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REVIEW

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A brief overview of drug-induced liver damage

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Abstract

Drug-induced liver injury (DILI) is a prevalent disorder that can be led on by almost all drug types. The majority of benign DILI cases become better after drug discontinuation. To stop the development of acute or chronic liver failure, it is crucial to identify and get rid of the offending substance as soon as feasible. DILI does not have any identified risk factors, but certain people may be more susceptible due to genetic vulnerability and previous liver disease. Some patients may exhibit indications of systemic hypersensitivity, even though the majority of patients have clinical symptoms that are the same as those of other liver illnesses. Rapid drug withdrawal and supportive care aimed at reducing uncomfortable symptoms comprise the treatment for drug- and herbal-induced liver damage.

Keywords Liver injury, Drug, Hypersensitivity, Toxicity, Serum biomarkers

Introduction

The liver plays a remarkable range of crucial functions in maintaining, running, and homeostasis in the body. It is necessary for almost every metabolic process that promotes growth, disease prevention, nutrition delivery, energy production, and reproduction [1]. The key functions of the liver include glucose, protein, and lipid metabolism, as well as detoxification, bile secretion, and vitamin storage. As a result, maintaining a functioning liver is critical for general health and well-being [2].

Hepatotoxicity refers to liver damage caused by substances. Certain medications have the potential to injure the organ when taken in excess or even when administered within therapeutic parameters. Hepatotoxicity can also be attributed to other chemical agents utilized by industry and laboratories, natural compounds (such as microcystins), and herbal remedies. The term "hepatotoxins" refers to compounds that are toxic to the liver. Liver illness is the most common reason for a medicine recall, which has been related to over 900 different medications. Subclinical liver damage caused by toxins typically manifests solely as well as abnormal liver enzyme testing. Drug-persuaded liver damage reckons for about 50% of all the acute liver failures and 5% of all hospital admissions [3].

Adverse drug reactions are a significant factor in liver damage, which may necessitate stopping the offending medication, staying in the hospital, or even undergoing liver transplantation [4]. Indeed, the most prevalent cause of abrupt failure of the hepatic system in the USA is drug-persuaded hepatotoxicity [5]. The liver is a target for medication-induced harm because it concentrates and metabolizes the bulk of medicines. Acetaminophen (paracetamol) is the hepatotoxic medication that is most frequently researched. However, a wide range of pharmacological chemicals, including anaesthetics, anticancer therapies, antibiotics, antituberculosis medicines, antiretrovirals, and cardiac medications, might injure the liver. Numerous conventional medical treatments and natural cures may also be the reason for hepatotoxicity.

The liver damage caused by drugs is characterized as acute or chronic, as hepatitis, cholestatic disease, or a combination of the two, based on the degree of the injury

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and histological findings. Hepatocellular necrosis distinguishes the hepatitis structure and is associated with a bleak prognosis. Cholestatic medication may provoke three types of acute damage. Mild cholestasis is caused by irregular bile secretion and does not cause severe hepatic damage. Cholestatic cirrhosis (mixed type) is cholestasis with parenchymal liver injury. The occurrence of bile duct damage or cholangitis defines a third kind of acute cholestasis. Drugs may induce persistent cholestasis by means of two other approaches. The two conditions are secondary sclerosing cholangitis and extrahepatic bile duct obstruction, often known as vanishing bile duct syndrome and bile duct obstruction, respectively [6–9].

Mechanism of drug-induced liver injury

Drug-persuaded liver injury can be attributed to either the immediate toxicity of the delivered medication or its metabolites or by immune-triggered mechanisms (Fig. 1). Despite the aforementioned processes have distinct characteristics, they may be intertwined. A secondary inflammatory response, for example, may accelerate early hepatocyte destruction triggered by direct drug toxicity. It is also important to understand that oral medications that significantly speed up the liver's metabolism are more likely to result in DILI [10]. The overwhelming majority of medications are lipid-soluble and undergo degradation in the liver prior to ending up in bile or urine. The phase I reaction, typically orchestrated through enzymes found in the liver's cytochrome p450 framework, is the first phase in the absorption of drugs [11]. This stage releases bioactive intermediates which can interact with multiple organelles (such as mitochondria) and trigger hepatocyte collapse and death of cells [12]. In adhering to phase II procedures, glucurono, glutathione, or sulfa linkages disable these potentially toxic intermediates. For averting hepatotoxicity, the rate of production of phase I compounds should not go above the liver's inactivation competence. Depletion or a lack of chemical compounds utilized in phase II interaction processes could result in potentially dangerous metabolite buildup. This is prevalent in patients who consume alcohol while consuming paracetamol. Even very small amounts of paracetamol may trigger serious liver damage in the present instance [13, 14].

The limitation of the respiration chain of mitochondria is one of the primary steps in DILI, which leads to a spike in the amount of reactive oxygen species (ROS) and a fall in adenosine triphosphate (ATP) [15]. A variety of mechanisms trigger mitochondrial breakdown. The mitochondrial oxidative chain is hampered by decreased ATP generation and more substantial ROS levels [16]. Moreover, particular drugs, such as amiodarone, could inhibit fatty acid oxidation, which results in steatosis and steatohepatitis [17]. Dideoxynucleotide analogues, which are frequently administered to treat HIV, can disrupt mitochondrial DNA synthesis [17, 18]. Drug toxicity can also arise from the opening of the mitochondrial permeability transition pore (MPTP), which is intimately linked to cell death [19].

Intracellular disruption may arise from the combination of the formation of ROS, diminished ATP levels, and the earlier characterized mitochondrial breakdown.

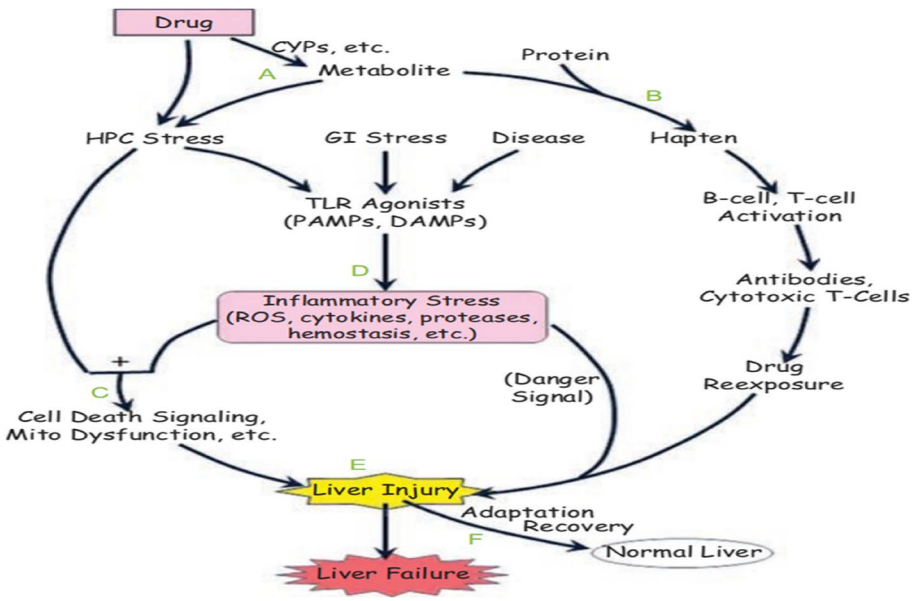

Fig. 1 Mechanism of drug-induced liver injury

Hepatocytes eventually perish because of apoptosis, an action that needs energy (ATP), which could not be attainable due to mitochondrial breakdown or poor ATP storage. Hepatocyte loss may occur via the necrotic mechanism in this instance, leading to further liver inflammation [20].

Immune-intervened injury could possibly represent an essential aetiology of DILI, which is identified by an extended gap between the administration of medication and detection of liver toxicity. Both the adaptive as well as innate immune systems can be observed in the liver. Drugs with bioactive drug metabolites attach to cellular proteins and are recognized by MHC molecules on cells that express antigens [21]. This association leads to a reaction from the immune system targeted towards liver cells. For instance, halothane causes the development of antibodies that block cytochrome p450 CYP2E1. Thus, a diagnostic test involves looking for drug-induced antibodies in a patient's blood. Locally generated cytokines and ROS, in conjunction with antibody-mediated cell death, boost liver damage [22]. Immune-intervened DILI, originally proved with halogenated anaesthetics, could become more frequent and deadly with repetitive administration of the drug [23]. A detailed drug history provides vital details on complications that have occurred upon past treatment of every drug.

Pathogenesis

Particularity DILI is a multivariate origin, that signifies that an array of internal as well as environmental factors could affect how an adverse outcome appears in an individual at risk. Please consult other exceptional analyses that go beyond the purview of this review for an in-depth examination of the mechanisms related to specific hepatotoxicity [24, 25]. This DILI was triggered by a variety of risk variables, such as host attributes, drug-dependent issues, and environmental conditions. Age has been proved to influence DILI resistance to specific drugs [26] (such as isoniazid) and is believed to be one of the host-specific variables related to the DILI phenotype, and further age correlated to an elevated cholestatic pattern of hepatic damage [27, 28]. Furthermore, younger age has been related to hepatocellular pattern. It is something unique. However, opinions on the impact gender plays as a potential factor for DILI are extensively uneven. Pathogens including minocycline and nitrofurantoin are associated with greater risk in women [29]. Additionally, women are more inclined than men to experience drug-induced acute liver failure (ALF) [30, 31]. Risk factors for DILI development include host variables, drug-dependent factors, and environmental conditions (Fig. 2). Age plays a role in susceptibility to DILI caused by specific drugs, such as isoniazid. The cholestatic pattern of liver damage is associated with older age, while the hepatocellular type is associated with younger age [25].

The effect of the primary illness on DILI vulnerability is uncertain yet probably applies only to a small number of medications. Obesity and diabetes, which are fundamental components of syndrome X, have been connected to both an increased risk and a worsening of drug-induced fatty liver inflammation in people taking methotrexate and tamoxifen, respectively [32, 33] Other than ongoing

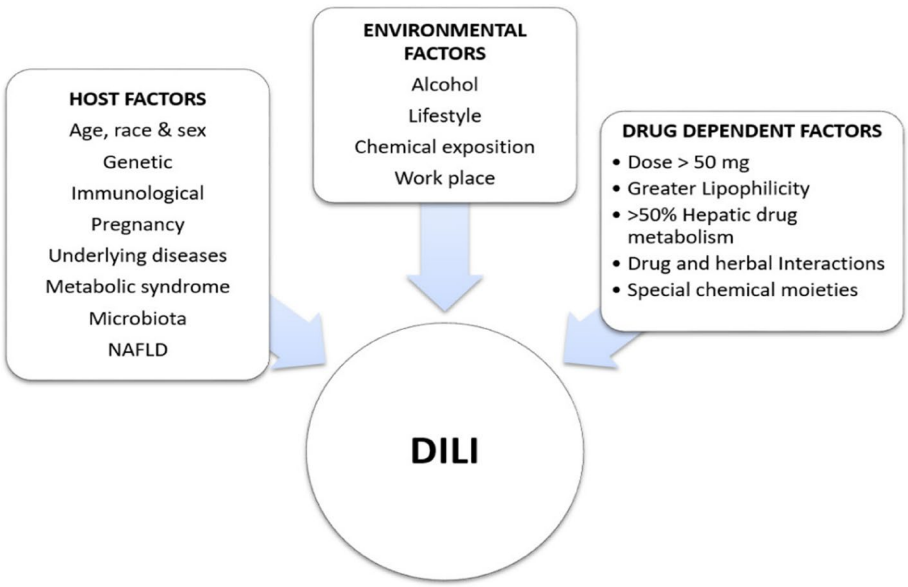

Fig. 2 Drug-induced liver injury (DILI) has a complex aetiology with several risk factors

infections with hepatitis B or C and DILI correlated to anti-HIV and anti-tuberculosis medication, there is very little evidence that indicates pre-existing liver illness forms a risk factor for having DILI [34–36].

DILI can be evaluated using parameters such as damage improvement after drug removal, a compatible drug signature, adequate histology results, or immunoallergic characteristics (Fig. 3). Although liver biopsy is not commonly performed to evaluate suspected DILI, it can offer valuable information regarding the severity and type of liver injury, as well as rule out other potential causes of liver disease [37].

Drugs can induce several types of liver damage [38–40]. Drugs can impact all cells in the liver (Fig. 3). Drugs can cause almost any type of liver injury. This helps to explain why physicians, health authorities, and pharmaceutical corporations are concerned about medication hepatotoxicity.

Specific evidence supporting alcohol intake as a potential cause for DILI is available only for a few medications, including isoniazid, methotrexate, and halothane [41]. Drug characteristics that may increase the risk of specific DILI include daily doses > 50 mg, hepatic metabolism > 50%, increased lipophilicity, and mitochondrial and bile salt export pump (BSEP) examples including combinations of inhibition [42–45].

Biomarkers for diagnosis and prognosis

DILI strives to conduct globally synchronized research in an attempt to generate more precise and sensitive biomarkers in order to overcome the hinders of traditional methods for diagnosis. A biological marker is a quantitative marker of a biological condition or symptom. Chemicals that are objectively evaluated and analysed as markers of healthy biological activities, detrimental processes, or pharmacological responses to therapies are further included in the definition [45]. DILI biomarkers can be distinguished as mechanistic, epigenetic (micro RNA, exosomes), or genetic (Table 1). The discovery and validation of new, heavily protein-based biomarkers are being investigated with the goal to improve DILI detection early on, acquire mechanistic awareness, and predict injury prognosis due to challenging cell damage pathways in DILI.

The levels of serum liver enzymes and bilirubin that are measured are the most often implemented markers for diagnosing liver damage in all countries all over the world. Cytolytic enzymes (ALT, AST), cholestatic enzymes (GGT, AP), and cholestatic enzymes are all advantageous. Yes, nonetheless there are limitations. These are not especially related to DILI and can be exacerbated by any type of liver trouble. Damage to sections other than the liver, such as bone and muscle, may result in spikes in aminotransferases and alkaline phosphatase. In addition, because these serum markers do not diffuse into the bloodstream until after the damage has taken place, they can be utilized for predicting the potential toxicity of treatments before or in the earliest phases of toxic liver damage. You cannot. Finally, regardless of taking the medication, higher liver enzymes may revert to normal.

DILI determines, characterizes, and verifies an extensive variety of mechanistic (prognostic) biomarkers. Studies of APAP-induced liver damage and specific DILI

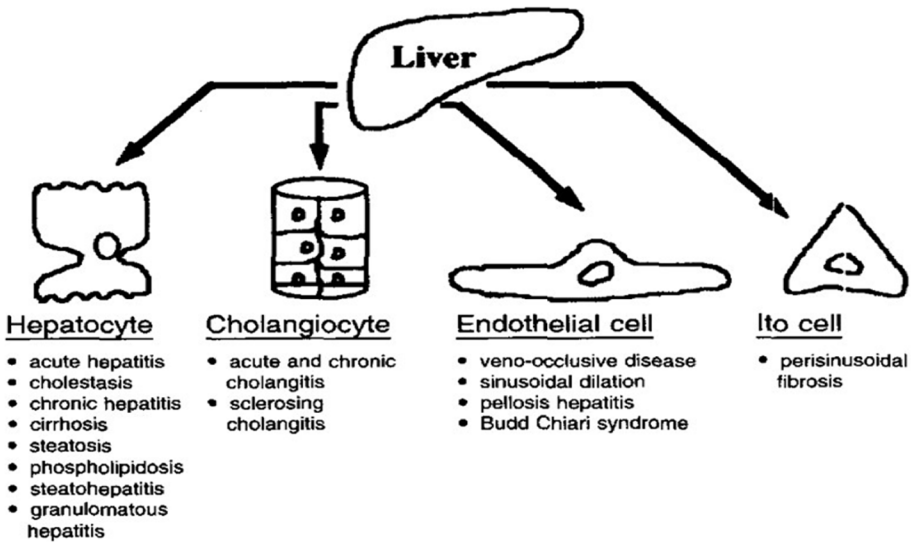

Fig. 3 Cells involved in drug-induced liver injury

Table 1 A list of biomarkers and techniques for evaluating potential liver damage brought on by drugs

LIVER INJURY SERUM BIOMARKERS

MARKERS AND SCALES	MECHANISM	ADVANTAGES	LIMITATIONS
Alanine Transaminase(ALT)	Released from hepatocytes that are damaged	ALT1 is highly specific to liver Prognostic value: Hy's law	Damage has already occurred.
Aspartate Aminotransferase(AST)	Damaged hepatocyte release	Modified Hy's Law prognostic value (nR)	No liver-specific damage has already occurred.
Alkaline Phosphatase(ALP)	Injuries to the canalicular membrane or biliary epithelial cells	Cholestatic phenotype	There is no liver-specific (bone, salivary glands, intestinal, or biliary)
International Normalized Ratio(INR)	Impairment of hepatic function		Deficiency of vitamin K; anticoagulants
Bilirubin	Impairment of hepatic function Changes in the generation, processing, or release of bilirubin.	Prognostic value: Hy´s Law	Nothing specific. There are two types: indirect (unconjugated) and direct (conjugated).
Albumin	Impairment of hepatic function		Malnutrition, nephrotic syndrome, cirrhosis (any cause)

MECHANISTIC BIOMARKERS

MARKERS AND SCALES	MECHANISM	ADVANTAGES	LIMITATIONS
Glutamate deshidrogenase GLDH	Mitochondrial dysfunction	Specific to the liver Early detection is critical. It is useful in distinguishing between muscle and hepatic injuries.	
Malate deshidrogenase MDH	MDH is a periportal enzyme whose presence in the blood suggests that the liver has been damaged.	Excellent association with ALT	It is not particular to the liver.
High-morbility group box 1-HMGB1 (Hyperacetilated form)	DAMP (Damage-Associated Molecular Pattern) molecule Immune activation marker	Greater sensitivity predicts outcome	APAP DILI
Glutathione S transferases (GSTs) and alfa-GST	Reactive compounds are metabolised by phase II detoxification enzymes.	DILI susceptibility is conferred by GST gene polymorphisms. More specific and sensitive than alpha-GST Increased earlier than ALT	APAP DILI
Macrophage colony-stimulating factor receptor 1 (MCSFR1)	Marker of immune activation	Prognostic indicator Death and transplant risk factors	
Osteopontin (OPN)	Because of the activation of hepatic stem cells, it is linked to liver regeneration.	Prognostic indicator Death and transplant risk factors	
Alfa-fetoprotein	Because of the activation of hepatic stem cells, it is linked to liver regeneration.	Prognostic indicator Death and transplant predictors	Worse than Osteopontin in terms of performance

Hepatotoxicity is defined by the WHO as	
Class 1 (Mild)	<2.5 times ULN (ALT 51–125 U/L)
Class 2 (Mild)	2.5–5 times ULN (ALT 126–250 U/L)
Class 3 (Moderate)	5–10 times ULN (ALT 251–500 U/L)
Class 4 (Severe)	>10 times ULN (ALT > 500 U/L)

in both preclinical and clinical settings have shown that this measure rises quicker than ALT and permits the determination of the fraction of hepatocytes undergoing apoptosis versus necrosis [46–50].

Models of intrinsic DILI

Technically speaking, the unique DILI animal model is easy to use. In most cases, hepatotoxicity can be achieved simply by administering high doses of the targeted drug to the animal. However, proper application of these models requires a fundamental understanding of the respective toxicological processes. Table 2 contains a selection of the most commonly used intrinsic hepatotoxicity models. In specific DILI studies, paracetamol (APAP) and carbon tetrachloride (CCl4) are the two most commonly used models.

Updates in treatment and prevention

Removing the offending substance and offering supportive therapy are common treatments for DILI. Other than intravenous N-acetylcysteine (NAC) [51], enhancing transplant-free survival in acute liver failure without acetaminophen use has few alternatives. Numerous articles about the use of NAC to treat DILI have been published in the last year [49, 50]. The efficacy of NAC in treating anti-TB-DILI was evaluated in a randomized controlled study. While NAC did not shorten the time to ALT < 100 U/L in individuals with anti-TB-DILI, the study did find that it considerably shortened hospital stays—from 18 to 9 days—when compared to placebo. Alternative therapies for DILI, such as clausenamide (CLA) and 18β-glycyrrhetinic acid derived from licorice, have been studied recently. It has been demonstrated that CLA, an extracted substance from a well-liked fruit tree in southern China, enhances hepatic glutathione synthesis [52]. A study on the effects of CLA on the liver discovered ferroptosis, a type of hepatic cell death that occurs with apoptosis in DILI [53]. This study found that CLA can prevent ferroptosis and thereby DILI. To completely comprehend the process of ferroptosis and how it affects DILI in clinical practice, more research is required. Derivatives of licorice are frequently used in China, Japan, and other Asian nations to treat suspected DILI.

Licorice's primary ingredient, 18β-glycyrrhetinic acid, is commonly used in Chinese medicine for its antioxidative, anti-inflammatory, antiviral, and immune-regulating characteristics [54]. Studies reveal that 18β-glycyrrhetinic acid can shield the liver by reducing inflammation, oxidative stress, and acute liver injury while also preventing hepatic fibrosis [55]. While 18β-glycyrrhetinic acid and steroid hormones are comparable, because of their low water solubility, their hepatoprotective effects are yet only studied in lab settings.

Table 2 Several significant animal models of liver damage brought on by drugs

Drug	Favoured species	Typical dose	Strengths	Weaknesses
Acetaminophen	Mouse	200–600 mg/kg	Easily accessible and therapeutically conforming	Probable metabolic interference
CCl4	Rat, mouse	1–2 mL/kg (10–20 mmol/kg)	Simple to use, it may also represent chronic DILI	Probable influence with assimilation; little therapeutic congruity
Thioacetamide	Mouse, rat	100–300 mg/kg	Easily accessible	Probable influence with assimilation; little therapeutic congruity
Furosemide	Mouse	200–500 mg/kg	Easily accessible	Probable influence with assimilation; little therapeutic congruity
Bromobenzene	Mouse, rat	0.5–1 mL/kg (5–10 mmol/kg)	Easily accessible	Probable influence with assimilation; little therapeutic congruity
Isoniazid, rifampicin, pyrazinamide	Mouse, Rat	INH (7.5 mg/kg), RMP (10 mg/kg), PZA (35 mg/kg)	Easily accessible	Probable influence with assimilation; little therapeutic congruity
Galactosamine	Rat	500 mg/kg	Easily accessible	Probable influence with assimilation; little therapeutic congruity
Halothane	Mouse		Easily accessible and therapeutically conforming	Probable influence with assimilation; little therapeutic congruity
Diclofenac	Rats	50 mg/kg	Easily accessible and therapeutically conforming	Probable influence with assimilation; little therapeutic congruity
Ketoconazole	Rats	20 mg/kg	Easily accessible and therapeutically conforming	Probable influence with assimilation; little therapeutic congruity
Streptozotocin	Rats	35 mg/kg	Easily accessible and therapeutically conforming	Probable influence with assimilation; little therapeutic congruity

DILI miscellany

Several studies suggest using hepatocyte loss to predict DILI severity and hepatotoxicity during preclinical drug screening. To calculate hepatocyte loss from DILI under various ALT elevation patterns, Chung et al. used DILIsym [55]. Four patterns of ALT were replicated by the authors during DILI: numerous peaks with growing and falling ALT, slow onset and moderate decrease, moderate onset and extended reduction (>1 month), and swift onset and rapid decrease. They found that the area under the curve (AUC) of ALT and the ranges of predicted hepatocyte loss for each pattern were independently correlated with the serum ALT peak. DILIsym was used to find this. Nevertheless, they found that by utilizing a unique parameter PALT—which combines peak and AUC—they were able to estimate hepatocyte loss across each time course with more accuracy (ALT_AUC*Peak ALT0.18/105 ((IU/L)2*h) [56]. This is unique in that, although more research is needed before it can be used in real-world human trials, it may supersede Hy's rule as a more accurate method of predicting the severity of DILI and the probability of acute liver failure. The Council for International Organizations of Medical Sciences has released a unanimous resolution [55] about the assessment and reporting of DILI for manufacturers of pharmaceuticals and medical professionals. It includes definitions of the disease and its various phenotypes, an assessment of causality, an evaluation of DILI risk at different stages of drug development, novel biomarkers for liver safety, post-marketing liver safety surveillance, and a section on liver injury related to dietary supplements and herbal remedies, among many other topics related to drug-induced liver injury (DILI). This consensus statement should serve as a fundamental guide for researchers, drug developers, and healthcare practitioners as they continue to explore DILI [57–59].

Conclusion

Hepatotoxicity is an undesirable side effect of practically all therapies. The majority of DILI instances are benign and improve following drug discontinuation. To prevent the progression of permanent liver damage, it is critical to identify and eliminate the contaminating substance as soon as feasible. Although there are no particular risk factors for drug-persuaded liver damage, certain persons may be predisposed due to pre-existing liver disease or genetic susceptibility. Despite the majority of people have clinical symptoms comparable to other liver illnesses, some may develop systemic hypersensitivity symptoms. The treatment for liver impairment caused by drugs and herbal remedies is quick drug withdrawal combined with supportive care to reduce uncomfortable symptoms.

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SR conceived and designed the study, collected and analysed the data, and wrote the manuscript. Ms. ZS contributed to the interpretation of the results, critically revised the manuscript for important intellectual content, and provided final approval for publication.

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