. However, recent studies have not shown a systematic risk factor for DILI. Women are more susceptible to liver injury caused by medications like halothane, flucloxacillin, isoniazid, nitrofurantoin, chlorpromazine, or erythromycin, while men have an increased risk of azathioprine-induced liver injury. Recent studies have shown a relationship between female sex, the hepatocellular pattern of DILI, and poor outcomes, such as acute liver failure, liver transplantation, and death (Chalasanani *et al.*, 2010).

### Daily dose

Idiosyncratic liver injury (DILI) is not entirely dose-independent, but some medications, such as diclofenac, amoxicillin/clavulanate, and flucloxacillin, have a relationship to the daily dose. A study found that daily doses of oral medications were significantly associated with liver failure, liver transplantation, and death from DILI. Further studies are needed to develop safe medications and understand the relationship between drug doses and DILI risk (Chalasanani *et al.*, 2010).

### Metabolism characteristics

Hepatic metabolism is commonly prescribed oral medications significantly increases the risk of drug-induced liver injury (DILI) and liver failure. Compounds with 50% or greater hepatic

metabolism cause higher ALT levels, liver failure, liver transplantation, and fatal DILI. Compounds with biliary excretion increase jaundice incidence. CYP pathways are associated with more DILI (Chalasanani *et al.*, 2010).

### Alcohol consumption

Alcohol consumption is linked to idiosyncratic diastolic liver injury (DILI), but its role in idiosyncratic DILI is unclear. RUCAM criteria indicate alcohol consumption increases liver injury risk from medications like methotrexate, isoniazid, and halothane. Studies show no significant association between alcohol consumption and DILI severity or chronicity (Chalasanani *et al.*, 2010). Acute alcohol co-ingestion may be protective, as alcohol consumption is a significant factor in APAP-related liver damage. Malnutrition may raise the incidence of DILI while chronic alcohol usage enhances APAP hepatotoxicity. A risk factor for DILI from isoniazid, methotrexate, and halothane is chronic alcohol use (Sandhu *et al.*, 2020).

Idiosyncratic liver injury (DILI) is a complex genetic disorder with multiple variants and environmental risk factors. Understanding the genetic basis is challenging due to the vast number of compounds, variable clinical presentation, and diagnostic difficulties. A multistep model has been proposed, involving upstream drug-specific pathways and downstream common pathways causing cell stress and death. Variations in cytochrome P450 enzyme activity are essential for the pathogenesis of DILI. Several studies have investigated the role of CYP3A, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP2D6 enzymes in the pathogenesis of idiosyncratic DILI. However, evidence is not strong to support their role, except for a few compounds. CYP3A, CYP2C9, CYP2D6, and CYP2E1 are the usual suspects in DILI pathogenesis, but their variants do not support a major role (Chalasanani *et al.*, 2010).

### Risk factors in relation with liver injury

Drug-induced liver injury (DILI) can occur due to various risk factors that contribute to an individual's susceptibility to liver injury when exposed to certain medications. Here are some of the common risk factors associated with DILI:

Drug induced liver injury (DILI) risk is complicated and involves a number of interconnected factors. According to some research, DILI is more likely to affect women, the elderly, and

people who have chronic liver disease, HIV, or who are obese. However, there isn't much actual evidence to back up the relevance of these elements. Age has been mentioned as a risk factor for DILI, but the age ranges that are most at risk vary depending on the medicines. A risk factor for DILI caused by isoniazid is older age, but a risk factor for DILI caused by valproate and aspirin (Reyes syndrome) is youth. It is biologically plausible that older people have a higher risk or incidence of DILI because their essential absorption, distribution, metabolism, and elimination components may change from those of younger people. In both Sweden and the United States, Lammert *et al.* ( discovered a significant correlation between the dosage of an oral drug and hepatotoxicity. In Sweden and the United States, a higher daily dose was linked to liver failure, LTx, and death from DILI (Leise *et al.*, 2014).

**Numerous drugs and medications have been associated with drug-induced liver injury (DILI). The following is a non-exhaustive list of drug classes and specific examples that have been implicated in causing DILI**

This provides general information and not an exhaustive list of drugs or potential liver injuries. It's always important to consult a healthcare professional or refer to the drug's prescribing information for accurate and up-to-date information on drug-induced liver injury (Einar *et al.*, 2016).

Drug-induced liver injury (DILI) encompasses a wide range of pathological and clinical manifestations. The specific pathological and clinical

features can vary depending on the drug involved, individual susceptibility, and other factors. Here are some key aspects of the pathological and clinical relationship in DILI.

Treatment with 2% cholestyramine improves hepatic BA retention, tumor-suppressive microRNA expressions, and microbial gut communities. No pharmacological interventions are currently licensed for NAFLD treatment. Pharmacologic options like metformin, vitamin E, omega-3 fatty acids, and lipid-lowering drugs have been studied in NAFLD patients. However, poor patient compliance and the gut-liver axis' role in NAFLD have led to research interest in manipulating the gut microbiome. Techniques include antibiotics, probiotics, prebiotics, and synbiotics. Limited human data exists on the impact of gut microbiome modification on NAFLD (Jennison *et al.*, 2020).

#### Prevalence of Drug-Induced Liver Injury (DILI)

- Prospective studies in the general population
  - France: 3.9 cases per 100,000 persons/year
  - Iceland: 19.1 cases per 100,000 persons/year
  - Spain: 13.42 cases per 100,000 persons/year
  - Delaware (USA): 2.7 cases per 100,000 persons/year
  - Korea: 12 cases per 100,000 persons/year
  - GPRD (UK): Varies depending on the drug studied
- Other studies reporting the incidence of DILI in the general population
  - Spain: 3.7 cases per 100,000 NSAIDs users or 1.1 cases per 100,000 NSAID prescriptions

**Table 6.** Examples of drugs or potential liver injuries.

S. No.	Drug category	Examples	Associated injury
1.	Acetaminophen (paracetamol)	Acetaminophen	Acute liver failure, overdose
2.	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Diclofenac, Ibuprofen, Naproxen	Mild to severe liver injury, hepatitis, liver failure
3.	Statins	Atorvastatin, Simvastatin, Lovastatin	Rare liver injury
4.	Antibiotics	Amoxicillin-clavulanate, Erythromycin, Nitrofurantoin, Sulfonamides	Different patterns of liver injury, hepatitis, cholestasis
5.	Antiepileptic Drugs (AEDs)	Phenytoin, Carbamazepine, Valproic Acid, Lamotrigine	Mild to severe liver injury
6.	Herbal and Dietary Supplements	Kava, Green Tea Extract, Black Cohosh, Anabolic Steroids	Potential liver harm
7.	Antituberculosis Drugs	Isoniazid, Rifampicin, Pyrazinamide	Liver injury in individuals with underlying liver disease or risk factors
8.	Antiarrhythmics	Amiodarone, Propafenone	Rare liver injury
9.	Antidepressants	Fluoxetine, Sertraline, Amitriptyline	Associated with liver injury

- GPRD (UK): Varies depending on the drug studied
- 3. Prevalence of DILI in hospitalized patients
  - Toulouse (France): 6.6 cases per 1,000 inpatients/week
  - Singapore: Varies depending on the drug studied
  - Colombia: 18.6 cases per 100 in patients with altered liver tests
  - Japan: Varies depending on the hospital studied
  - USA: Varies depending on the study and patient population
- 4. Prevalence of DILI in patients with jaundice
  - Sweden: 2.3% of patients with severe jaundice
  - USA: Approximately 4% of patients with new-onset non-alcoholic jaundice
- 5. Prevalence of DILI in acute liver failure (ALF) patients
  - USA: Varies depending on the study and period (ranging from 11% to over 50% of ALF cases)
  - UK: 57% of ALF cases are caused by acetaminophen (APAP)

Please note that these prevalence rates may vary depending on the population studied, the specific drugs involved, and other factors (Li *et al.*, 2022).

The worldwide prevalence of drug-induced liver injury (DILI) can be challenging due to variations in study methodologies, differences in reporting systems, and limited data availability from certain regions. However, several studies and research initiatives have aimed to investigate DILI on a global scale. Here are some notable examples:

- **International DILI Registry:** The International DILI Registry is an ongoing effort to collect information on DILI cases from multiple countries. It aims to provide a comprehensive view of the global occurrence of DILI, including data on drugs commonly associated with liver injury, risk factors, and outcomes (Danan *et al.*, 2015).
- **Pharmacovigilance Databases:** Pharmacovigilance systems and databases, such as the FDA's Adverse Event Reporting System (FAERS) and the EMA's Eudra Vigilance database, collect reports of adverse drug reactions, including cases of DILI, from various countries. Analyzing these databases can provide insights into the prevalence and patterns of DILI worldwide (Crepin *et al.*, 2014).
- **Population-Based Studies:** Some population-based studies have been conducted in specific regions or countries to estimate the incidence

and prevalence of DILI. These studies often utilize healthcare databases or cohort data to identify cases of DILI and provide insights into regional variations (Li *et al.*, 2022).

Acetaminophen toxicity treatment mainly involves NAC therapy, with conflicting studies on oral or intravenous therapy. Current recommendations include treating according to protocol, rechecking AST and acetaminophen levels, and using INR normalization as a marker of resolution. Amanita mushroom ingestion can cause liver injury due to amatoxin, which inhibits RNA polymerase II and causes hepatocyte necrosis. The presentation consists of a gastrointestinal phase followed by a hepatic phase. Treatment includes dehydration and electrolyte abnormalities (Giardano *et al.*, 2014).

Repeated activated charcoal administration is recommended to prevent amatoxin reabsorption. Silibinin, penicillin G, and the Molecular Adsorbent Recirculating System can be used to treat amatoxin poisoning. Patients with fever, rash, and eosinophilia should be diagnosed with drug-induced autoimmune hepatitis. Liver assist devices, such as the Hepat Assist Liver Support System, have shown potential in treating patients with DILI, subacute fulminate failure, and fulminate failure. Advances in bioartificial livers are ongoing, and King's College criteria determine when patients should be referred for transplantation (Giardano *et al.*, 2014).

#### Treatment approach for drug-induced liver injury (DILI)

The primary treatment approach for drug-induced liver injury (DILI) involves discontinuing the use of the offending drug. The specific management strategies may vary depending on the severity of liver injury and the clinical presentation. Here are the key aspects of treatment for DILI:

#### Specific Therapies

**N-acetylcysteine (NAC):** NAC, commonly used as an antidote for acetaminophen overdose, has been studied in certain cases of non-acetaminophen-related DILI. It may have a hepatoprotective effect and can be considered in selected cases, especially when there is evidence of oxidative stress or mitochondrial injury (Sanabria *et al.*, 2022).

**Ursodeoxycholic Acid (UDCA):** UDCA, a bile acid derivative, has been used in some cases of cholestatic DILI. It may help improve bile flow and

reduce liver injury in certain individuals (Robles *et al.*, 2021).

### Management of Complications

Early drug withdrawal is necessary in the treatment of drug-induced autoimmune-like hepatitis (DILI) in order to prevent the development of acute liver failure (ALF). The usefulness of corticosteroids in treating drug-induced autoimmune-like hepatitis (DILI) has not been sufficiently researched. Although its use is not FDA-approved, N-acetylcysteine (NAC) is being investigated for non-APAP-related DILI. While natural compounds including silymarin, resveratrol, curcumin, and ginkgo are being researched for potential hepatoprotective properties, ursodeoxycholic acid has been utilised to treat cholestatic DILI. ALF management also makes use of plasma exchange, molecular adsorbent recirculatory devices, fractionated plasma separation, and adsorption (David *et al.*, 2010).

### Follow-Up and Monitoring

Regular follow-up visits with healthcare professionals experienced in liver diseases are essential to assess the progression of liver injury, monitor recovery, and manage any potential long-term complications or recurrence.

Artemisinin (TCM) is a single component extracted from *Artemisia annua* L. that has been shown to treat various diseases, including allergic, anti-tumor, cognitive impairment, anti-malaria, and cardiovascular diseases. However, TCM may cause irreversible side effects. Intelligent drug delivery systems (DDSs) have been developed to target TCM, and if applied to treating liver injury (DILI), the use of TCM will be further improved. Future research aims to reduce TCM toxicity and improve targeting while reviewing natural drug monomers and signaling pathways for treating DILI (Sun *et al.*, 2022).

### Advances in tissue engineering with respect to drug induced liver injury

Advances in tissue engineering have the potential to contribute to the field of drug-induced liver injury (DILI) by providing tools and technologies for studying liver injury mechanisms, drug screening, and potentially even liver regeneration. Here are a few ways in which tissue engineering advancements can intersect with DILI research:

- **Liver-on-a-Chip Models:** Liver-on-a-chip models

are microscale platforms that aim to mimic the structure and function of the human liver. These models incorporate liver cells, such as hepatocytes, along with other cell types and microfluidic systems to recreate the liver's physiological environment. Liver-on-a-chip models can be utilized to study the effects of drugs on liver cells and assess their potential for inducing liver injury in a more controlled and representative setting (Deng *et al.*, and 2020).

- **3D Liver Tissue Models:** Tissue engineering techniques allow the construction of three-dimensional (3D) liver tissue models that closely mimic the complex architecture and cellular organization of the liver. These models can be used to investigate drug-induced liver injury by exposing the tissue to specific drugs and assessing their impact on cell viability, liver function, and injury mechanisms. They provide a more physiologically relevant platform for studying drug toxicity compared to traditional two-dimensional cell culture systems (Serras *et al.*, 2021).
- **Biomaterial Scaffolds for Liver Regeneration:** In severe cases of DILI, where liver failure or extensive damage occurs, tissue engineering approaches can offer solutions for liver regeneration. Biomaterial scaffolds can be used to provide a supportive structure for the growth and organization of liver cells, facilitating tissue repair and regeneration. These scaffolds can be seeded with patient-derived hepatocytes or stem cell-derived liver cells to create functional liver tissue (Kaur *et al.*, 2020).
- **Drug Screening and Predictive Models:** Tissue engineering techniques can be integrated with high-throughput screening methods to develop drug testing platforms that assess the potential hepatotoxicity of drugs. By combining engineered liver tissues with robotic systems and advanced imaging technologies, it is possible to screen a large number of drugs or drug candidates for their potential to induce liver injury. These screening approaches can help identify safer and more effective drugs while minimizing the risk of DILI (Weaver *et al.*, 2020) (Kia *et al.*, 2013).
- **Personalized Medicine and Liver-on-a-Chip:** Tissue engineering approaches, coupled with patient-specific induced pluripotent stem cells (iPSCs), hold promise for personalized medicine in DILI. iPSCs can be derived from patient cells,



differentiated into liver cells, and incorporated into liver-on-a-chip models. This enables the testing of individual patient responses to specific drugs and allows for the identification of potential susceptibility to DILI on a patient-specific basis.

- Zhong *et al.* created a 3D hydrogel scaffold using a bioprinter, ensuring cell viability and enzyme content. Jeon *et al.* constructed an alginate 3D-printed liver structure, resulting in better liver properties. Caddeo *et al.* used sequential 3D bioprinting of human hiPSC-derived liver cells in a hexagonal lobule structure, while Liu *et al.* (1999) used a multilayer photopatterning platform to embed cells in complex hydrogels. Liu *et al.* (1999) developed a micropatterned electrode device using lithography technology, forming multilayer liver lobule tissue. Lee *et al.* printed gel sheets using a 3D bioprinter. Researchers have developed a 3D bioprinting technology to create liver tissue by seeding liver cells and attaching them to gel sheets. The gel sheets contain galactosylated alginate (GA) that binds easily to the salivary glycoprotein receptor. Liver lobules are prepared using 3D bioprinting technology, and liver cell coagulation tablets are prepared using the decellularization-cellularization culture method.

This method has developed into important technologies for constructing vital organs, such as livers, which can be used to treat end-stage liver diseases. High shear stress oscillatory decellularization is a method for bioengineering human livers, removing immunogenic cellular material while retaining extracellular matrix proteins. This process preserves cellular material, collagen, and elastin, unlike fresh human livers. Recellularized liver transplantation using stem cells and decellular scaffolds is a promising approach. Nanofiber scaffold culture methods, such as electrostatic spinning, are widely used due to their simplicity, wide application range, and high production efficiency (Yang *et al.*, 2022).

### Abbreviations

DILI-Drug induced liver injury, ALF-Acute Liver Failure, iPSC-induced Pluripotent Stem cell, TCM-Traditional Chinese medicine, DDS-Drug delivery system, NAC-N-acetylcysteine,

APAP-Acetaminophen, UDCA-Ursodeoxycholic Acid, FAERS- FDA's Adverse Event Reporting System

### NSAID- Non-Steroidal Anti-Inflammatory Drug, NAFLD- Non-Alcoholic fatty liver disease

IDLI-Idiosyncratic drug induced liver injury, AST-Aspartate, ROS- Reactive oxygen species, SOS-Sinusoidal Obstruction Syndrome, CYP-CytochromeP450.

**Conflict of Interest:** None

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