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## Role of immune dysfunction in drug induced liver injury

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### Abstract

Drug-induced liver injury (DILI) is one of the leading causes of liver failure and withdrawal of drugs from the market. A poor understanding of the precipitating event aetiology and mechanisms of disease progression has rendered the prediction and subsequent treatment intractable. Recent literature suggests that some drugs can alter the liver's repair systems resulting in injury. The pathophysiology of DILI is complex, and immune dysfunction plays an important role in determining the course and severity of the disease. Immune dysfunction is influenced by the host response to drug toxicity. A deeper understanding of these processes may be beneficial in the management of DILI and aid in drug development. This review provides a structured framework presenting DILI in three progressive stages that summarize the interplay between drugs and the host defence networks.

**Key Words:** Immune dysfunction; Liver damage; Hepatotoxic drugs; Drug-induced liver injury; High mobility group box 1

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**Core Tip:** This review demonstrates the critical role of the immune system in the progression of drug-induced liver injury and also in determining the severity of the damage. Drugs affect the normal functioning of hepatocytes through several direct and indirect mechanisms leading to the dysfunctional immune response. The major effector cells in amplifying liver damage are Kupffer cells, monocytes and neutrophils. Genetic predispositions and environmental factors also make individuals vulnerable to immune dysfunction.

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## INTRODUCTION

The liver plays a central role in the complex process of metabolism and elimination of drugs from the body. The liver is equipped with a wide array of detoxification systems that have evolved over time with exposure to xenobiotics. The primary role of this system is to convert a drug to a more hydrophilic form so that it can be eliminated through bile or urine. Despite the liver's detox potential, certain drugs can still cause hepatotoxicity that can range from mild asymptomatic liver damage to liver failure[1, 2].

A study showed that, out of the 462 pharmaceuticals withdrawn due to adverse drug reactions between 1953 and 2013, hepatotoxicity ranked first with 81 cases (18%). It is estimated that over 1000 drugs currently available on the market that cause liver damage[3] despite these drugs passing the safety measures of clinical trials before entering the market. Some drugs that are hepatotoxic at doses higher than the therapeutic range can also cause drug-induced liver injury (DILI) at doses within the therapeutic range[2,4-6]. This implies that the dose may not be the only contributing factor.

Despite large number of drugs known to cause liver injury, the incidence of DILI is rare. DILI is reported in 1 in every 10000 to 100000 individuals annually. This suggests that drug-host interactions in these susceptible individuals may play an important role in DILI[7-9]. Recent data shows that this interaction can result in an imbalance between damage and repair mechanisms resulting in DILI with immune dysfunction being cited as an important precipitating event in the pathophysiology of DILI[10-12]. This is supported by evidence from experimental studies. Some drugs that are hepatotoxic in humans do not cause liver damage in animal models, but the administration of these drugs along with low doses of lipopolysaccharide (LPS) result in a similar pattern of liver injury as observed in humans. For example, Trovafloxacin (TVX) is a broad-spectrum fluoroquinolone antibiotic, and a study reported that TVX use caused 140 severe hepatic reactions resulting in 14 cases of liver failure. Examination of the case reports suggest that the duration of TVX therapy in patients does not correlate with the toxic response, so TVX hepatotoxicity is classified as idiosyncratic. In rodent models, TVX did not cause liver damage, even at high doses. However, further studies with a normally nontoxic dose of TVX coupled with LPS induced inflammatory stress caused acute liver injury[13,14].

The upcoming sections provide a structured framework presenting DILI in three progressive stages, summarizing the interplay between drugs and the host defence networks that lead to immune system dysfunction.

## STAGES OF DILI

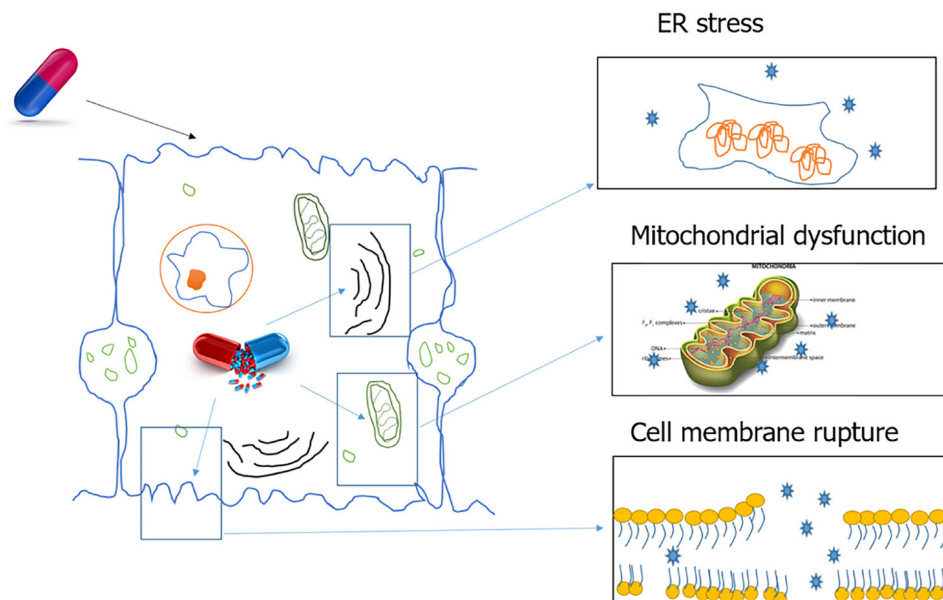
### Initiation of DILI

**Direct initiation:** The metabolism of drugs by phase 1 enzymes results in the production of intermediary metabolites and free radicals, in some instances. These intermediary metabolites may also be unstable and reactive, but they are subsequently neutralized by phase 2 conjugation. DILI is initiated when there is an imbalance between the production of reactive metabolites and their subsequent detoxification[2, 5] (Figure 1).

Certain drugs and reactive metabolites can bind to cellular organelles resulting in loss of function and likely cell death. One such case is the damage caused by drugs acting on the endoplasmic reticulum (ER). The ER plays an important role in protein synthesis, folding, assembly, trafficking, and regulation of intracellular calcium homeostasis. Drug related oxidative stress can disturb ER function and lead to the accumulation of unfolded proteins in the ER. This process is termed ER stress. A variety of common drugs cause ER stress, including paracetamol, lopinavir, ritonavir, saquinavir, nelfinavir, atazanavir, and amprenavir[15].

During drug metabolism, free radicals are released that are normally detoxified by cell defence mechanisms. Excessive free radical generation can be caused by enzyme induction or genetic defects in enzyme systems. Free radicals damage the cellular organelles and the lipid bilayer, which results in amplification of damage. Lipid





**Figure 1 Initiation of drug-induced liver injury - Direct damage by drug and metabolite.** Drugs and their metabolites damage organelles and cell membrane of liver cells causing damage. ER: Endoplasmic reticulum.

bilayer damage can lead to the release of cytosolic components and alarmins that attract the liver's resident immune cells. This initial immune response can amplify the sterile damage. Some of the alarmins associated with DILI are high mobility group box 1, S100 proteins, hepatoma-derived growth factor and heat shock proteins[16-20].

Free radicals can also damage the mitochondrial membrane leading to cell dysfunction and death. Mitochondrial dysfunction includes disruption or disturbance to different metabolic pathways and damage to mitochondrial components. In addition, these mitochondrial alterations can have several deleterious consequences, such as oxidative stress, ATP depletion, triglycerides accumulation, and necrotic cell death[21].

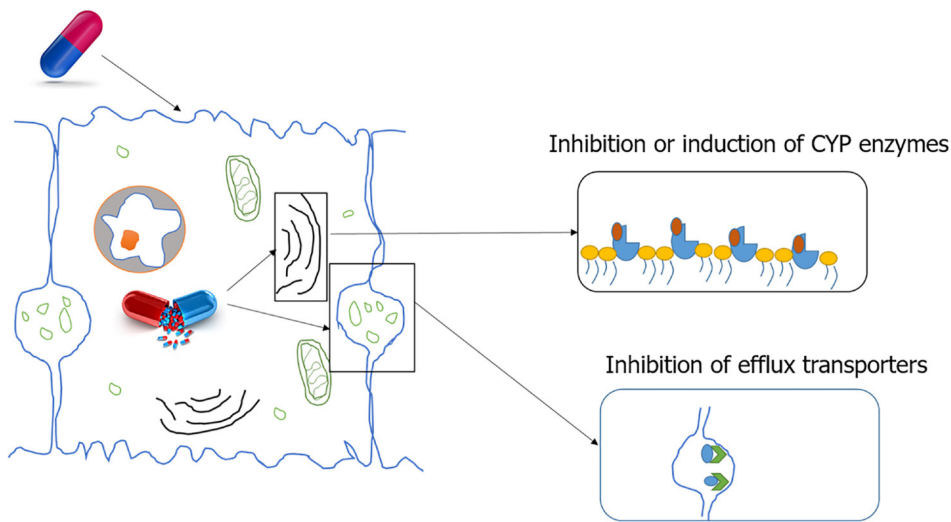
**Indirect initiation of DILI:** There are two main mechanisms of indirect initiation of DILI. Inhibition of efflux transporters. Bile salt export pump (BSEP) is a member of the ABC transporter superfamily located in the canalicular membrane of hepatocytes. BSEP is responsible for the biliary excretion of bile acids. Drug metabolites inhibit BSEP function, resulting in toxicity. One such metabolite, Troglitazone sulphate, a metabolite of troglitazone, inhibits BSEP mediated taurocholate transport which contributes to troglitazone toxicity. Other potent BSEP inhibitors with the potential to cause DILI include cyclosporin A, bosentan, sulindac, rifamycin, and glibenclamide[2, 22].

**Enzyme induction:** Paracetamol is known to cause liver injury through enzyme induction due to CYP2E1 induction by ethanol. A minor percentage of ethanol is metabolised by CYP2E1. When ethanol and paracetamol are taken simultaneously, ethanol slows the degradation of the CYP enzyme increasing its half-life from 7 h to 37 h. Until ethanol is present in the body more CYP2E1 is induced and a portion is blocked from paracetamol for ethanol metabolism. Once ethanol is completely removed, CYP2E1 enhances paracetamol metabolism resulting in the excess production of toxic intermediary metabolite, NAPQI, causing liver injury[2,23] (Figure 2).

## PROGRESSION

The initiation of DILI does not necessarily result in adverse outcomes. In experimental models, the progression of DILI mainly depends on the persistent and recurrent assault by the toxins that deplete the liver's resources leading to irreversible damage. This is unlikely at the therapeutic dose of most drugs, as the liver has highly developed protective and regenerative mechanisms. Experimental and clinical data suggest that a myriad of host and drug-related factors contribute to the progressive dysfunction of survival mechanisms that lead to DILI. This is further complicated by





**Figure 2 Initiation of drug-induced liver injury - Indirect damage by drugs.** Drugs can modulate the functioning of enzymes and transporters involved in drug metabolism and elimination that may lead to toxicity.

the fact that each drug can cause multiple patterns of liver disease, implying an important role for host-drug interactions in the progression of DILI. Immune dysfunction is a major determinant of hepatic cell death and DILI progression[2,4,6,24-26].

This section covers the two main mechanisms of immune reactions induced by drugs and the influence of host factors on them.

### **Immune allergic DILI**

A drug or its metabolites alone cannot activate an immune response due to their small size, but a drug's reactive metabolites or the drug itself can bind to cellular proteins and form protein-drug adducts that elicit an immune response. In normal individuals, this complex is degraded by cellular detoxification but in susceptible individuals, these adducts act as immunogens and are taken up by antigen-presenting cells and presented by major histocompatibility complexes to helper T cells, and further activation by cytokines stimulates an immune response and anti-drug antibodies are also produced, resulting in extensive death of cells where the drug has accumulated[6, 27-29] (Figure 3).

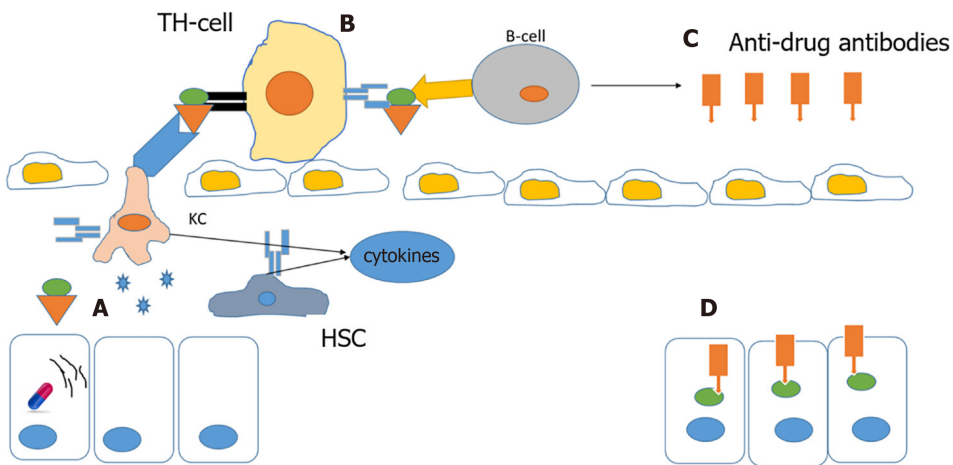
It is hypothesized that ER stress is a contributing factor for this type of reaction. Accumulation of drug/metabolite causes ER stress, which results in misfolding of proteins. These misfolded proteins are more susceptible to drug-protein adduct formations that elicit an immune response[15].

An example of this type of reaction is abacavir, a reverse transcriptase inhibitor employed in the treatment of AIDS, which causes a rare, but serious hypersensitivity reaction that resembles an immune allergic drug reaction. Several genetic variants in the HLA regions are identified as risk factors for DILI, the incidence of hypersensitivity reactions to abacavir is markedly elevated in subjects who carry the B\*57:01 variant in the human leukocyte antigen B (*HLA-B*) gene. Furthermore, carriers of this genotype are at increased risk of flucloxacillin-induced DILI. Studies have shown an association between HLA-B1\*15:01 and amoxicillin/clavulanate DILI. The HLA-B\*35:02 allele is reported to have a significant association with minocycline DILI[10,25,30, 31]. DILI caused by other drugs such as amoxicillin-clavulanate, lumiracoxib, ticlopidine, lapatinib, and ximelagatran is also associated with HLA genotypes, suggesting an important role of the immune system in DILI[25,31].

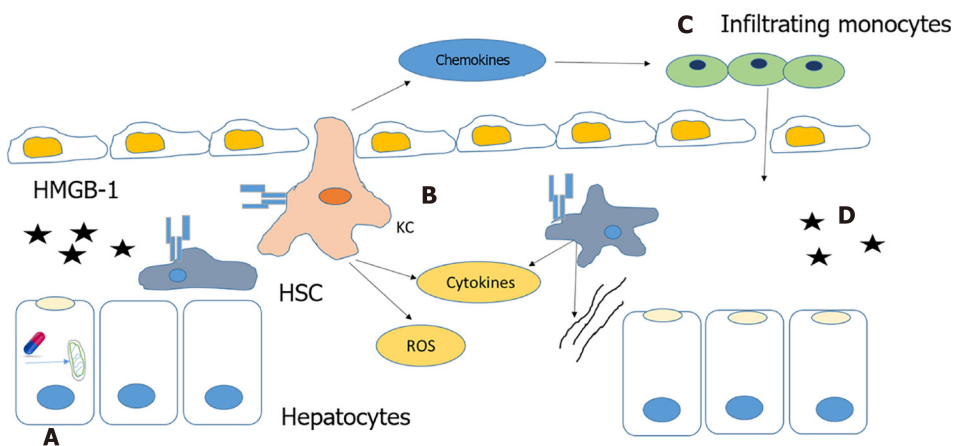
### **Autoimmune DILI**

Autoimmune DILI is caused by the release of alarmins from necrotic cells or cells with leaky cell membranes. This results in the activation of innate immune cells. Alarmins are rapidly released following necrotic cell death that are not released by apoptotic cells. The immune system also can be induced to produce and release alarmins to recruit and activate innate immune cells[19,32] (Figure 4).

Mitochondrial dysfunction is reported to play a critical role in the pathogenesis of autoimmune DILI. NSAIDs, such as diclofenac and nimesulide, and other drugs can cause mitochondrial dysfunction that leads to the formation of the mitochondrial



**Figure 3 Immune allergic drug-induced liver injury.** A: Endoplasmic reticulum stress by drug, causes misfolded protein resulting in cell death and release of stress signals and drug-protein complex. Kupffer cells ingest the drug-protein complex to T-helper cells; B: T-helper cells process it and present it to B-cells; C: B-cells produce anti-drug antibodies; D: These antibodies target the tissues, where drug is accumulated. KC: Kupffer cell; HSC: Hepatic stellate cells.



**Figure 4 Mechanism of autoimmune drug-induced liver injury.** A: Drug causes mitochondrial dysfunction resulting in cell death and release of HMGB-1 and other stress signals; B: Kupffer cells and Stellate cells get activated. Release cytokines, chemokines and toxins; C: Chemokines attract monocytes; D: Amplification of injury and cell death. KC: Kupffer cell; HSC: Hepatic stellate cells; ROS: Reactive oxygen species.

permeability transition pore (MPTP). MPTP formation is induced by increased oxidative stress that results in a dissipation of membrane potential, uncoupling of oxidative phosphorylation leading to necrotic cell death and the release of alarmins[18, 21,33].

HMGB-1 is an alarmin released by necrotic cells that binds to TLR4 receptors of kupffer cells (KCs) and hepatic stellate cells (HSC), and activates them. Activated KCs produce mediators that directly induce cell death, such as tumor necrosis factor (TNF)- $\alpha$ , Fas ligand and reactive oxygen species, or indirectly cause death through the recruitment of neutrophils by cytokines and chemokines like IL-1 $\beta$  and CXCL2. Production of chemokine, CCL2 (MCP-1) recruits monocytes from the bone marrow to the liver. These infiltrating monocytes produce inflammatory chemokines resulting in the activation of HSCs and the promotion of fibrosis[18,34].

Host sex and sex hormones influence immune response. Studies have shown that female patients with DILI are at higher risk of developing acute liver failure (ALF) with more severe hepatitis and higher levels of pro-inflammatory cytokines. In a halothane-induced experimental DILI model, oestrogen reduced liver injury while progesterone increased liver damage, both hormones influenced immune response. Another important factor affecting DILI is race. A study reported that African-Americans are at a higher risk of developing chronic DILI, while Asian individuals are at increased risk of ALF, liver-related death, or damage that precipitates a need for liver transplantation[4,7,10,24,35].

## ADVERSE OUTCOMES

In normal individuals, DILI resolves completely without any residual liver injury. But there are three major exceptions. They are ALF, cirrhosis and acute-on-chronic liver failure (ACLF). These conditions are relatively rare but severe and may result in death or require a liver transplant.

### ALF

Even in the absence of pre-existing liver disease, drugs can cause a rapid loss of liver function either directly, as seen in overdoses, or through inflammatory cell mediated mechanisms such as cytokine overproduction. Drug-induced ALF is defined by the signs or symptoms of hepatic failure and encephalopathy during the course of acute DILI. The time to onset of ALF after the start of a medication can vary from a few days to months, but not exceeding six months[4,24,36-38].

In Western countries, paracetamol overdose is the most common reason behind ALF. In India, anti-TB regimens with isoniazid, rifampicin and pyrazinamide are reported as the leading cause of ALF. Other drugs that are reported to cause ALF include phenytoin, carbamazepine, valproate, nitrofurantoin, propylthiouracil, disulfiram, diclofenac, ketoconazole, flutamide, sulphonamides, terbinafine, fluoroquinolone antibiotics and macrolide antibiotics. Drug-induced ALF is a major cause for withdrawal from the market or restricted use of a medication (troglitazone, bromfenac, nefazodone, halothane, telithromycin). ALF occurs in cases with acute hepatocellular injury with characteristics similar to acute viral hepatitis[10,23,39-41].

Paracetamol is responsible for more than 50% of drug related ALF and about 20% of liver transplant cases in the United States[42]. In case of paracetamol overdose, the drug metabolite NAPQ1 depletes GSH and causes organelle damage, the most significant resulting in mitochondrial stress. Thereby the NAPQ1 accumulation triggers necrosis[43,44]. Hepatocyte necrosis passively releases various DAMPs such as HMGB-1, HSP and DNA fragments. These DAMPs activate the resident immune cells such as Kupffer cells and natural killer (NK) cells. Cytokines and chemokines such as TNF- $\alpha$ , IL-1 $\beta$  and CCL2 produced by the activated immune cells and the DAMPs enter systemic circulation and cause infiltration of neutrophils and monocytes into the liver. In conditions of sterile injury, the immune cells function to clear the dead cells by producing chemokines and free radicals to digest it. Once the cellular debris is cleared the immune cells undergo phenotypic change and support in liver regeneration. However, in case of paracetamol overdose, the overwhelming amount of cellular debris and DAMPs causes excess immune activation, whose products such as superoxide, nitric oxide and peroxynitrite result in further amplification of liver injury leading to massive necrosis and organ failure[45-48].

### Cirrhosis

Cirrhosis is characterized by islands or nodules of regenerative parenchymal cells surrounded by excessive deposition of fibrous tissue and portal hypertension. Cirrhosis is rarely the initial manifestation of DILI and is most often a cumulative response to long-term exposure to hepatotoxic drugs. It usually occurs at least six months after starting the drug treatment. The time to onset of cirrhosis due to medications is typically long; at least 6 month after starting the medication but usually several years afterwards. The drugs that are most commonly cause cirrhosis are vitamin A, amiodarone, statins, tamoxifen, valproic acid, fibrates, and methotrexate[4, 25,26,49-51]. Drugs such as dantrolene, phenytoin, trazadone and nitrofurantoin are also associated with chronic hepatitis with autoimmune features that may lead to cirrhosis[52-54].

Amiodarone is a benzofuran derivative mainly used in the treatment of arrhythmia. The safety of long-term use of amiodarone is well established however there are several reports of reversible and irreversible liver injury from its long-term use. Even though rare amiodarone can cause asymptomatic continuous liver injury that has histological features similar to alcoholic hepatitis such as nodular formation, fibrosis, steatosis and neutrophil infiltration[55-61]. Due to its lipophilic nature and long half-life, amiodarone accumulates in the hepatocytes affecting cellular organelles such as ER and mitochondria causing misfolding of proteins. Amiodarone affects the cholesterol metabolism by blocking enzymes emopamil binding protein and dehydrocholesterol reductase 24. As cholesterol plays an important role in maintaining membrane fluidity and composition this affects the function of potassium channels and other membrane proteins resulting in "lipid traffic jam"[62-67]. The immune cells in the liver get activated in response to cellular debris, misfolded

proteins and accumulating cholesterol precursors such as desmosterol[63,66,68]. Unless diagnosed in an early stage, this leads to irreversible end stage liver disease[62, 69].

### Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) as the name suggests is characterized by ALF due to a different cause in patients with chronic liver disease (compensated) resulting in short term mortality. It consists of two components: a chronic underlying liver disease and an acute trigger[70,71]. Devarbhavi *et al*[72] reported that drugs contributed to 10.5% cases in the Asia-Pacific region. Among these drugs, the most common culprits were complementary and alternative medications (71.7%), followed by anti-TB drug combination therapies (27.3%). Anti-TB drug isoniazid is also observed to cause severe hepatitis that leads to liver failure[72-74].

Studies suggest that excessive focal liver and systemic inflammatory response play a significant role in the development of ACLF. Reports have shown high levels of cytokines in patients with ACLF. This may be due to the activation of monocytes and macrophages in response to DAMPs, microbial toxins or drug adducts[19,75,76].

Paracetamol induced liver failure in patients with alcoholic hepatitis is a typical example of drug induced ACLF. Alcoholic hepatitis is reported in approximately 25% of the cases of ACLF. The trigger due to paracetamol toxicity can occur in two ways- the first is due to direct toxicity by paracetamol and the second due to immune response that is secondary to the hepatocellular damage due to the direct toxicity. The activation of innate immune response due to the paracetamol acute toxicity results in upregulation of cytokine and chemokine production that initiates severe systemic inflammation, liver damage and mortality[70,75,77,78].

The dysregulation in innate immune response plays important roles in disease progression as well as disease severity. In the liver, systemic inflammation plays a significant role in the development and course of chronic alcoholic hepatitis. Similar to the acute toxicity, immune activation in alcoholic liver disease results in activation of resident Kupffer cells and dendritic cells as well as the infiltrating immune cells- monocytes and neutrophils lead to progression towards fibrosis and cirrhosis. This disrupts the liver architecture and function setting stage for liver failure, that can be actuated by an acute trigger[75,78,79].

## CONCLUSION

Drugs and their metabolic products can cause liver damage through multiple mechanisms. Under normal conditions, the liver is well equipped to neutralize potential drug-related damage, but in susceptible individuals, this same drug use can result in severe liver injury. This is further amplified by a dysfunctional immune responses that is influenced by host factors like genetics, age and sex. The severe adverse outcomes of DILI are ALF, cirrhosis and acute-on-chronic liver injury. All these injuries are associated with concurrent immune dysfunction. A better understanding of immune mediators may offer new targets for the management of DILI. Individualized therapy that focuses on early detection of risk factors, triggers and stage of the liver injury may play a significant role in effectively attenuating this disorder.

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