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# Research Process on Drug-induced Liver Injury

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**Abstract:** ***Drug-induced liver injury (DILI) is one of the most challenging adverse drug reactions in clinical practice and new drug development; it is the leading cause of acute liver failure in Europe and the United States, and its incidence has been on the rise in Asia in recent years. With the widespread adoption of multidisciplinary treatment approaches and the advent of an ageing society, the complexity of patients' drug exposure has increased, leading to continuous evolution in the aetiology, clinical phenotypes and diagnostic and treatment pathways of DILI. This study systematically synthesises recent research advances in DILI, providing an in-depth discussion on epidemiology, risk factors and pathogenesis, diagnosis, treatment and prognosis, as well as the specific characteristics of the elderly population and precision prevention and control. It aims to review the latest developments in drug-induced liver injury research, explore its mechanisms, diagnostic and therapeutic strategies in depth, and provide a reference for future academic research.***

**Keywords:** Drug-induced liver injury, Epidemiology, Biomarkers, Pharmacogenomics, Immune-mediated, Elderly**.**

## 1. Introduction

Drug-induced liver injury (DILI) refers to a pathological condition in which prescription medicines, over-the-counter medicines, Chinese herbal preparations, biologics or dietary supplements cause parenchymal liver damage or cholestasis during clinical use [1]. Clinically, DILI can present as anything from asymptomatic mild elevations in transaminases to jaundice, coagulation disorders, hepatic encephalopathy and even acute liver failure (ALF). DILI is not only a significant challenge in clinical diagnosis and treatment, but also a key focus in drug development and pharmaceutical safety regulation. According to statistics, in the United States and Europe, DILI has become a major cause of acute liver failure, with cases of liver failure caused by acetaminophen (APAP) overdose accounting for more than half of all patients with acute liver failure due to DILI in the United States; in China, the incidence of DILI has risen from 2.21 per cent in 2002 to 6.70 per cent in 2022 [2,3]. In the field of drug development, DILI has frequently led to the withdrawal of medicines from the market: the antidiabetic drug troglitazone, which was launched in the United States in 1997, caused acute liver injury in approximately 40 patients and led to the deaths of 26 patients due to severe liver failure, resulting in its eventual withdrawal by the FDA; the non-steroidal anti-inflammatory drug fenoxoprofen was also withdrawn from the market due to severe hepatotoxicity.

DILI is typically classified into three types based on serum biochemical markers: the hepatocellular type (characterised by alanine aminotransferase (ALT) levels ≥3 times the upper limit of normal), the cholestatic type (predominantly characterised by alkaline phosphatase (ALP) levels ≥2 times the upper limit of normal) and the mixed type (meeting the criteria for elevated ALT and ALP simultaneously) [4, 5]. The hepatocellular type of DILI is the most common, accounting for approximately 55–60 per cent in large-scale registry studies, whilst the cholestatic and mixed types each account for around 20 per cent [6]. The different DILI subtypes not only reflect differences in underlying pathophysiological mechanisms but also provide important guidance for prognostic assessment. For example, hepatocellular DILI accompanied by elevated bilirubin levels often indicates a higher risk of acute liver failure, whereas cholestatic DILI, although characterised by pronounced symptoms, has a relatively better long-term prognosis.

Against the backdrop of an ageing population, the number and variety of medicines taken by elderly patients have increased significantly; at the same time, elderly patients often suffer from multiple chronic conditions requiring combination therapy, which increases their risk of developing DILI. Epidemiological studies indicate that the incidence and distribution of DILI subtypes exhibit significant age-dependent differences: in one retrospective study, children accounted for 6.57 per cent of DILI cases, young adults for 24.82 per cent, middle-aged adults for 49.06 per cent, and older adults for 19.54 per cent [6, 7]. However, there are marked differences in distribution patterns between different age groups: in the paediatric group (<18 years), hepatocellular drug-induced liver injury was more common (70.65%), whilst in the elderly group (≥65 years), cholestatic drug-induced liver injury was more prevalent (30.42%) [6]. These findings indicate that age and subtype differences must be fully taken into account in clinical practice and integrated into individualised risk assessment, early warning systems and the formulation of treatment strategies.

In recent years, herbal medicine-induced liver injury (Herb-induced liver injury, HILI) has attracted increasing attention. The results of a large-scale retrospective study covering 308 medical centres in mainland China showed that, among 25,927 confirmed cases of DILI, cases related to herbal medicines and health supplements accounted for as much as 26.8 per cent, representing the leading cause of the condition [8]. Another epidemiological study showed that, among 1,985 patients with DILI/HILI admitted to a military hospital in Beijing between 2009 and 2014, 563 cases (28.4 per cent) were associated with the use of traditional Chinese herbal medicines [9]. In a single-centre analysis conducted at a South Korean hospital, traditional Chinese herbal medicines were the primary cause of DILI, accounting for 43.1 per cent [10]. In a 26-month prospective study conducted in Singapore, liver injury caused by traditional Chinese herbal medicines accounted for 55 per cent [11]. Common Chinese herbal medicines implicated in these reports include He Shou Wu (Polygonum multiflorum), Tripterygium wilfordii, plants of

the Aristolochiaceae family, and herbs containing pyrrolizidine alkaloids (PAs) [12]. It is worth noting that certain Chinese herbal medicines or their active constituents (such as silybin, glycyrrhizic acid and tanshinone) have demonstrated antioxidant, anti-inflammatory and anti-fibrotic effects in experimental and clinical studies, and may be used as adjunctive treatments for drug-induced liver injury and other liver diseases.

From the perspective of Traditional Chinese Medicine (TCM) theory, the onset of DILI is not merely due to the toxic effects of exogenous drugs, but rather the invasion of 'medicinal toxins' or 'pathogenic toxins', which disrupt the balance of qi, blood, yin and yang within the body. According to TCM theory, the liver stores blood and governs the regulation of the flow of qi and blood; this regulatory function not only ensures the normal flow of qi and blood within the liver, but is also closely related to the smooth circulation of qi and blood throughout the body and the body's ability to eliminate toxins. Exogenous drug toxins are regarded as 'pathogenic toxins'; after being metabolised by the liver, they may lead to pathological changes such as the generation of internal damp-heat, impaired circulation of qi and blood, and blood stasis. These pathological changes disrupt the balance of qi and blood in the liver, impairing its functions of regulation, detoxification and discharge [13]. According to Traditional Chinese Medicine, qi stagnation obstructs the flow of qi and blood, thereby leading to an imbalance in the qi mechanisms between the zang-fu organs [14]. Impaired circulation of qi and blood in the liver not only damages liver function but may also affect other organs via the liver, such as causing dysfunction of the spleen and stomach, obstructing the excretory function of the gallbladder, and even interfering with the detoxification and metabolic functions of the kidneys. Therefore, drug-induced liver injury is not merely a problem of the liver itself, but rather the result of systemic functional imbalance across the organs.

Research into DILI has gradually evolved from early clinical epidemiological and pathological observations to the exploration of molecular mechanisms and the discovery of novel biomarkers. Traditional diagnosis relies on liver function tests and histopathological examination of liver tissue; however, these methods lack sufficient specificity and sensitivity, making it difficult to promptly detect the onset or severity of DILI. In recent years, the emergence of multi-omics technologies has significantly transformed this landscape. At the transcriptomic level, relationships have been identified between hepatocyte stress and apoptosis, the misfolded protein response, and the gene expression of bile acid–nuclear receptor (Farnesoid X receptor/Pregnane X receptor/Constitutive androstane receptor, FXR/PXR/CAR) genes, which help to distinguish between differences in the hepatocyte-mediated and cholestatic pathways [15] ; proteomics and proteo-fragomics studies suggest that full-length and caspase-cleaved keratin 18 (Full-length Keratin 18/Cleaved Keratin 18 fragment, M65/M30) can reflect the ratio of necrosis to apoptosis [16, 17], in conjunction with the DILI marker high-mobility group box 1 (HMGB1) isoforms [18, 19] and glutamate dehydrogenase (GLDH) [20, 21], as well as miR-122 [20, 22], can detect mitochondria-mediated damage more specifically at an early stage. Analyses at the metabolomic and lipidomic levels indicate that changes in the bile acid profile (including the ratio of glucose- and taurine-conjugated to secondary bile acids), acylcarnitines and oxylipids are associated with cholestatic liver injury related to the transporters BSEP, NTCP and OATP [23]. This article provides a systematic review of the epidemiological characteristics, risk factors and pathogenesis, clinical manifestations and diagnostic strategies, as well as treatment and prognostic management of DILI, with a particular focus on the specific features of DILI in the elderly population. It aims to serve as a reference for future academic research and to promote the development of precision medicine for DILI.

## 2. Epidemiology of Drug-Induced Liver Injury

The incidence of DILI varies significantly across different countries and regions. Antibiotics are the primary drugs associated with DILI in Europe and the United States, whilst traditional Chinese medicines are the main cause of DILI in the Asia-Pacific region [24]. Several population-based studies and prospective registry studies in European and American countries indicate that, overall, the annual incidence of DILI in these regions is approximately 10–20 cases per 100,000 people. A European multicentre study reported an annual incidence of DILI of approximately 13–19 cases per 10 100,000 people ;A prospective registry study by the US DILI Network indicates that the annual incidence of DILI in the United States is around 10–15 cases per 100,000 people [26] ; furthermore, some studies in Northern Europe have found that the incidence of DILI among hospitalised patients can reach 0.7 per cent [27], reflecting the correlation between the level of exposure to medication during hospitalisation and the risk of DILI.

A multicentre study in China estimated the annual incidence of DILI in the general population to be approximately 23.8 cases per 100,000 people, which is higher than figures reported in Europe and the United States. The proportion of DILI cases among hospitalised patients with liver disease is even higher, reaching 30–40 per cent, and shows an upward trend year on year; this is closely related to China's unique practices regarding the use of traditional Chinese herbal medicines and proprietary Chinese medicines. Surveys in Japan and South Korea also indicate that DILI associated with herbal medicines and dietary supplements accounts for a significant proportion of cases in Asian populations [28]. The epidemiology of DILI also exhibits differences based on gender and age. Most studies suggest that the incidence of DILI is slightly higher in women than in men [1, 29], a finding that is particularly pronounced in immune-mediated cases. With regard to age, the risk of DILI is significantly increased in the elderly due to a decline in hepatic metabolic capacity and the prevalence of polypharmacy. Furthermore, polymorphisms in drug-metabolising enzyme genes across different populations may lead to variations in DILI incidence between different ethnic groups and regions [30, 31].

Overall, although the individual incidence of DILI is relatively low, its impact on public health cannot be overlooked. With the increase in the variety and dosage of medicines, the widespread use of traditional Chinese medicines and supplements, and the accelerating global ageing of the population, the burden of DILI is on the rise. In

the future, it will be necessary to establish more comprehensive drug adverse reaction monitoring networks and multicentre registry systems to accurately assess the true epidemiological characteristics of DILI, thereby providing a basis for personalised medication strategies and public health interventions.

## 3. Risk Factors and Pathogenesis

The occurrence of DILI is usually the result of the combined effects of patient susceptibility and the characteristics of the drug itself. Patient susceptibility plays a central role in DILI. With advancing age, liver volume and blood flow gradually decline, mitochondrial functional reserve becomes insufficient, and cytochrome P450(Cytochrome P450, CYP450)—which is primarily responsible for mediating Phase I drug metabolism—and uridine diphosphate glucuronosyltransferase (UGT)—which is primarily responsible for mediating Phase II drug metabolism—show an overall decline in activity [32, 33] ;Concurrently, reduced plasma albumin levels and muscle mass, coupled with a decrease in glomerular filtration rate, lead to an increase in the proportion of free drug and a prolongation of exposure time in the body, thereby enhancing potential toxicity [34]. Gender differences are also a factor that cannot be overlooked; studies show that women are more commonly affected by immune-mediated DILI, which may be closely related to the regulatory role of oestrogen in bile acid transport, T-cell responses and susceptibility to autoimmunity [29]. The presence of underlying liver disease further lowers the liver's tolerance threshold to drug-induced damage. Chronic HBV/HCV infection, non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease all exacerbate the severity of drug-induced liver injury, whilst pre-existing liver fibrosis may amplify the damaging effects of the same drug exposure. Genetic susceptibility is also one of the key determinants of DILI. Numerous studies have demonstrated a consistent association between HLA-B*57:01 and flucloxacillin-associated DILI [35, 36], and between HLA-A*33:01 and sulphadiazine-associated DILI [37, 38] as well as a consistent association between HLA-B*58:01 and allopurinol hypersensitivity [39, 40] ; furthermore, the NAT2 slow acetylator phenotype may increase the risk of isoniazid-induced hepatotoxicity [41], whilst polymorphisms in genes such as CYP2E1 [42], NAT2 [43], GST and SLCO1B1 [44] and other genes have also been progressively shown to be associated with DILI phenotypes for various drugs. However, genetic susceptibility is not an independent determinant; rather, it interacts with the intensity of drug exposure, the immune environment and the characteristics of the gut microbiota to ultimately determine the severity of DILI.

In addition to patient susceptibility factors, the characteristics of the drug itself and the exposure profile may also influence the occurrence of DILI. In terms of physicochemical properties, high lipophilicity and a large topological polar surface area (TPSA) are often associated with higher levels of hepatic drug exposure and an increased risk of mitochondrial toxicity [45]. Most drugs undergo Phase I metabolism via the CYP enzyme system; the resulting metabolites may bind to proteins or nucleic acids to form adducts, inducing cellular damage or immune recognition; whereas an imbalance in Phase II metabolism, such as glutathione depletion, reduces detoxification capacity and amplifies toxic reactions [44, 46]. Furthermore, drug interactions play a significant role in DILI [47]. Inhibition or induction of drug-metabolising enzymes, competition for drug transporters, competition for protein-binding sites, and interference with bile acid transport can all significantly alter intrahepatic drug exposure levels, thereby increasing the risk of DILI. Repeated exposure is also a significant risk factor [48] ; patients with a history of DILI often experience a more rapid onset and more severe damage upon re-exposure to the same drug or a drug from the same class, a phenomenon that is particularly pronounced in immune-mediated cases.

In recent years, research into the interaction between the gut microbiota and the liver has provided new insights into the mechanisms of DILI. The gut microbiota not only participates in drug metabolism, deconjugation and reabsorption, but also regulates hepatic inflammatory responses and nuclear receptor (e.g. FXR, PXR, CAR) signalling pathways via lipopolysaccharide (LPS) and secondary bile acids [49, 50]. A decline in gut microbiota diversity and the dominance of pathogenic bacteria can trigger cholestasis and inflammatory responses, lowering the liver's tolerance threshold to drug toxicity and thereby altering the risk and phenotype of DILI. Conditions such as antibiotic use, proton pump inhibitor therapy or chronic constipation may all influence drug metabolism and immune homeostasis via the 'microbiota–bile acid–immune' axis [51], making patients more susceptible to developing specific types of DILI.

At the level of pathogenesis, DILI typically involves two main mechanisms. One is direct toxic action, whereby the drug or its metabolites directly damage hepatocytes via pathways such as oxidative stress, mitochondrial dysfunction and calcium homeostasis imbalance. Oxidative stress and mitochondrial dysfunction are central to this process. For example, an overdose of paracetamol can lead to the accumulation of NAPQI and glutathione depletion, thereby inducing the opening of mitochondrial permeabilisation channels, ATP depletion and extensive cell necrosis [52, 53]. Other drugs may trigger a reactive oxygen species (ROS) storm by inhibiting electron transport chain complexes or β-oxidation [54–56]. Endoplasmic reticulum stress and disruption of protein homeostasis, inducing the unfolded protein response and CHOP-mediated apoptosis, are also key mechanisms of DILI [57], whilst abnormalities in the mitochondria-associated membranes (MAM) further exacerbate calcium ion imbalance. Drug-induced inhibition of transporters such as BSEP, MRP2, NTCP and OATP1B1/3 can lead to bile acid retention and cause cell membrane damage [58], which constitutes cholestatic DILI. It is worth noting that various forms of programmed cell death are observed in DILI, including necrotic apoptosis, pyroptosis and ferroptosis; these pathways suggest that the onset of DILI is in fact triggered by multiple parallel pathways. At the same time, autophagy and mitophagy may play a dual role under different conditions: whilst they exert a protective effect when moderately activated, they are often suppressed under conditions of severe oxidative stress and energy crisis, creating a positive feedback loop of 'damage–protection imbalance' that exacerbates the progression of the disease.

Another aetiological mechanism of DILI is the immune-mediated mechanism. Immune-mediated damage plays a significant role in the pathogenesis of DILI. Small-molecule drugs or their reactive metabolites may bind to endogenous proteins to form haptenes; when these co-exist with damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) released during cellular damage [59–61], they can activate dendritic cells and induce a T-cell response, thereby triggering an immune attack. Genetic background plays a key role in this process; several HLA alleles (such as HLA-B57:01, HLA-A33:01 and HLA-B*58:01) show strong associations with the occurrence of immune-mediated DILI [62, 63], suggesting a central role for drug-specific peptide–HLA–TCR interactions; however, the limited penetrance of these genetic loci indicates that, in actual clinical practice, the combined effects of factors such as drug exposure, patient susceptibility and the gut microbiome collectively induce the onset of DILI. Clinically, immune-mediated DILI often presents as a delayed-onset reaction, accompanied by rash, eosinophilia, elevated immunoglobulin levels and positive autoantibodies; histopathological examination reveals interface hepatitis and bile duct damage. Recent studies have also suggested that impaired regulatory T-cell function and an imbalance in checkpoint molecules (such as PD-1/PD-L1 and CTLA-4) [64, 65] may be key mechanisms underlying the breakdown of immune tolerance and disease chronicity.

At the molecular level, multiple signalling pathways are closely associated with the development of DILI. Previous studies have shown that the activation of the MAPK [66] and NF-κB [67, 68] pathways is directly linked to inflammatory responses and cell death; whilst imbalances in the PI3K/AKT [69, 70] and AMPK [71], whilst an imbalance in these pathways affects cellular energy metabolism and the regulation of autophagy. Recent studies have shown that CYP450-mediated metabolic activation of drugs is a key step in the aetiology of most drug-induced liver injury (DILI), and that the resulting reactive oxygen species can further damage mitochondria and activate the apoptotic cascade. Furthermore, endoplasmic reticulum stress plays a significant role in DILI; its reciprocal regulation with autophagy, inflammation and immune responses forms a highly complex network. These mechanisms not only elucidate the pathophysiological basis of DILI but also provide important molecular targets for the development of drug toxicity prediction models.

In summary, the occurrence of DILI is the result of the interaction between multiple factors, including host susceptibility and drug toxicity, and its pathogenesis is complex and diverse. A deeper understanding of the relevant risk factors and pathogenic mechanisms will aid in identifying high-risk populations, formulating prevention strategies, and providing a theoretical foundation for future personalised medicine and targeted interventions.

## 4. Clinical Features, Diagnosis, Treatment and Prognosis

The clinical phenotype of DILI is highly heterogeneous, and the diagnostic process is complex and relies primarily on a process of exclusion. Clinical manifestations vary significantly from mild to severe; mild cases may present only with fatigue, loss of appetite or transient elevations in liver enzymes, whilst severe cases may rapidly progress to acute liver failure and even become life-threatening. Typical clinical symptoms include signs of cholestasis such as jaundice, dark urine and pruritus [1]. Laboratory tests remain a key pillar of diagnosis, with routine markers including ALT, aspartate aminotransferase (AST), ALP and total bilirubin (TBil). Based on the pattern of elevation in different markers, DILI can be classified into subtypes such as the hepatocellular type (characterised by a marked elevation in ALT), the cholestatic type (predominantly characterised by elevated ALP and/or TBil), and the mixed type. This classification of DILI not only aids in inferring the mechanism of injury but is also of significant value in prognostic assessment: generally speaking, patients with the hepatocellular type complicated by hyperbilirubinaemia have a poor prognosis, whilst those with the pure cholestatic type, although presenting with marked symptoms, have a relatively better long-term prognosis.

The diagnosis of DILI requires a comprehensive evaluation of clinical, laboratory and imaging data. A detailed medication history is crucial, covering the use, dosage and duration of all prescription medicines, over-the-counter (OTC) medicines and health supplements, combined with a comprehensive analysis of the temporal relationship with the onset of liver injury. In addition to routine liver function tests, laboratory investigations should also rule out other common causes such as viral hepatitis, autoimmune liver disease and metabolic liver disease. Imaging investigations (such as liver ultrasound, CT or MRI) can assist in ruling out liver space-occupying lesions or biliary obstruction. Clinically, the RUCAM (Roussel Uclaf Causality Assessment Method) scoring system is commonly used to quantitatively assess the causal relationship between a drug and liver injury; however, although this tool is widely used in clinical research and practice, its subjectivity and inter-centre consistency remain limited. In recent years, several novel biomarkers have shown potential for clinical application, including full-length and cleaved keratin 18 (cCK18),, exosome-associated molecules, and oxidative stress products [72]. Their value in the early diagnosis and prognostic prediction of DILI has been confirmed in some studies; however, they are not yet ready for routine clinical use.

With regard to treatment, discontinuation of the suspected causative drug is the primary measure. Building on this, symptomatic and supportive treatment should be provided, including nutritional support, antioxidant and hepatoprotective drugs, and maintenance of fluid and electrolyte balance. For patients with cholestatic DILI, ursodeoxycholic acid may be appropriately administered to alleviate cholestasis. If the condition progresses to acute liver failure, close monitoring in an intensive care unit is required, along with active therapeutic measures such as artificial liver support; some patients may even require a liver transplant. DILI with specific aetiologies has corresponding specific treatment regimens; for example, early administration of N-acetylcysteine in cases of liver injury caused by paracetamol overdose can significantly reduce the risk of acute liver failure and death; whereas for patients with immune-mediated features or clinical presentations resembling drug-induced autoimmune hepatitis, glucocorticoid therapy may be attempted following rigorous

assessment; however, further evidence-based research is required to support its efficacy and suitability for specific patient groups.

In terms of prognosis, most patients recover gradually after discontinuing the medication, with liver function typically returning to normal within a few weeks to several months. However, some patients may develop chronic DILI, characterised by persistent liver function abnormalities lasting more than six months, which may even progress to liver fibrosis or cirrhosis. Several studies suggest that hepatocellular DILI complicated by elevated bilirubin levels is a high-risk indicator for acute liver failure and death, signalling a very poor prognosis; by contrast, although the purely cholestatic type presents with significant clinical symptoms, its long-term prognosis is generally more favourable. Overall, early identification of high-risk patients, timely discontinuation of medication and intervention, and the implementation of individualised management are key to improving the prognosis of DILI. In the future, further exploration of precision diagnosis and treatment strategies, the establishment of early risk prediction models, and the development of novel biomarkers will be important directions for advancing the management of DILI.

## 5. Chinese Herbal Medicine-related Liver Injury

Large-scale Chinese multicentre epidemiological studies have shown that herb-induced liver injury (HILI) is the leading cause of DILI in hospitalised patients [8]. Compared with DILI associated with chemical drugs, HILI more frequently presents as hepatocellular injury [73].

The pathogenesis of HILI is closely associated with the formation of reactive metabolites (RMs) mediated by drug-metabolising enzymes. He Shou Wu is a typical herbal medicine that causes hepatocellular injury; its anthraquinone constituents (such as emodin and rhein) are metabolised by CYP2C19 to form reactive intermediates that can induce mitochondrial dysfunction and oxidative stress [74]. Tripterygium, which contains tripterygiol, can suppress the expression of MHC-I molecules in hepatocytes, leading to hepatic intolerance to exogenous lipopolysaccharides and NK-cell-mediated cytotoxicity directed against the body's own hepatocytes, thereby causing hepatocyte necrosis [75]. Psoralen, the main constituent of Psoralea corylifolia, is metabolised by CYP1A2, CYP2D6 and CYP3A4 to form reactive metabolites such as γ-ketoenal [76], which induce glutathione (GSH) depletion and exacerbate hepatotoxicity. Herbs containing pyrrolizidine alkaloids (PAs), such as Clematis chinensis and Notoginseng, are closely associated with the occurrence of hepatic sinusoidal obstruction syndrome (HSOS) [77], and are one of the major causes of HILI in northern China. Other herbal medicines, such as Xanthium seeds, Akebia (containing aristolochic acid) and Toona sinensis (containing alkaloids), have also been reported to possess clear hepatotoxicity.

Some Chinese herbal medicines are also used in the treatment of DILI. Silybin possesses antioxidant, cell membrane-stabilising, anti-fibrotic and anti-inflammatory effects, and has been shown in several clinical studies to have a certain protective effect against drug-induced and alcoholic liver disease [78]. Liquorice acid preparations exert anti-inflammatory, immunomodulatory and hepatocyte proliferation-promoting effects by activating β-catenin, and are widely used in China as an adjunctive treatment for various types of liver injury [79]. Extracts from Salvia miltiorrhiza, such as cryptotanshinone [80] and salvia polysaccharides [81], have been shown in animal studies to alleviate oxidative stress and inflammatory responses, demonstrating their potential as effective treatments for DILI.

## 6. Specific Considerations for the Elderly Population

As the global population continues to age, the risk of drug-induced liver injury (DILI) in elderly patients is attracting increasing attention. The liver in older adults undergoes significant structural and functional changes, including a reduction in liver volume and weight, decreased hepatic blood flow, and reduced activity of the CYP450 enzyme system. These physiological changes result in impaired drug absorption, distribution, metabolism and excretion in older adults, leading to a significant decrease in drug clearance, which facilitates drug accumulation in the body and increases the risk of toxicity. Previous studies have shown that liver weight in the elderly can decrease by 20–40 per cent, whilst hepatic blood flow is reduced by approximately 30–50 per cent [82] ; these changes all reduce the efficiency of drug metabolism and clearance. Consequently, the elderly population exhibits markedly reduced tolerance to the same drug doses and is prone to accumulation-related hepatotoxicity. Furthermore, the immune microenvironment and immunological ageing play a particularly prominent role in DILI among the elderly. Immune ageing is typically accompanied by a decline in T-cell diversity, dysregulation of regulatory T-cell function, and an excessive inflammatory response in the innate immune system, which reduces the body's efficiency in clearing drug-protein conjugates and increases the likelihood of low-dose, delayed-onset and protracted phenotypes. Concurrently, the diminished barrier function of hepatic sinusoidal endothelial cells and the pro-inflammatory phenotype of Kupffer cells in elderly patients [83] often amplify liver damage through cascade reactions involving inflammatory cytokines such as TNF-α, IL-1β and IL-6, thereby further exacerbating disease progression.

Epidemiological data indicate that elderly patients with DILI exhibit several distinctive characteristics. Results from multicentre registry studies show a significantly higher proportion of cholestatic DILI among elderly patients [84, 85], often accompanied by peripheral eosinophilia, positive autoantibodies and slow recovery of liver function. This is associated with the prevalence of multiple chronic conditions and polypharmacy in elderly patients. Common drugs associated with DILI in the elderly include cardiovascular medications (such as amiodarone and statins), non-steroidal anti-inflammatory drugs (NSAIDs) and psychotropic drugs, as well as traditional Chinese medicines and health supplements. In a case-control study involving 307 patients from 27 hospitals, patients aged 70 years and over accounted for 30.3 per cent (93 cases) [86] ; their average length of hospital stay was significantly longer than that of younger

patients, reflecting the longer course and more complex management of DILI in older adults.

The risk of DILI in elderly patients is also influenced by polypharmacy and drug interactions. Elderly patients typically use multiple prescription and over-the-counter medicines concurrently; these medicines may interact through mechanisms such as competitive inhibition or induction of the CYP450 enzyme system, or alterations in protein binding, leading to elevated blood drug concentrations and an increased risk of hepatotoxicity. For example, the combination of the anti-tuberculosis drugs isoniazid, rifampicin and pyrazinamide results in a significantly higher incidence of liver injury in the elderly population than in younger individuals. Furthermore, the Beers criteria proposed by the American Geriatrics Society list numerous potentially inappropriate medications [87]. These drugs (such as certain NSAIDs, benzodiazepines and some antidepressants) have established hepatotoxicity and should be avoided as far as possible in elderly patients.

The diagnosis of DILI in older adults presents additional challenges. Older adults often have comorbidities such as chronic liver disease, heart failure, diabetes or infections, and their baseline liver function may already be abnormal, making it more difficult to establish a causal relationship between the medication and liver injury. Furthermore, mental health issues such as cognitive decline or dementia, which are relatively common in older adults, may affect the accurate collection of medical history, leading to uncertainty regarding the triggers of DILI. The presence of multiple comorbidities complicates the aetiology, making DILI prone to delayed or misdiagnosis. Therefore, clinicians must carefully assess the medication history of elderly patients and, in conjunction with laboratory tests and imaging results, prudently determine the cause of liver injury.

In the treatment and prevention of DILI in elderly patients, emphasis should be placed on individualised and comprehensive management. Reducing the number of medications prescribed to elderly patients is a key strategy for lowering the risk of DILI. The necessity of medication should be assessed regularly, and potentially risky drugs should be discontinued, particularly in elderly patients receiving multiple medications. For high-risk drugs that must be used long-term, screening for drug metabolism-related genes (such as NAT2, CYP2E1 or HLA-B*57:01) can help identify susceptible individuals and guide medication use [88–90]. At the same time, a liver function monitoring protocol for high-risk medications should be established; for example, liver function tests should be repeated at weeks 2, 4, 8 and 12 after initiation of treatment, and the medication should be discontinued as soon as ALT levels exceed three times the upper limit of normal. Strengthening education for patients and their families, ensuring they understand the potential hepatotoxicity of over-the-counter medicines and health supplements and use them with caution, is also a crucial aspect of preventing DILI in the elderly.

In summary, the occurrence of DILI in the elderly involves multiple factors, including physiological decline in liver function, polypharmacy and comorbidities. Its clinical presentation is more insidious, predominantly cholestatic in nature, with a longer course of disease and a higher risk of adverse outcomes. Future research should focus on establishing dedicated cohorts for DILI in the elderly and identifying individualised risk indicators, with a view to reducing the incidence of DILI and adverse outcomes through optimised prescribing and monitoring strategies.

## 7. Future Prospects and Conclusions

As our understanding of DILI continues to deepen, multi-omics and data science methods are playing an increasingly important role in its study. Future early diagnosis and risk assessment will rely on the integration of multi-omics data—including genomics [91], proteomics, metabolomics [92] and gut microbiota [93] —with clinical characteristics. For example, whole-genome sequencing and genome-wide association studies (GWAS) can identify genetic markers associated with drug-induced hepatotoxicity, whilst metabolomics and transcriptomics analyses can detect early-stage damage markers linked to oxidative stress and mitochondrial dysfunction. When combined with patients' clinical characteristics and drug exposure data, these biomarkers hold promise for the development of highly accurate, personalised risk prediction models. In future, the applicability and accuracy of these markers across different age groups, genders and populations with comorbidities will need to be validated in large-scale prospective cohorts.

Artificial intelligence (AI) [94] and machine learning [95] methods also offer new approaches to the prediction and management of DILI. By utilising algorithms such as deep learning, support vector machines and ensemble learning, and inputting data such as drug chemical structures, patient genetic information and clinical indicators into the models, preliminary studies have achieved high accuracy (up to 80 per cent or more) in predicting the risk of severe DILI and acute liver failure. However, to ensure the clinical applicability of AI models, it is necessary to rely on multi-centre clinical big data and dynamic monitoring indicators to improve the models' generalisation ability and interpretability.

In drug development and mechanistic research, the application of novel in vitro/in vivo models will significantly advance DILI research. Humanised liver mouse models, three-dimensional liver organoids [96], induced pluripotent stem cell (iPSC)-derived hepatocytes and liver microfluidic chip technology can more realistically simulate the processes of drug metabolism and immune responses in the human liver. These platforms can be used not only to screen for drugs with potential hepatotoxicity but also serve as important tools for investigating the mechanisms underlying specific types of DILI; they are expected to accelerate the early detection of high-risk drugs and provide experimental evidence for personalised medicine.

In recent years, the clinical burden of HILI has become increasingly apparent; compared with drug-induced liver injury (DILI) associated with chemotherapeutic agents, HILI is less predictable and its mechanisms are more complex. HILI can range from self-limiting liver injury to rapidly progressing acute liver failure, placing higher demands on clinical monitoring and early intervention. The occurrence of HILI is closely associated with the generation of reactive

metabolites mediated by drug-metabolising enzymes; consequently, polymorphisms in the CYP450 enzyme system or variations in drug transporters are valuable as potential susceptibility markers for HILI [97]. Future research may focus on identifying genetic susceptibility factors in high-risk populations, elucidating key toxicological pathways, and developing active ingredients with controllable safety profiles.

As a specific high-risk group for DILI, the elderly will also be a key focus for future research and management. It is recommended that prospective DILI cohorts be established for the elderly to define age-specific biomarker thresholds and to explore the role of optimised prescribing, management of drug interactions and personalised monitoring in reducing the incidence of DILI and improving prognosis. At the same time, strengthening medication education, adherence management and guidance on the use of over-the-counter medicines and health supplements for elderly patients should also be key components of research and clinical practice.

## 8. Summary

In summary, drug-induced liver injury is a major issue spanning drug development, clinical treatment and public health; its pathogenesis is complex and variable, its clinical manifestations are heterogeneous, and challenges remain in diagnosis and treatment. Due to physiological decline, polypharmacy and comorbidities, DILI in elderly patients is more insidious, predominantly cholestatic in nature, associated with longer hospital stays and a significantly increased risk of mortality. Future research should integrate genetics, metabolomics and artificial intelligence technologies to establish personalised risk prediction and monitoring models and develop more precise early diagnostic tools. At the same time, optimised prescribing and personalised intervention strategies should be formulated for the elderly population to achieve precise prevention and control of DILI and improve patient prognosis.

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