Journal of Holistic Integrative Pharmacy 6 (2025) 308–321

Contents lists available at ScienceDirect

Journal of Holistic Integrative Pharmacy

journal homepage: www.keaipublishing.com/en/journals/journal-of-holistic-integrative-pharmacy

Review on clinical diagnosis, pathogenesis and therapeutic strategies of drug-induced liver injury

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ARTICLE INFO

Keywords:
Drug-induced liver injury
Biomarkers
Pathogenesis
Traditional Chinese medicine

ABSTRACT

Drug-induced liver injury (DILI) is a severe adverse reaction caused by various drugs and their metabolites, with complex clinical manifestations, and severe cases may progress to acute liver failure (ALF) or even death. Currently, the pathogenesis of DILI has not been fully elucidated, and specific diagnostic indicators and effective therapeutic strategies are lacking, so it is crucial to deeply analyze its pathogenesis and develop precise intervention strategies. This review explores key pathogenic mechanisms in the development of DILI, with a focus on mitochondrial dysfunction, ferroptosis, immune responses and the gut-liver axis. It further systematically summarizes the clinical diagnostic approaches for DILI, including common diagnostic methods and potential biomarkers. Additionally, the review discusses therapeutic strategies for DILI, encompassing western medical treatments, ethnomedical treatments and non-pharmacological treatments. Although N-acetylcysteine (NAC) remains the FDA-approved standard treatment for acetaminophen (APAP) overdose, superior therapeutic options for DILI need to be explored urgently due to its therapeutic limitations and side effects. In the future, the prevention and treatment strategy of DILI will rely on deeper mechanistic investigations, development of novel biomarkers, and further exploration of multi-targeted traditional Chinese medicine (TCM) therapies.

1. Introduction

Drug-induced liver injury (DILI) is liver damage caused by drugs and their metabolites, which can occur either predictably at toxic doses or unpredictably with routine use.[1] Clinically, the presentation of DILI varies, ranging from mild cases with asymptomatic slight liver enzyme elevations, to severe cases with jaundice, coagulopathy, and even acute liver failure (ALF), which can be life threatening in the severe condition.[2] The incidence of DILI is estimated to range from 14 to 19 cases per 100,000 people, and contributes to high morbidity and mortality rates.[3] The main causative agents of DILI, however, vary by region. For example, in South America, Australia, Sweden, and the UK, acetaminophen (APAP) is the main drug cause of ALF, whereas antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are more commonly responsible in Spain and Germany. Meanwhile, in Asia, particularly in India and China, antitubercular drugs and traditional medicines are major contributors to DILI and drug-induced ALF.[4] Additionally, a prospective observational cohort study of adults with ALF in the U.S. revealed that APAP overdose is the most common cause of ALF, with its incidence increasing from 31.8% to 53.0% over a 15-year period, representing nearly half of ALF cases.[5,6] Overall, liver injury is primarily associated with drug abuse, particularly APAP overdose, and places a significant burden on healthcare systems. Therefore, APAP-induced liver injury (AILI) is precisely the focus of this review.

The development of DILI involves multiple mechanisms, including mitochondrial dysfunction, ferroptosis, immune response and the role of gut microbiota. These mechanisms are not only related to the direct toxic effects of the drugs, but also regulated by the physiological state of the host and environmental factors.[7,8] According to the mechanism of hepatotoxicity, DILI can be categorized into direct injury and idiosyncratic injury. Direct injury is usually caused by drugs with intrinsic hepatotoxicity, such as APAP, when exposed in excess of a certain dose, and is predictable and dose dependent. Idiosyncratic injury, on the other hand, is caused by specific interactions between the host and the drug or by immune responses, manifesting as unpredictable and non-dose dependent.[3,9] Usually, through drug dosage modification, monitoring

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Peer review under the responsibility of Editorial Board of Journal of Holistic Integrative Pharmacy.

https://doi.org/10.1016/j.jhip.2025.09.002
Received 23 April 2025; Received in revised form 2 September 2025; Accepted 5 September 2025

for prevention and emphasis on individual susceptibility screening, it is helpful to select individualized therapeutic strategies.

To ensure the safe use of drugs in the clinic as much as possible and reduce the harm of DILI, it is crucial to identify potential DILI at an early stage. Currently, the detection of DILI is no longer limited to traditional detections such as serum biochemical indicators and imaging examinations. The detection and research of biomarkers based on the mechanism of DILI provide new possibilities for early diagnosis of DILI, such as high mobility group box 1 (HMGB1).[10] Ideal DILI biomarkers should have high specificity, high sensitivity, and stability, and be able to indicate the mechanism of DILI to optimize clinical decision making and improve the accuracy of prognostic assessment.

In recent years, the efficacy and safety of DILI treatment, including both pharmacological and non-pharmacological measures, still need to be improved. For pharmacological treatment, N-acetylcysteine (NAC) still remains the FDA-approved standard treatment for APAP overdose.[11] In addition, magnesium isoglycyrrhizinate (MgIG) has also been approved by the Chinese FDA for treating acute hepatocellular injury caused by DILI.[12] However, there is an urgent need to develop safer and more effective treatment options for DILI due to the narrow efficacy window and adverse effects such as nausea and vomiting of NAC, as well as adverse effects such as granulocytopenia and fever of MgIG. Meanwhile, traditional Chinese medicine (TCM) has received increasing attention due to its multi-target and multi-pathway mechanism of effects. Studies have shown that some TCM and their active ingredients have demonstrated hepatoprotective effects in animal research.[13] For example, *Bupleuri radix* alleviates oxidative stress by preventing the depletion of hepatic glutathione (GSH),[14–16] while *Paeonia lactiflora* mitigates ferroptosis by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway,[17] and geniposide of *Gardenia jasminoides* inhibits the Toll-like receptors (TLRs) to inhibit inflammatory responses.[18] These studies provide a potential source of natural drugs for mechanism targeted therapy of DILI, although large-scale clinical trials are still needed to validate their safety and efficacy.

This review aims to explore the potential mechanisms of DILI, summarize current diagnostic methods, and review current therapeutic approaches with a focus on potential TCM, while seeking new therapeutic strategies targeting the underlying mechanisms.

2. Pathogenesis of DILI

Currently, research into the pathogenesis of DILI is primarily focused on immune system and oxidative stress in organelles such as mitochondrial dysfunction. Moreover, emerging mechanisms such as ferroptosis and gut microbiota have garnered increasing attention. Studies have shown that drugs or their metabolites can induce excessive production of reactive oxygen species (ROS), which contributes to oxidative stress and triggers hepatocyte injury and death. These processes subsequently trigger inflammatory cascades, hepatic stellate cell activation, and fibrosis, thereby exacerbating liver injury.[19] In addition, the gut microbiota may promote liver injury by increasing intestinal permeability, disrupting microbial metabolite homeostasis, and promoting inflammation and oxidative stress.[20]

2.1. Mitochondrial dysfunction

Mitochondrial dysfunction has been identified as an important pathogenetic mechanism in DILI, which may be caused by parental drugs and/or reactive metabolites generated through CYP-mediated metabolism.[21,22] Dysfunctional mitochondria, characterized by impaired metabolic pathways and structural damage, can lead to oxidative stress, triglyceride accumulation (steatosis), disrupted energy production, and ultimately cell death.

In AILI, mitochondrial proteins are primary targets of N-acetyl-p-benzoquinone imine (NAPQI). By interfering with complex I/II of the mitochondrial electron transport chain (ETC), NAPQI induces electron leakage and superoxide radical formation.[23] Under normal conditions, low-molecular weight antioxidants such as GSH, vitamin E, or ubiquinone, and antioxidant enzymes such as catalase (CAT), peroxiredoxin (Prx), or glutathione peroxidase (GPx) protect mitochondria from the toxic action of ROS.[23,24] However, GSH depletion following APAP overdose exacerbates ROS and peroxynitrite production, leading to oxidative/nitrosative stress and activation of the c-Jun-N-terminal kinase (JNK). The phosphorylation and translocation of JNK to mitochondria exacerbate oxidative damage, leading to disruptions in the tricarboxylic acid (TCA) cycle, adenosine triphosphate (ATP) production, and β-oxidation, ultimately triggering mitochondrial permeability transition pore (MPTP) opening.[25] This cascade eventually causes the translocation of mitochondrial proteins like apoptosis-inducing factor (AIF) and endonuclease G (Endo G) to the nucleus, leading to fragmentation of nuclear DNA and eventually necrotic cell death[23,25] (Fig. 1). Additionally, certain drugs can sequester coenzyme A, inhibit mitochondrial β-oxidation enzymes, ATP synthase, or transfer of electrons along the respiratory chain, thereby leading to disruption of energy metabolism. Furthermore, some drugs can directly damage mitochondrial DNA, inhibit DNA replication (e.g., dideoxynucleoside analogues), reduce mitochondrial transcription to decrease the gene expression related to mitochondrial function (e.g., TNF-α), or impair mitochondrial protein synthesis, which can further impair mitochondrial structure and function.[26,27] Ultimately, they lead to disorders of energy synthesis, excess ROS, and cell death, which ultimately exacerbates the process of liver injury.

Among DILI mechanisms, phosphorylation of JNK is considered to play a key role in inducing mitochondrial injury and hepatocyte death.[28] Notably, ample evidence indicates that preserving GSH levels and limiting downstream oxidative stress can effectively inhibit the phosphorylation of JNK, thus offering mitochondrial protection and alleviating liver injury.[29]

2.2. Ferroptosis

In AILI, ferroptosis has been proven to initiate early in the pathological process (3 h post-APAP), leading to structural destruction of hepatocytes. Subsequently, cellular contents such as DNA and HMGB1 are released outside the cell, further activating the immune system and causing an inflammatory response leading to liver injury.[30] Furthermore, the onset of ferroptosis relies on the accumulation of intracellular iron and is accompanied by elevated lipid peroxidation.[31,32]

In the mechanism studies of AILI, the "two hit" hypothesis suggests that mitochondrial NAPQI-protein adducts increase ROS production (e.g., $O_2\bullet^-/H_2O_2$) in the first hit. In the second hit, lysosome injury caused by NAPQI results in the release of Fe^{2+}, which then enters mitochondria *via* the mitochondrial electrogenic Ca^{2+}, Fe^{2+} uniporter (MCFU). The loaded Fe^{2+} and H_2O_2 induce the formation of highly toxic hydroxyl radicals (•OH) through the Fenton reaction, subsequently damaging DNA, proteins, and membranes, culminating in mitochondrial permeability transition (MPT), mitochondrial depolarization, and cell death[33] (Fig. 1).

Nuclear receptor coactivator 4 (NCOA4) functions as a selective cargo receptor for ferritin turnover, mediating ferritinophagy by binding to ferritin and delivering it to autolysosome. Then the free iron amplifies ROS production, exacerbating ferroptosis and its downstream effects on cellular integrity.[34] Ferroptosis is hypothesized to arise from the interplay of multiple metabolic pathways, broadly encompassing: (1) the GSH/GPx4, X_c^-, sulfur transfer, and p53 pathways, (2) iron metabolic pathways affecting cellular iron concentration, involving the autophagy protein 5 and 7 (ATG5-ATG7)-NCOA4 pathway and iron-responsive element-binding protein 2 (IREB2) related to ferritin metabolism, as well as the p62-Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 pathway, (3) lipid metabolism pathways affecting fatty acid regulation and ferroptosis, such as the p53-spermidine/spermine N1-acetyltransferase 1 (SAT1)-arachidonate lipoxygenase 15 (ALOX15), acyl-CoA

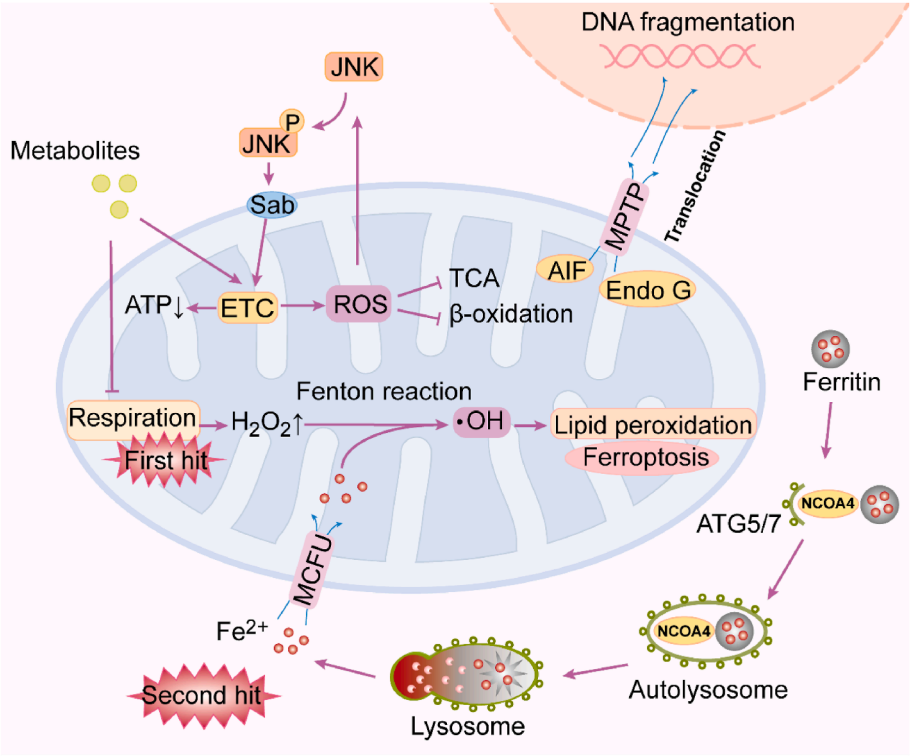

Fig. 1. Drugs induce mitochondrial dysfunction and ferroptosis. Drugs can interfere with the ETC, triggering the overproduction of ROS, activating JNK signaling to amplify oxidative stress, and leading to cell necrosis. Meanwhile, NCOA4 mediates the release of Fe^{2+}, which undergoes a Fenton reaction with H_2O_2, inducing mitochondrial depolarization and cell death.

synthetase long-chain family member 4 (ACSL4), and lysophosphatidylcholine acyltransferase 3 (LPCAT3) pathways.[35] Disorders of these metabolic pathways can cooperatively contribute to the development of DILI by decreasing antioxidant capacity of hepatocytes, increasing intracellular free iron concentration to promote the Fenton reaction leading to the excessive generation of ROS, and inducing the lipid peroxidation. In addition, cells employ multiple defense systems to counter lipid peroxidation and suppress ferroptosis, including the classical cyst(e)ine/GSH/GPx4 axis, the NAD(P)H/ferroptosis suppressor protein 1 (FSP1)/coenzyme Q_{10} (CoQ_{10}) system, and the guanosine triphosphate cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH_4)/dihydrofolate reductase (DHFR) system.[34]

With increasing research on the effects of lipid peroxidation and ferroptosis in DILI, targeting ferroptosis for DILI treatment may offer a promising new therapeutic approach. And given that ferroptosis is the initial event in AILI, it seems to be a better therapeutic target than inflammation.

2.3. *Immune system*

Immune-mediated DILI, also termed idiosyncratic DILI, is hypothesized to involve the formation of reactive metabolites or drug-protein adducts that directly or indirectly impair intracellular proteins and/or organelles, triggering a cascade of immune responses.[36] Two primary

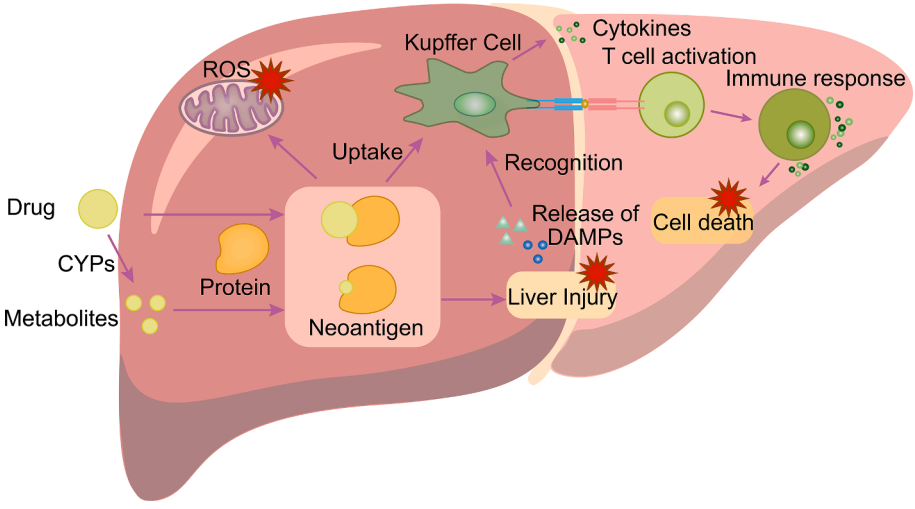

Fig. 2. The immune system mediates the onset of DILI. Kupffer cells can recognize drug-protein adducts as neoantigens, activate the release of inflammatory factors, and trigger adaptive immune responses. Meanwhile, damaged hepatocytes release DAMPs, which further amplify the immune response and contribute to cell death.

pathways are implicated in the pathogenesis of DILI. First, drug- or metabolite-protein adducts can act as neoantigens, which are recognized by the immune system *via* human leukocyte antigen (HLA). This recognition triggers immune responses and activates $CD8^+$ T cells, leading to hepatocyte destruction.[37] Second, injured hepatocytes release "danger signals", the cellular DNA or the damage-associated molecular patterns (DAMPs) such as HMGB1 and heat shock proteins. These signals recruit immune cells and stimulate the release of pro-inflammatory cytokines, further amplifying immune responses against the liver[36,38] (Fig. 2).

Liver-resident macrophages, such as Kupffer cells, play a central role in idiosyncratic DILI by phagocytosing antigens, recognizing, and presenting them.[39] Through pattern recognition receptors, such as TLRs, Kupffer cells bind to DAMPs released from drug-damaged hepatocytes, becoming activated and releasing pro-IL-1β and pro-IL-18[40]. These precursors are cleaved by caspase-1 into mature IL-18 and IL-1β, which recruit neutrophils and monocytes from the bloodstream to the liver. This immune cell infiltration amplifies inflammation *via* chemokines such as CCL2, CXCL1, CXCL2, and CXCL8.[40] Additionally, active caspase-1 mediates cleavage of gasdermin D (GSDMD), which generates N-terminal fragments that translocate to the cell membrane and form pores that release active IL-1β and IL-18, thereby activating the onset of pyroptosis.[41] Meanwhile, under the stimulation of pro-inflammatory factors such as infection, endotoxin, and hypoxia, M1 macrophages polarize and release large amounts of TNF-α, IL-6, and iNOS, which further stimulate inflammatory cells and aggravate the inflammatory response. TNF-α also induces the release of HMGB1, which acts as a danger signal to mediate the process of pyroptosis and aggravate liver injury.[42]

Furthermore, activated antigen-presenting cells can activate $CD4^+$ regulatory T cells, which secrete cytokines such as IL-10 to suppress immune responses and limit hepatocyte damage.[43] However, these regulatory processes may be insufficient to prevent severe liver injury in susceptible individuals.

2.4. Gut-liver axis

In recent years, increasing evidence suggests that gut microbiota dysbiosis, microbial metabolites, and intestinal barrier dysfunction play a crucial role in DILI.[44] Specifically, gut microbiota and their bioactive metabolites modulate drug absorption, hepatic drug metabolism, antioxidant capacity, hepatocyte survival, inflammation, and liver regeneration.[29] The key foundation of the mechanism is the anatomical and functional connection of the gut-liver axis. When the intestinal barrier is damaged, intestine-derived products like lipopolysaccharide (LPS) can be transported through portal vein directly to the liver, where they can regulate hepatic immunity and metabolism, thereby triggering inflammation and oxidative stress.[20] At the same time, the liver can secrete bile and antibodies back to the gut, affecting the composition and function of gut microbiota, which establishes the interaction between the gut, its microbiome, and the liver.[45]

Further research has shown that the gut microbiota influences host susceptibility to AILI through several mechanisms. Gut microbial-derived metabolites may regulate the expression of certain liver CYP enzymes and competitively inhibit liver sulfonation pathways, thereby reducing the detoxification capacity of APAP.[46,47] Additionally, gut microbiota can hydrolyze conjugated drugs such as APAP, releasing free APAP for reabsorption in the enterohepatic circulation. Interestingly, it has also been found that compared with the conventionally fed animals, the germ free mice showed a lighter hepatotoxicity phenotype, including lower creatinine level, lower plasma bilirubin, and a tendency to increase glucose.[46]

Furthermore, metabolites like 1-phenyl-1,2-propanedione (PPD) from gut microbiota participate in regulating the diurnal variation of AILI.[48] Metabolomics analysis showed that PPD levels were increased in the cecum and liver of mice at the start of active period when the light was off. And the quinone like structure of PPD enables it to act as a redox cycling compound to generate excess ROS and thus trigger oxidative stress in cells, consuming a large amount of GSH to remove the ROS, which leads to a reduction in the hepatic antioxidant capacity and consequently enhances the APAP toxicity. Therefore, APAP may cause more aggravated liver injury when taken at active period than at the resting period, with antibiotics treated mice showing reduced liver necrosis, indicating circadian modulation of gut microbiota affects APAP toxicity.[48]

The integrity of the intestinal barrier also plays a crucial role in AILI progression. Studies have shown that drug treatment increases intestinal permeability, leading to bacterial translocation.[49] These bacteria and pathogen-associated molecular patterns (PAMPs), such as LPS, can enter the liver *via* the portal vein and trigger an inflammatory response by activating pathogen recognition receptors like TLR4 on liver macrophages (Kupffer cells).[50,51] This immune activation contributes to liver injury in AILI. Moreover, translocated PAMPs, bacteria and their metabolites can enter the systemic circulation through the liver, further exacerbating the damage (Fig. 3).

Recent studies have also uncovered the protective role of *Akkermansia muciniphila* in alleviating AILI in mice. This bacterium can exert effects in alleviating liver injury by reducing oxidative stress and inflammation in the liver, and activating the PI3K/Akt pathway for phosphorylating target proteins like Nrf2, Bcl-2, and NF-κB. In addition, it can regulate the composition of gut microbiota to further protect against liver injury.[52] These findings highlight the key regulatory effects of gut microbiota in DILI, which not only can influence drug absorption and hepatic metabolism, but also participate in the development of liver injury by affecting hepatic inflammation and oxidative stress. Therefore, gut microbiota seems to be a potential therapeutic target for improving DILI. In the future, adjusting the composition of the gut microbiota or intervening in the production and effect of gut microbial-derived metabolites has the potential to provide effective strategies for the DILI treatment.

It is worth noting that research on mechanisms of mitochondrial dysfunction, ferroptosis, and the immune system has been mainly derived from DILI animal models or in vitro cell experiments. These studies have provided significant clues in elucidating potential molecular mechanisms, but their validation in human DILI patients remains limited. Currently, direct evidence based on human samples or patient data remains lacking, therefore the clinical translation of these mechanisms remains to be further confirmed.

3. Clinical diagnosis

In clinical practice, the diagnosis of DILI still faces certain challenges, especially in the early stages of the disease when the symptoms are atypical and the pathogenesis is complex. Traditional detection methods are centered on biochemical indicators such as liver enzymes, supplemented by imaging examinations, liver biopsy, and Roussel Uclaf Causality Assessment Method (RUCAM) to improve the comprehensiveness and accuracy of diagnosis. Despite widespread application, there are still limitations in specificity, sensitivity, and prediction of prognosis. With the ongoing exploration of mechanisms such as mitochondrial dysfunction, ferroptosis, and immune system, corresponding promising mechanistic biomarkers such as HMGB1 provide a new direction for the preliminary classification and early warning of DILI.

3.1. Common diagnostic methods

At present, detailed clinical evaluation remains essential, and serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB) are still important indicators for the assessment and classification of liver injury. Common clinical diagnostic criteria for DILI are established by comparing these serum indicators to multiples of their respective upper

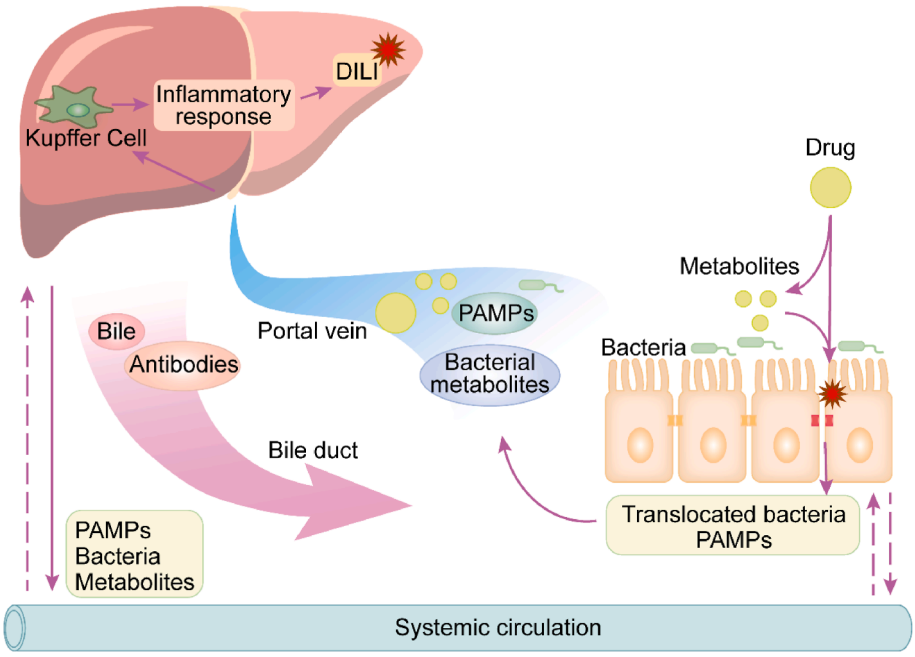

Fig. 3. The relationship between the gut-liver axis and DILI is illustrated. Under the effect of drugs, damage to the intestinal mucosal barrier allows translocated bacteria and PAMPs to enter the liver, where they are recognized by liver macrophages, triggering inflammatory responses.

limits of normal (ULN), which facilitates disease identification and therapeutic decision.[2] Notably, the criteria of ALT $\geq 3 \times$ ULN and TB $\geq 2 \times$ ULN define "Hy's Law", which indicates that the incidence of severe DILI exceeds 10% and is often associated with significant hepatocellular injury and higher mortality. Additionally, the R value, defined as R= (ALT/ULN): (ALP/ULN), is commonly used to categorize the phenotypes of idiosyncratic DILI into hepatocellular DILI ($R \geq 5$), cholestatic DILI ($R \leq 2$), and mixed-type DILI ($2<R<5$)[53-55].

Meanwhile, auxiliary imaging examinations such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) also play an irreplaceable role in the differential diagnosis of DILI. These techniques are particularly helpful in identifying cholestatic DILI arising from biliary obstruction (such as choledocholithiasis, pancreatobiliary malignancies, or lymphoma due to extrahepatic and pancreaticobiliary etiology).[53,56] However, it should be noted that most patients with acute DILI typically exhibit no significant changes in liver imaging or only mild liver enlargement.

In complex or persistent cases, liver biopsy serves as an auxiliary diagnostic tool that provides critical histological evidence to assess the severity of liver injury. It is usually recommended to consider performing a biopsy approximately 60 days after the onset of hepatic injury (usually extended to 180 days for patients with cholestatic DILI) when there is no significant improvement after discontinuation of the suspected medication.[53] The histological features vary with DILI phenotype. For example, hepatocellular DILI mainly presents with severe inflammation, necrosis, and apoptosis, whereas cholestatic DILI is commonly characterized by bile duct obstruction and paucity. For severe or fatal DILI, it is usually correlated with extensive hepatocyte necrosis, microbubble steatosis, fibrosis stage, etc.[57] However, liver biopsy is invasive and is not necessary for all patients with DILI, so decisions should be individualized according to the diagnosis.

In terms of evaluating the causal relationship between drug use and liver injury, the RUCAM is the most widely used diagnostic tool for DILI worldwide.[58] This scoring system is a diagnostic scale based on seven clinical criteria that scores the causal relationship between the suspected drug and the liver injury into five classes, including excluded, unlikely, possible, probable, and highly probable, with higher scores indicating a higher likelihood of DILI.[56,59] This tool enables clinicians to systematically assess the risk of liver injury caused by drugs when faced with polypharmacy and complex medical conditions. The widespread use of RUCAM has contributed to standardizing diagnostic processes and improving the consistency of clinical assessments. Although it may be influenced by subjectivity in scoring and limited accuracy in complex pathogenesis, it is still regarded as a key tool for clinical causality assessment and an important complement to the clinical global impression.

3.2. *Promising biomarkers*

The diagnosis of DILI has long relied on traditional biomarkers such as AST, ALT, ALP, and TB. However, these biomarkers have limited specificity and sensitivity, making it challenging to accurately assess the severity and type of DILI. Therefore, there is an urgent need to identify novel biomarkers with better targeted and diagnostic value. In recent years, with the advancement of high-throughput technologies, including transcriptomics, genomics, epigenomics, metabolomics, and proteomics, an increasing number of candidate biomarkers associated with DILI have been discovered and gradually applied in basic research and clinical investigation.[60]

Based on these findings, a multiple cohort clinical study systematically evaluated the diagnostic performance of 14 candidate DILI biomarkers using receiver operating characteristic (ROC) curve analysis. Biomarkers with both ROC-area under the curve (AUC) and the lower bound of their 95% confidence interval (CI) exceeding 0.5 were considered to have predictive utility of DILI. Notably, Glutamate dehydrogenase (GLDH), keratin-18 (K18) and caspase-cleaved K18 each demonstrated AUCs above 0.9, highlighting their high diagnostic accuracy for detecting DILI.[61] Furthermore, a prospective cohort study involving 875 patients with APAP overdose assessed the discriminatory ability of miR-122, HMGB1, full-length and caspase-cleaved K18, GLDH, and the traditional biomarker ALT in subsequent acute liver injury with ALT >100 U/L. The study revealed that miR-122, HMGB1, and full-length K18 had significantly higher predictive accuracy at presentation than ALT, with all AUCs exceeding 0.9. Building on these results, a combined model of miR-122, HMGB1, and K18 has been proposed for risk stratification in AILI, showing promising potential for clinical

translation.[10] The AUCs, specificity and sensitivity of miR-122, HMGB1, K18, caspase-cleaved K18, and GLDH in the two studies are presented in Table 1.

Regarding the above biomarkers, miR-122 is a liver-specific microRNA, and liver injury usually leads to its release into the bloodstream.[62,63] It has been found to be elevated in serum levels in amoxicillin/clavulanate-induced liver injury earlier than ALT, and is closely correlated with the elevated levels of ALT.[64,65] Clinically, due to its higher liver specificity and superior bioanalytical sensitivity, miR-122 is considered to be one of the most promising biomarkers for future clinical applications.[10] HMGB1 is a chromatin-binding protein that is passively released in a hypoacetylated form during hepatocyte necrosis and actively secreted in a hyperacetylated form during immune activation states.[62] Therefore, hyperacetylated HMGB1 is considered to be a promising candidate biomarker for assessing immune activation states. Clinical studies have found that in the early stage of APAP overdose, total HMGB1 levels in patient serum are elevated earlier than ALT, demonstrating good potential for early diagnosis.[66] Similar to HMGB1, the K18 is also passively released during cellular necrosis, whereas the caspase-cleaved K18 is released into the circulation during the early stages of apoptosis.[67] Thus, the proportion of these two proteins in the serum may serve as a marker for distinguishing apoptosis from necrosis.[68] And it is also used to predict the subsequent liver injury in patients presenting with early APAP overdose and to assess survival or mortality in DILI patients.[69] Nevertheless, due to its lack of liver specificity and expression being influenced by other diseases, its specificity in diagnosis of K18 is limited. In addition, GLDH is a highly expressed mitochondrial enzyme in the liver, which is released markedly into the circulation during mitochondrial dysfunction, and can be used as a mechanistic biomarker of mitochondrial damage in acute liver injury.[69] Clinically, it has been shown to predict the outcome of APAP-induced ALF.[70,71] However, it should be noted that despite the high specificity of GLDH, its sensitivity is still limited and it is primarily used to distinguish ALT elevations caused by hepatic versus muscle injury.[61]

In addition to the above biomarkers, the diagnostic performance of the remaining 10 novel candidate biomarkers was also systematically evaluated in the multiple cohort clinical study. These markers, ranked in descending order according to ROC-AUC, included fatty acid binding protein, macrophage colony stimulating factor receptor, α fetoprotein, glutathione *S*-transferase α, sorbitol dehydrogenase, osteopontin, cadherin-5, paraoxonase 1, arginase-1, and leukocyte cell-derived chemokine-2.[61] The results of the study showed that all candidates were able to identify patients with DILI to a certain extent, except for leukocyte cell-derived chemokine-2, which had a lower CI limit of only 0.45, which could not exclude random agreement between prediction and outcome. In addition, clinical studies have also identified biomarkers of mitochondrial dysfunction in serum, such as mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) fragments, whose elevated levels are closely related to the severity of necrotic hepatocellular injury in patients with drug overdose.[72] Meanwhile, the detection of APAP-protein adducts, particularly APAP-cysteine adducts, has been used to aid in the early diagnosis of ALF in pediatric patients, showing favorable prospects and translational potential in clinical application.[73]

An ideal biomarker for DILI should possess not only high sensitivity and specificity but also clinical practicality. Certain biomarkers have proven to be capable of indicating early liver injury even before the elevation of traditional liver function tests, thus enabling earlier intervention. Others, classified as "mechanistic biomarkers", provide insights into critical pathogenic processes such as mitochondrial dysfunction, apoptosis, and necrosis. Nevertheless, the research on and clinical application of DILI biomarkers continue to face several challenges. Many candidate biomarkers remain at the preclinical stage, and although promising in small-scale studies, their clinical application is hindered by the lack of unified detection standards, methodological complexity, and high detection costs. Given the complex pathogenesis of DILI and substantial interindividual variability, reliance on a single biomarker is often insufficient to fully capture the disease status. Consequently, future efforts should prioritize the development and validation of models combinating multiple biomarkers to enhance diagnostic accuracy and phenotypic classification in clinical practice.

4. Therapeutic strategies for DILI

Given the complex pathogenesis and diverse clinical phenotypes of DILI, current treatment strategies encompass multiple approaches, including pharmacological therapy, non-pharmacological supportive therapy, etc. Pharmacological treatments remain the primary intervention for DILI, including both western medical treatments and ethnomedical treatments, while non-pharmacological treatments provide essential organ support and life extension methods for severe patients. As mechanistic research advances and high-quality drug studies accumulate, treatment strategies for DILI are expected to become increasingly precise in the future.

4.1. Pharmacological treatments

Current research indicates that western medical treatments are mainly focused on antioxidants, immune resistance, improvement of bile excretion function, etc. Meanwhile, ethnomedicine provides a new direction for DILI intervention through the unique advantages of syndrome differentiation and treatment with multi-targeted, multi-mechanism TCM.

4.1.1. Western medical treatments

The primary step in treating suspected DILI is discontinuation of the causative drugs. In the case of drug overdose, preventing drug absorption into the liver and providing an antidote to halt further damage is crucial.[74] For example, following excessive intake of APAP, activated charcoal is used within 1–2 h to limit the absorption of APAP in the gastrointestinal tract. If more than 2 h have passed post-ingestion, NAC is administered orally or intravenously over the next 20–24 h.[75] NAC, a powerful antioxidant and ROS scavenger, functions by increasing GSH level and restoring mitochondrial redox homeostasis.[23]

However, the clinical utility of NAC is limited by its narrow efficacy window. Standard oral or intravenous administration of NAC is highly effective for patients with moderate overdose within 8 h of APAP ingestion. For patients in advanced stages or with massive overdoses, the efficacy of NAC will decrease. Moreover, adverse effects such as nausea and vomiting are commonly associated with NAC therapy.[11] Similarly, MgIG, an approved hepatoprotective agent in China, has demonstrated efficacy in improving DILI. Nevertheless, its use is constrained by side effects including granulocytopenia, fever and gastrointestinal discomfort.[76] These limitations highlight the clinical demand for alternative antidotes with extended efficacy windows and improved side effects.

In addition to traditional detoxification measures, several emerging therapeutic approaches for AILI have been researched in recent years. These include 4-methylpyrazole (4 MP), calmangafodipir (CMFP), metformin, and methylene blue.[77,78] 4 MP, a cytochrome P450 inhibitor, mitigates AILI by suppressing APAP metabolism and reducing the formation of oxidative APAP metabolites, such as APAP-cysteine, APAP-N-acetylcysteine, and APAP-GSH.[79] It is generally administered within 90 min after APAP overdose to reduce liver damage at an early stage. Unlike NAC, 4 MP treatment can also prevent APAP-induced kidney damage and promote liver regeneration in mice, and it may extend the therapeutic window of NAC for treatment of APAP overdose.[11] CMFP, a superoxide dismutase (SOD) mimetic and modified compound of mangafodipir, has shown good tolerability and limited side effects in patients with APAP overdose.[80] In a POP trial, it was shown that when used with NAC, it can reduce the toxicity of APAP.[80] Metformin, a drug widely used for type 2 diabetes, has also been found to reduce AILI by alleviating mitochondrial oxidative stress and preventing subsequent mitochondrial dysfunction.[81,82] Additionally,

Table 1
Biomarker performance in DILI identification.

Category	Biomarker	Multiple cohort clinical study[61]	Prospective cohort study[10]		
		ROC-AUC (95% CI)	ROC-AUC (95% CI)	Specificity	Sensitivity (95% CI)
Traditional	ALT	0.990 (0.984–0.996)	0.84 (0.79–0.89)	0.95	0.52 (0.42–0.62)
Candidate	miR-122	0.831 (0.779–0.883)	0.97 (0.95–0.98)	0.95	0.79 (0.70–0.87)
Candidate	HMGB1	–	0.95 (0.93–0.98)	0.95	0.82 (0.73–0.88)
Candidate	Full-length K18	0.947 (0.928–0.966)	0.95 (0.92–0.97)	0.95	0.56 (0.46–0.66)
Candidate	Caspase-cleaved K18	0.911 (0.887–0.935)	0.84 (0.78–0.89)	0.95	0.65 (0.56–0.75)
Candidate	GLDH	0.907 (0.870–0.945)	0.86 (0.82–0.90)	0.95	0.58 (0.48–0.68)

methylene blue, a redox-active agent, functions as an alternative electron carrier to improve mitochondrial function and prevent damage caused by APAP metabolism.[83] Therefore, the accumulated data suggest that other antidotes with different effects may be used as adjunctive treatments for NAC, particularly 4 MP and CMFP.

A systematic review has proposed different pharmacological interventions for the prevention and treatment of DILI, categorizing the available therapeutics into several classes: 1) hepatoprotective drugs that can enhance liver detoxification, promote hepatocyte regeneration, and/or improve liver function, including NAC and GSH, Glycyrrhizin acid preparation, Polyene phosphatidylcholine (PPC), Bicyclol, and Silymarin, which respectively play a role in detoxification, anti-inflammatory, hepatocyte membrane protection, and anti-oxidation; 2) anticholestatic drugs for addressing cholestatic DILI, aimed at alleviating cholestasis symptoms and promoting bile secretion, such as Ursodeoxycholic acid (UDCA), S-adenosylmethionine (SAMe), and Cholestyramine; 3) immunosuppressants like Glucocorticoids (GCs); and 4) specific therapeutic drugs such as L-carnitine and anticoagulants.[84,85] Currently, some drugs such as NAC, MgIG, and Bicyclol have shown some efficacy in clinical studies, but clinical evidence for most of these drugs is still limited and is not yet sufficiently comprehensive to support the widespread use of these drugs in different types of DILI. Regarding the efficacy and safety of drug combinations, there is also a lack of systematic studies at present. Internationally circulated guidelines for DILI do not recommend the combination of two or more drugs, mainly due to the lack of multicenter randomized controlled clinical trials with high quality and sufficient sample size. There is an urgent need for multicenter clinical studies with large samples to provide more sufficient medical evidence.

Another comprehensive review evaluated the therapeutic potential of several novel clinical approaches for DILI, with many showing varying degrees of efficacy. Using improvements in laboratory biomarkers as the primary efficacy indicators, it was reported that there was moderate evidence of liver function enhancement with MgIG compared to placebo, while Bicyclol showed low evidence compared to phosphatidylcholine. And the certainty of evidence for the remaining eight treatments, such as calmangafodipir, cytisin amidophospate, fomepizole, picroliv, radix Paeoniae Rubra, SAMe, livina-polyherbal preparation, and plasma exchange, was assessed as very low, despite showing some potential in small scale studies.[86,87]

Despite the ongoing research and increasing application of novel drugs, the long-term clinical efficacy and safety of these treatments still require further validation. Especially for complex and severe cases of DILI, therapeutic strategies must be more personalized and precise.

4.1.2. Ethnomedical treatments

For the treatment of DILI, ethnomedicine, with its unique advantages, has become an important complementary treatment besides western medical treatment. In recent years, with the intensive research on modern pharmacology, an increasing number of TCM and their active ingredients have gradually had their mechanisms revealed and been shown to have a better effect on improving DILI. These studies not only provide a scientific basis for the application of TCM, but also expand new research directions and intervention strategies for the treatment of DILI.

4.1.2.1. Ethnomedicine perspectives. Although DILI is not explicitly defined in ethnomedicine, its pathological manifestations are often categorized under jaundice, hypochondriac pain, or abdominal masses, and are closely associated with dysfunctions of the liver, gallbladder, spleen, stomach, and kidneys.

Clinically, patients with DILI commonly present with symptoms such as yellowing of the sclera, skin, and urine, which align with the ethnomedicine syndrome of dampness-heat jaundice.[88] Additionally, patients may experience nonspecific gastrointestinal symptoms, including fatigue, inappetence, aversion to greasy foods, epigastric discomfort, and liver pain.[88] From the ethnomedicine perspective, these symptoms are attributed to spleen deficiency with dampness accumulation. In more severe cases, DILI may manifest with fever, rash, tarry stools (indicating coagulopathy), or even coma.[89] As mentioned in ethnomedicine, bile excretion disorders can lead to dampness-heat, which further triggers pruritus and rash.

Therefore, TCM not only focuses on symptom relief in the treatment of DILI, but also emphasizes the identification of constitution and the regulation of internal organ functions, thus providing a theoretical basis for individualized treatment. Based on clinical symptoms, ethnomedicine classifies DILI into syndromes including dampness-heat jaundice, liver *qi* stagnation and spleen deficiency, internal retention of dampness-heat, *qi* stagnation and blood stasis, and liver-kidney *yin* deficiency in accordance with the International Standard Chinese-English Basic Nomenclature of Chinese Medicine.[90] Guided by the principles of syndrome differentiation and treatment, ethnomedicine may offer a unique therapeutic framework for managing DILI.

4.1.2.2. Hepatoprotective TCM. Ethnomedicine, with its roots in thousands of years of empirical practice, has demonstrated unique advantages in the treatment of DILI. The therapeutic effects of TCM mainly involve the regulation of multiple signaling pathways, including anti-inflammation, antioxidation, ferroptosis inhibition, anti-apoptosis, and so on, thereby achieving liver protection. In recent years, with the extraction and research of monomer components from TCM, an increasing number of bioactive monomers have been discovered, becoming valuable resources for exploring novel therapeutic agents for DILI.[91] Most studies have shown that TCM can significantly improve DILI through various mechanisms (Table 2).

Notably, different from modern medicine, ethnomedicine emphasizes syndrome differentiation and treatment. The medication regimens and dosages corresponding to different conditions and symptoms exhibit highly individualized characteristics. In addition, the same drug has different pharmacological activities at different doses, as in the case of *Bupleuri radix*, which makes the study of the dose-effect relationship of TCM complex. The processing methods and decoction processes of herbs are also important factors affecting the efficacy of TCM, and appropriate processing of herbs can enhance its efficacy and reduce toxicity. Traditionally, the extraction methods of TCM include decoction, maceration, percolation, and so on, among which decoction is the most commonly used method.[92] The efficacy of TCM not only depends on the quality control and standardized extraction of the herbs themselves, but also is

Table 2
Hepatoprotective TCM for DILI.

Pathogenesis	TCM	Active ingredient	Effects
Mitochondrial dysfunction	*Lysimachiae herba*[93]	Flavonoids	MDA↓, GSH↑, SOD↑
	Bupleuri radix[14–16]	Saikosaponins	GSH↑, CYP2E1 and CYP3A activity↓, Phosphorylation of AMPK, LATS1 and YAP↑, Oxidative stress↓
	Rhizoma atractylodis macrocephalae[95]	Polysaccharides	NOS, NO and MDA↓, SOD and GPx↑
	Radix gentianae[97]	Gentiopicroside	GSH, SOD and GPx↑, MDA↓, Caspase-3↓, Phosphorylation of JNK1/2 and ERK↓
	Angelica sinensis[98]	Polysaccharide	GSH and SOD↑, MDA↓, Caspase-3 and Bax↓, Bcl-2↑
Ferroptosis	*Paeonia lactiflora*[17,99]	Paeoniflorin	GSH and SOD↑, MDA↓, CYP3A4↓, PKC-ERK-P90RSK pathway↓, Nrf2/HO-1↑, Bax and Bad↓, Bcl-2↑
	Schisandra chinensis[101,102]	Schisandrol B	GSH↑, MDA↓, CYP2E1, CYP1A2 and CYP3A11↓, Nrf2, GCLC, GSR, NQO1, GSTs, MRP2, MRP3 and MRP4↑
	Leonurus japonicus[103]	Leonurine	Nrf2, NQO1, HO-1, and GCLC↑, ROS and MDA↓, GSH, GPx and SOD↑
Immune system	*Gardenia jasminoides*[18]	Geniposide	GSH↑, MDA↓, CYP2E1↓, TLR4/NF-κB signaling pathway↓, IL-1β↓, TNF-α↓
	Carthamus tinctorius[106–108]	Hydroxysafflor yellow A	Excretion of APAP↑, TNF-α, NF-κB, IL-6, iNOS and eNOS↓
	Sophora alopecuroides[109]	Aloperine	HMGB1/TLR4/NF-κB↓, NLRP3, Caspase-1, TNF-α and IL-1β↓
Gut-liver axis	*Lycium barbarum*[111]	–	*Akkermansia muciniphila*↑, LPS↓, Yes-associated protein 1↑
	Broussonetia papyrifera[112]	Polysaccharide	*Prevotellaceae_UCG-001*↑, IL-6, TNF-α and IL-10↓, CYP2E1↓, SOD, GPx and GSH↑, Nrf2, NQO1, HO-1, GCLm and GCLC↑
	Rabdosia rubescens[113]	Oridonin	*Bacteroides vulgatus*↑, Urea cycle-Nrf2 pathway↑, HO-1, and NQO1↑
Mitochondrial dysfunction and immune system	*Citri reticulatae pericarpium*[114,115]	Naringenin	GSH and GPx↑, MDA↓, TNF-α, IL-6 and IL-1β↓, Bax↓, Bcl-2↑, PPARA↑
Mitochondrial dysfunction, ferroptosis and immune system	*Scutellaria baicalensis*[117]	Wogonin	GSH↑, ROS and MDA↓, Keap1↓, Nrf2↑, TNF-α and IL-1β↓, Chemokines (CXCL1, CXCL2, CXCL10, CCL2, CCL3, CCL4 and CCL5) ↓
	Salvia miltiorrhiza[119–122]	Salvianolic acid A	GSH↑, TNF-α, IL-1β and NF-κB↓, MiR-485-3p↓, SIRT1↑
		Salvianolic acid B	PI3K↑, PKC↑, Nrf2, HO-1, GCLC↑
		Salvianolic acid C	CYP2E1↓, NF-κB, TLR4 and MAPKs↓, GSH, SOD, GPx, CAT and Keap1/Nrf2/HO-1 pathway↑, Bax and Caspase-3↓
		Tanshinone IIA	GSH, GST, GPx, SOD and CAT↑, MDA↓, Nrf2, GCLC, NQO1 and HO-1↑
	Cornus officinalis[123,124]	Ethanol extract	GSH↑, MDA↓, SOD, CAT and HO-1↑
		n-Butanol extract	TNF-α, IL-6 and IL-1β↓, Nrf2 and HO-1↑, p-AKT/AKT and p-NF-κB p65/NF-κB p65↓

affected by the pharmacokinetic properties and in vivo distribution pattern of the drug. The oral bioavailability of many active ingredients of TCM is relatively low, making it difficult to define their real effects in vivo. Therefore, strengthening the quantitative analysis of TCM components, the analysis of in vivo metabolic processes and the standardization of preparations are crucial for the promotion of the clinical translation and application of TCM.

In terms of specific applications, some TCM and their active ingredients have been shown to have hepatoprotective effects. In the research of DILI, mitochondrial oxidative stress is considered to be one of the key pathogenic mechanisms, so interventions targeting antioxidative stress have become an important direction for the treatment of DILI with TCM. A variety of TCM have demonstrated significant effects in alleviating oxidative damage in hepatocytes by modulating the activities of key antioxidant enzymes such as SOD and GPx. For example, *Lysimachiae herba*, known for its efficacy in jaundice, hepatitis, and gallstones, has been shown to ameliorate cholestatic liver injury in rats by decreasing MDA and increasing GSH and SOD activity levels, with flavonoids as its primary active constituents.[93] In addition, *Bupleuri radix*, a commonly used TCM in ethnomedicine with outstanding efficacy in the treatment of cold and fever, swelling pain in the chest and hypochondrium, and hepatitis,[94] has received attention for its application in DILI. Studies have shown that it is able to alleviate APAP-induced acute liver injury in rats effectively by preventing the depletion of hepatic GSH to attenuate oxidative stress and inhibiting the increase in the activity of liver cytochrome P450 (CYP450), with saikosaponin A identified as the key active ingredient.[14–16] Meanwhile, *Rhizoma atractylodis macrocephalae* can effectively reduce the damage of oxidative stress to the liver of mice by increasing antioxidative enzyme activity of SOD and GPx.[95] Its primary active ingredients, polysaccharides, are considered key substances in its hepatoprotective effects, although their application in DILI needs to be further investigated. It is worth mentioning that the hepatoprotective mechanism of *Radix gentianae* is closely related to its ability to scavenge free radicals, and enhance liver antioxidant and anti-inflammatory capacity.[96] Animal experiments showed that treatment with *Radix gentianae* enhances liver antioxidant capacity by upregulating the activities of antioxidant enzymes such as SOD and GPx, and also reduces apoptosis *via* inhibition of JNK/ERK MAPK activation and caspase-3 cleavage.[97] Thus, it effectively prevents AILI in mice and demonstrates powerful hepatoprotective effects. And the polysaccharides of *Angelica sinensis* not only improve oxidative stress and lipid peroxidation, but also inhibit apoptosis by regulating the expression of Bax, Bcl-2, and cleaved caspase-3, demonstrating significant alleviation of liver injury in rats with APAP overdose.[98] Overall, these TCM exert antioxidant effects by elevating the GSH and SOD levels and decreasing the MDA level, effectively inhibit mitochondrial oxidative stress in hepatocytes, and show good potential in mitigating DILI, which provides a rich source of natural drugs and theoretical basis for the intervention strategy of DILI targeting antioxidant mechanisms.

In addition to mitochondrial oxidative stress, ferroptosis, as a novel form of cell death that is iron-dependent and characterized by lipid peroxidation, has been suggested to play a key role in DILI in recent years. Intervention around the ferroptosis pathway has become a new exploratory direction for the regulation of DILI with TCM. For instance, *Paeonia lactiflora*, a commonly used TCM for the treatment of various liver diseases, has been shown to inhibit apoptosis and ameliorate oxidative stress by reversing the decrease of Nrf2/HO-1 expression, effectively ameliorating AILI in mice.[17] Further studies revealed that its main active ingredient, paeoniflorin, may exert a significant hepatoprotective effect by targeting and inhibiting JNK and its downstream apoptotic signaling to attenuate mitochondrial dysfunction.[99] In addition, the abundant lignans in *Schisandra chinensis* are its primary bioactive components,[100] especially schisandrol B, which can reduce toxic metabolite production by inhibiting the activities of various CYP450 enzymes, and also prevent the occurrence of lipid peroxidation by activating the Nrf2-ARE signaling pathway and enhancing the GSH synthesis, thus having a significant protective effect against AILI in mice.[101,102] Leonurine, a natural alkaloid extracted from *Leonurus*

japonicus, significantly inhibited APAP-induced hepatotoxicity by activating the Nrf2 pathway, promoting Nrf2 nuclear translocation and up-regulating the expression of antioxidant target genes like NQO1, GCLC, and HO-1 to enhance the antioxidant defense capacity of hepatocytes in mice with AILI.[103] In summary, more and more studies have shown that TCM and its active ingredients are involved in intervening in the ferroptosis process by enhancing GSH synthesis, activating the Nrf2 pathway and inhibiting lipid peroxidation, thus demonstrating a remarkable potential in the treatment of DILI. Continued research on the mechanism of ferroptosis not only broadens the theoretical basis for the treatment of DILI with TCM, but also provides important insights for the development of novel ferroptosis intervention drugs.

The immune cascade likewise plays a key role in the pathogenesis of DILI. A variety of natural ingredients can be used to intervene and treat DILI by inhibiting immune signaling pathways and immune regulatory mechanisms. Therefore, exploring the hepatoprotective effects of TCM in suppressing immune mechanisms has important theoretical significance and application prospects. For instance, *Gardenia jasminoides* is also often used together with other drugs in the treatment of jaundice.[104] Its main active ingredient, geniposide, mitigates AILI in mice through multiple mechanisms. On the one hand, it attenuates oxidative stress by reducing NAPQI formation *via* CYP2E1 inhibition. On the other hand, it inhibits the activation of the TLR4/NF-κB signaling pathway, which effectively reduces the infiltration of hepatic inflammatory cells.[18] It is worth mentioning that geniposide also shows the ability to alleviate cholestasis in rats, as it reduces bile acid synthesis by downregulating CYP enzymes, inhibits bile acid uptake *via* OATP2, and activates bile salt export pump (BSEP) to promote bile acid secretion, indicating its therapeutic potential in DILI-related cholestasis.[105] And the active components of *Carthamus tinctorius,* hydroxysafflor yellow A (HSYA) and HSYC, demonstrate superior efficacy to NAC in reducing APAP toxicity in mice, probably by accelerating APAP excretion,[106] suppressing oxidative stress and inflammation, and modulating calcium, estrogen, and cGMP-PKG signaling pathway.[107,108] Another TCM, *Sophora alopecuroides*, the bioactive component of which is aloperine. The hepatoprotective effect in AILI is closely related to the inhibition of the activation of the HMGB1/TLR4/NF-κB signaling pathway. By blocking this pathway, aloperine can effectively inhibit the activation of the NLRP3 inflammasome, thereby reducing the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which results in the reduction of inflammatory responses and the amelioration of hepatic damage in mice.[109] These studies have demonstrated that the mechanisms of multiple TCM and their active ingredients in DILI are focused on immune modulation and inhibition by targeting TLR4, NF-κB, and NLRP3 inflammasome. Despite these advances, there are still some immune related mechanisms that have not yet been elucidated, and the specific targets of different active components still need to be further validated and integrated.

In recent years, growing attention has been paid to the interaction between oral TCM and gut microbiota in the treatment of DILI. Research has shown that the metabolism and compound transformation of orally administrated TCM in the intestine depend on the enzymes expressed by the gut microbiota. At the same time, TCM can indirectly affect the immune and disease status of the liver by regulating composition and metabolism of gut microbiota.[110] For instance, *Lycium barbarum* has been shown to promote the proliferation of activated *Akkermansia muciniphila*, which would improve the gut barrier function, upregulate the expression level of Yes-associated protein 1 (YAP1) and decrease content of LPS, thereby improving the liver injury induced by APAP.[111] Meanwhile, polysaccharides from *Broussonetia papyrifera* alleviate AILI not only by upregulating antioxidant protein levels and inhibiting hepatocyte oxidative stress and apoptosis, but also by improving the abundance and diversity of gut microbiota like *Prevotellaceae_UCG-001*, which in turn affects flora metabolism and liver injury.[112] Furthermore, oridonin, the principal active component of *Rabdosia rubescens*, alleviates AILI by modulating the gut microbiota, primarily through the enrichment of intestinal *Bacteroides vulgatus* to activate the urea cycle-Nrf2 pathway, thus exerting an antioxidant role in liver protection.[113] TCM comprises a wide range of compounds that interact with gut microbiota upon oral administration, and investigations into these interactions offer innovative approaches for enhancing the treatment of DILI. However, further studies are required to elucidate the mechanisms by which TCM improves DILI through its interactions with gut microbiota.

For the treatment of DILI, TCMs and their active ingredients often possess the properties of multi-targets and multi-mechanisms synergistic effects, conferring them with distinct therapeutic advantages. Examples include the following TCM. First, naringin, the main active ingredient of *Citri reticulatae pericarpium*, has been shown to have significant hepatoprotective effects both in mice and in LO2 cells. On the one hand, naringin can inhibit inflammation by down-regulating the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while on the other hand, it can ameliorate the oxidative stress of hepatocytes by regulating the levels of MDA, GSH, and GPx.[114,115] In addition, naringenin upregulated PPARA expression to alleviate hepatic oxidative damage. These findings suggest that *Citri reticulatae pericarpium* has multiple mechanisms with both anti-inflammatory and antioxidant effects in DILI treatment. Meanwhile, the active flavonoids of *Scutellaria baicalensis*, including baicalin, wogonin, and oroxyloside, have been extensively studied in the context of DILI.[116–118] In particular, wogonin has been shown to inhibit hepatic inflammatory response and ferroptosis to reduce AILI in mice by regulating the PI3K/AKT signaling pathway to downregulate the expression of pro-inflammatory cytokines such as TNF-α and IL-1β and chemokines, and meanwhile cooperates with the Keap1-Nrf2 antioxidant pathway.[117] And traditionally used for the treatment of cardiovascular disease, *Salvia miltiorrhiza*, whose active ingredients salvianolic acids and tanshinones have been shown to improve AILI. Salvianolic acid A improves liver oxidative stress and inflammation by regulating miR-485-3p/SIRT1 pathway,[119] while salvianolic acid B and C and tanshinone IIA attenuate ferroptosis, inflammation, and/or apoptosis by modulating the expression of genes such as Nrf2, NF-κB, and Bax, and protect hepatocytes against injury in mice.[120–122] Furthermore, although the specific effective ingredients of some TCM have not been clearly identified, their therapeutic efficacy has been demonstrated. For example, *Cornus Officinalis* shows that its ethanol extract effectively alleviates oxidative stress by inhibiting lipid peroxidation through increasing the activities of GSH and antioxidant enzymes such as SOD, CAT, and HO-1.[123] It was also found that key active ingredients in its *n*-butanol fraction include ellagic acid, quercetin, caffeic acid, ursolic acid, and so on. They can exert hepatoprotective effects by inhibiting ferroptosis and anti-inflammation in rats through the activation of key proteins in the AKT/Nrf2 signaling pathway, such as AKT1, TNF-α, Nrf2, and HO-1.[124] These findings highlight the multifunctional properties of *Cornus Officinalis* in alleviating liver injury. In summary, these TCM and their active ingredients demonstrate the pharmacological characteristics of multi-mechanism cooperative effects in DILI therapy through the inhibition of oxidative stress, ferroptosis, and inflammatory responses simultaneously. This characteristic not only reflects the advantages of TCM in overall regulation, but also provides direction for the development of novel, multi-targeted drugs for DILI therapy. Further studies should focus on the validation of active ingredients, the analysis of effect mechanisms, and the establishment of individualized therapeutic strategies, so as to promote the modernization transformation and clinical promotion of TCM in the treatment of DILI.

4.1.3. Hepatoprotective Chinese medicinal formulas

In the treatment of DILI, with the continuous and intensive research on the effect mechanisms of Chinese medicine formulas, it has gradually become an important strategy for intervening in DILI due to its multi-component, multi-target, and co-regulatory characteristics. Chinese medicine formulas can inhibit multiple mechanisms, including

inflammation, oxidative stress, ferroptosis, and apoptosis, and regulate bile acid metabolism to alleviate liver injury cooperatively, thereby exhibiting significant clinical translational potential. Potential Chinese medicine formulas are listed and their effect mechanisms are discussed (Table 3).

Yinchenhao decoction, a classical formula used primarily for the treatment of cholestasis, has been shown to exert hepatoprotective effects by up-regulating the levels of hepatic metabolic enzymes and transporters in rats, thereby accelerating the metabolism of bilirubin.[125] And the potential mechanism underlying its effects also involves inhibition of bile acid synthesis and transport *via* FXR, which upregulates BSEP expression and promotes bile acid transport from hepatocytes into bile ducts, thus alleviating bile acid-related hepatotoxicity.[126] Moreover, in another study on obstructive jaundice in rats, Yinchenhao decoction was reported for the first time to promote the nuclear translocation of Nrf2 and to up-regulate the expression of the antioxidant factors GSH and NQO1.[127] These results suggest that Yinchenhao decoction has significant potential in the treatment of cholestatic DILI, although its clinical efficacy and mechanisms still require further experimental validation.

Secondly, Sangyu granule is a Chinese patent medicine from Xijing Hospital. Studies have shown that it can inhibit inflammatory response by downregulating IL-1β and TNF-α levels. It also mediates FXR to regulate bile acid synthesis by up-regulating the expression of key bile acid secretion proteins such as SHP and FGF-15 through both liver and intestinal mechanisms, thereby significantly improving AILI.[128] These mechanisms collectively promote liver repair and protection, highlighting the potential of Sangyu granule in the treatment of DILI.

Meanwhile, Liuweiwuling tablets have shown significant efficacy in alleviating APAP-induced acute liver injury.[129] The hepatoprotective mechanisms include the inhibition of ROS release by schisandrin A and schisandrin B, and the significant reduction of IL-1β and TNF-α by active ingredients like esculetin, luteolin, schisandrin A, and schisandrin B[130]. The synergistic action of these components provides enhanced protection against liver injury by mitigating oxidative stress and inflammation.[130]

In a study on the prevention of anti-tuberculosis drug-induced liver injury in mice, Xiao-Yao-San has shown favorable hepatoprotective effects in improving cellular mitochondrial function. And its effects are mainly through mediating Grsf1 to up-regulate the expression of mitochondrial synthesis-related proteins like PGC-1α, and to reverse the expression of ferroptosis-related proteins, such as GPx4 and FTH1.[131]

Furthermore, Yinhuang oral liquid has shown significant protective effects against AILI in mice. Its mechanism mainly involves inhibiting lipid peroxidation and increasing the activities of antioxidant enzymes such as SOD and GSH, thereby ameliorating oxidative stress. Meanwhile, it can also reduce oxidative damage and maintain cellular homeostasis by activating the Nrf2 signaling pathway and up-regulating autophagy-related genes, thus exerting a protective effect against AILI. According to study results, it is more effective than the control therapeutic drug NAC and has a favorable application prospect.[132]

In summary, these Chinese medicinal formulas show promising therapeutic prospects in the combination intervention of DILI by co-regulating multiple key mechanisms. Although the main active ingredients and specific effect mechanisms of these drugs still need to be further clarified, they provide an important pharmaceutical experimental basis for intervention in DILI and offer new insights for clinical treatment.

It is worth mentioning that although TCM has shown certain advantages in the treatment of DILI, it is still necessary to acknowledge its limitations and potential problems. Currently, relatively few clinical studies have been conducted on single TCM, and most of the studies remain in animal experiments, resulting in a lack of sufficient evidence for their in vivo efficacy and safety. In addition, although compound TCMs show better efficacy, they are often difficult to be clearly attributed to a certain active ingredient due to their complex formulas, which increases the difficulty of their clinical application and mechanism research. Meanwhile, due to the complexity and unpredictable safety of TCM, some of them, such as *Carthamus tinctorius* and *Schisandra chinensis,* are harmful to human beings under overdose, suggesting that the monitoring and risk assessment of adverse reactions should be strengthened in clinical application. In addition, TCM is less recognized in the international medical community and faces cultural and scientific obstacles that affect its wide application. And the data from large-scale randomized controlled trials of TCM in the treatment of DILI are very limited and are the main focus of future studies to further confirm the efficacy and safety of TCM. This will help to elucidate the potential advantages and limitations of TCM in the treatment of DILI, provide more powerful evidence for clinical application, and facilitate further exploration of its mechanisms.

Table 3
Hepatoprotective Chinese medicinal formulas for DILI.

Pathogenesis	Chinese medicinal formulas	Formula	Effects
Ferroptosis	Yinchenhao decoction[125]	*Artemisia capillaris*, *Gardenia jasminoides* and *Rheum rhabarbarum*.	UGT1A1, BSEP, MRP2, OATP1A4↑, Nrf2, GSH and NQO1↑
Immune system	Sangyu granules[128]	*Fragrant solomonseal rhizome*, *Rhizoma polygonati*, *Semen coicis*, *Fructus mori*, *Semen hoveniae*, *Semen ziziphi spinosae* and *Fructus gardeniae*.	CYP7A1↓, FXR and SHP↑, IL-1β and TNF-α↓
Mitochondrial dysfunction and immune system	Liuweiwuling tablets[129]	*Schisandra chinensis*, *Fructus ligustri lucidi*, *Forsythia suspensa*, *Rhizoma curcumae*, *Field sowthistle herb* and *Ganoderma lucidum spore*.	ROS↓, HMGB1↓, TNF-α and IL-1β↓, PCNA and CyclinD1↑, p21↓
Mitochondrial dysfunction, ferroptosis and immune system	Xiao-Yao-San[131]	*Bupleurum chinense*, *Angelica sinensis*, *Paeonia lactiflora*, *Atractylodes macrocephala*, *Poria cocos*, *Glycyrrhiza uralensis*, *Zingiber officinale* and *Mentha haplocalyx*.	MDA and ROS↓, GSH and SOD↑, TNF-α and IL-6↓, IL-10↑, Grsf1, GPx4 and FTH1↑, TfR1↓
Mitochondrial dysfunction and ferroptosis	Yinhuang oral liquid[132]	*Artemisiae Scopariae* and *Scutellaria baicalensis*.	GSH and SOD↑, MDA↓, Nrf2 and HO-1↑, Keap1↓, p62↓, LC3↑, Beclin-1, Atg4B, Atg5, Atg16L1 and Atg7↑

4.2. Non-pharmacological treatments

The treatment of DILI not only involves identifying implicated drugs and timely cessation, as well as monitoring hepatic biochemistry to evaluate the risk and benefit of drug withdrawal, but also requires selecting appropriate pharmacological interventions based on clinical manifestations of patients. However, for DILI patients with severe hepatic encephalopathy, ALF, decompensated cirrhosis, or coagulopathy, non-pharmacological support treatment becomes particularly important. Therapeutic interventions such as artificial extracorporeal liver support, hemodialysis, peritoneal dialysis, and liver transplantation play a crucial role in the management of these critically ill patients.[84]

High-volume plasma exchange is an effective treatment that can remove protein-bound toxins from circulation while replenishing deficient plasma factors, with clinical studies demonstrating improved

survival rates in both adult and pediatric ALF patients.[133,134] European guidelines have included high-volume plasma exchange as level 1 recommendation for ALF management, and a systematic review has shown that compared to standard medical treatment, plasma exchange significantly enhances 30-day and 90-day survival rates in non-transplant ALF patients.[135]

Currently, artificial liver support mainly relies on extracorporeal albumin dialysis, which efficiently clears both hydrosoluble and albumin-binding molecules, drugs, and toxins in patients with advanced liver disease, thereby improving their metabolic environment. Studies have reported short-term survival benefit at 15 and 21 days, respectively, in patients with acute liver failure and acute-on-chronic liver failure.[136] Although its therapeutic effects still need further validation, it offers a potential for extending survival in liver failure patients.

For end-stage liver failure caused by DILI, liver transplantation remains a critical salvage therapy when conservative treatment fails and the patient meets transplantation criteria. Although transplantation can significantly improve the short-term survival and prognosis of patients, there are still certain risks and challenges in the long-term survival. According to the data, the survival rate for patients undergoing liver transplantation is 83% in the first year, with survival rates declining by approximately 10% every five years.[137] Additionally, liver transplantation remains challenging due to donor shortages, risk of immune rejection, and complexity of postoperative management, making its implementation associated with certain risks and difficulties.

5. Conclusions and future perspectives

DILI can lead to severe consequences, affecting not only patients and their caregivers but also regulatory agencies and the development of new pharmaceuticals. Currently, DILI is induced by various types of prescription or over-the-counter chemical drugs, biological agents, TCM, natural medicine, health products, dietary supplements, and their metabolites and even excipients. A deeper understanding of the pathophysiological mechanisms of DILI and the development of effective prevention and treatment strategies are the keys to individualized treatment.

Current studies mainly focus on immune-mediated inflammatory response and mitochondrial dysfunction, while mechanisms such as ferroptosis and role of gut-liver axis are gradually attracting attention, which enriches the understanding of the complex pathologic process of DILI. However, evidence for these mechanisms is mostly based on in vitro cellular experiments and animal models. Despite providing valuable clues to reveal the pathogenesis of DILI, there are obvious limitations in simulating the complex pathological state and drug responses in humans. For example, although mitochondrial dysfunction and ferroptosis have been validated in rodent models, the direct clinical evidence in human patients with DILI is not yet sufficient.

Corresponding to the research on the mechanism of DILI, the development of the diagnostic system is also constantly deepening. Despite the availability of certain clinical diagnostic methods, there are still many difficulties in the accurate diagnosis of DILI. Currently, the clinical diagnosis of DILI mainly relies on liver function tests and the RUCAM causality scoring system, but these traditional methods have limitations of insufficient sensitivity and specificity. In recent years, candidate biomarkers, including miR-122, HMGB1, full-length and caspase-cleaved K18, and GLDH, have potential advantages in enhancing diagnostic sensitivity and specificity, and have shown promising prospects in early identification, subtyping diagnosis and prognostic evaluation. In the future, the clinical validation and application of highly sensitive and specific biomarkers and multiple indicators combined with a diagnostic model should be accelerated to achieve advance warning and individualized classification of DILI.

In terms of therapeutic strategies, interventions for DILI are still relatively limited. Today, NAC remains the FDA-approved standard treatment for APAP overdose. In addition, the Chinese FDA approved MgIG for the treatment of acute hepatocellular injury caused by DILI. In the future, the discovery of more drugs and the development of non-pharmacological treatments are expected to provide new strategies for the treatment of DILI. TCM and Chinese medicinal formulas, due to their characteristics of multiple components, multiple targets, and multiple pathways, have shown certain potential in inhibiting inflammation, mitochondrial dysfunction, and ferroptosis, and regulating intestinal microbiota, which may provide a complement to the pharmacological treatment of DILI. However, there are common problems in TCM research, such as complex composition, unclear bioactive components, confusion regarding ethnomedicine theories, and lack of large-scale randomized controlled trials, which hinders its effective translation and international recognition. In conclusion, attention should be paid to the mechanism exploration, development and clinical validation of biomarkers, and application research in ethnomedicine to lay the foundation for individualized and precise prevention and treatment strategies for DILI.

CRediT authorship contribution statement

Xinxin Tan: Writing – review & editing, Writing – original draft, Visualization. **Jiajia Gao:** Writing – review & editing, Investigation. **Chao Wang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 31871315), the Natural Science Foundation of Guangdong, China (No. 2018A030310693).

Abbreviations

ACSL4, Acyl-CoA synthetase long-chain family member 4; AIF, Apoptosis-inducing factor; AILI, APAP-induced liver injury; ALF, Acute liver failure; ALOX15, Arachidonate lipoxygenase 15; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; APAP, Acetaminophen; AST, Aminotransferase; ATG5-ATG7, Autophagy protein 5 and 7; ATP, Adenosine triphosphate; AUC, Area under the curve; BH_4, Tetrahydrobiopterin; BSEP, Bile salt export pump; CAT, Catalase; CoQ_{10}, Coenzyme Q_{10}; COX-2, Cyclooxygenase 2; CT, Computed tomography; CYP, Cytochrome P450; DAMPs, Damage-associated molecular patterns; DHFR, Dihydrofolate reductase; DILI, Drug-induced liver injury; Endo G, Endonuclease G; ETC, Electron transport chain; FSP1, Ferroptosis suppressor protein 1; FXR, Farnesoid X receptor; GCH1, Guanosine triphosphate cyclohydrolase 1; GCs, Glucocorticoids; GLDH, Glutamate dehydrogenase; GPx, Glutathione peroxidase; GSDMD, Gasdermin D; GSH, Glutathione; HLA, Human leukocyte antigen; HMGB1, High mobility group box 1; HSYA, Hydroxysafflor yellow A; IREB2, Iron-responsive element-binding protein 2; JNK, c-Jun-N-terminal kinase; K18, Keratin-18; Keap1, Kelch-like ECH-associated protein 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; LPS, Lipopolysaccharide; MCFU, Mitochondrial electrogenic Ca^{2+}, Fe^{2+} uniporter; MDA, Malondialdehyde; MgIG, Magnesium isoglycyrrhizinate; miRNAs, MicroRNAs; MPT, Mitochondrial permeability transition; MPTP, Mitochondrial permeability transition pore; MRI, Magnetic resonance imaging; mtDNA, Mitochondrial DNA; NAC, N-acetylcysteine; NAPQI, N-acetyl-p-benzoquinone imine; NCOA4, Nuclear receptor coactivator 4; nDNA, Nuclear DNA; Nrf2, Nuclear factor erythroid 2-related factor 2; NSAIDs, Non-steroidal anti-inflammatory drugs; PAMPs, Pathogen-associated molecular patterns; PPC, Polyene phosphatidylcholine; PPD, 1-phenyl-

1,2-propanedione; Prx, Peroxiredoxin; ROC, receiver operating characteristic; ROS, Reactive oxygen species; RUCAM, Roussel Uclaf Causality Assessment Method; SAMe, S-adenosylmethionine; SAT1, Spermidine/spermine N1-acetyltransferase 1; SOD, Superoxide dismutase; TB, Total bilirubin; TCA, Tricarboxylic acid; TLRs, Toll-like receptors; UDCA, Ursodeoxycholic acid; ULN, Upper limit of normal; YAP1, Yes-associated protein 1.

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