

## Review Article

# Potential Effects of Dietary Isoflavones on Drug-Induced Liver Injury

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Numerous prescribed drugs and herbal and dietary supplements have been reported to cause drug-induced acute liver injury, which is a frequent cause of acute liver failure (ALF). It is a tremendous challenge with ever-increasing drug application in the medication system for huge populations. Drug-induced acute liver injury can lead to diverse pathologies similar to acute and chronic hepatitis, acute liver failure, biliary obstruction, fatty liver disease, and so on. Recently, extensive work demonstrated that isoflavones play an essential and protecting role in drug-induced liver injury (DILI). The isoflavones mediated hepatoprotection by modulating specific genes linked with control of cellular redox homeostasis and inflammatory responses. Isoflavones upregulate oxidative stress-responsive nuclear factor erythroid 2-like 2 (Nrf2), downregulate inflammatory nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathways, and modulate a balance between cell survival and death. Moreover, isoflavones actively inhibit the expression of cytochromes P450 (CYPs) enzyme during drug metabolism. Moreover, isoflavones are also linked with farnesoid X receptor (FXR) activation and signal transducer and activator of transcription factor 3 (STAT3) phosphorylation in hepatoprotection DILI. *In vivo* and *in vitro* studies clearly stated that isoflavones bear strong antioxidant potential and promising agents for hepatotoxicity prevention and stressed their potential role as therapeutic supplements in DILI. The current review will elaborate on isoflavones' preventive and therapeutic potential concisely and highlight various molecular targets to exert a protective effect on DILI.

## 1. Introduction

Drug-induced liver injury (DILI) is a highly recognized issue that leads to withdrawal of the drugs from the market due to its prognosis with significant adverse effects such as asymptomatic transaminitis, acute and chronic hepatitis, cholestasis, and even death. It is caused not only by prescribed medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), anti-infective drugs, and anticancer drugs but also by herbal and dietary supplements (HDS) [1, 2],

particularly acetaminophen (APAP), which is a crucial cause of acute liver failure (ALF) [3].

Acute DILI takes about three months to develop. The type of injured target cells set helps to classify acute DILI into three types using  $R = (\text{ALT patient}/\text{ULN})/(\text{ALP patient}/\text{ULN})$ . These types include (1) hepatocellular type:  $\text{ALT} \geq 3 \text{ ULN}$  and  $R \geq 5$ , (2) cholestatic type:  $\text{ALP} \geq 2 \text{ ULN}$  and  $R \leq 2$ , and (3) hepatocellular-cholestatic mixed type:  $\text{ALT} \geq 3 \text{ ULN}$ ,  $\text{ALP} \geq 2 \text{ ULN}$ , and  $2 < R < 5$  [1]. DILI is the frequent cause of ALF and accounts for 20–40% of all instances of fulminant

hepatic failure throughout the United States and Europe [4, 5]. The incidence of DILI is as low as 1 in 10,000 to 100,000 [6]. It is difficult to find any particular drug ascribed to hepatic injury. Recent studies indicated the involvement and association of multiple factors in developing DILI. These DILI inducing factors include various environmental factors [1], genetic background [7], drug types [8], age [9], gender [10], pregnancy [11], and underlying liver diseases [12, 13].

The in-time diagnosis of DILI is a big challenge. The viral diseases (hepatitis A, B, C, and E virus, cytomegalovirus, and Epstein-Barr virus), autoimmune (antinuclear antibody and antismooth muscle antibody), and metabolic (Wilson's disease and  $\alpha$ 1-antitrypsin deficiency) disorders mostly mimic any form of acute hepatocellular DILI [14]. Therefore, it is necessary to exclude other liver diseases before clinical diagnosis and treatment of DILI. The frequently used tool for DILI diagnosis is the Roussel Uclaf causality assessment method (RUCAM) [15], which remains highly rational, comprehensive, and convenient. To date, the severity of acute DILI can be classified into five grades, namely, grade 0–5, where 0 is no liver injury, 1 is mild liver injury, 2 is moderate liver injury, 3 is severe liver injury, 4 is acute liver failure, and 5 is lethal [16].

Different people who are exposed to certain potential hepatotoxic drugs may react differently. The tolerators or nonsusceptible will not have the clinical manifestation of DILI. Mild and transient liver injury can recover naturally after withdrawal of the toxic drug. In certain severe liver injury cases, timely clinical salvage is also needed. Isoflavones are polyphenolic compounds having strong bioactivities primarily found in fruits, flowers, and vegetables. Moreover, isoflavones have been reported to possess estrogen-like effects and hence often called phytoestrogens [17]. The isoflavones have drawn much attention and are considered promising molecules to cure cancer, liver injury, neurodegenerative diseases, osteogenic issues, cardiovascular diseases, and hematotoxicity problems [18–20]. Common isoflavones (biochanin A, formononetin, and genistin) are often found as glycosides are also recognized as mild antioxidants, whereas gut flora help convert these glycosides into aglycones [21]. The isoflavones found in soy are reported to replenish the progress of acetaminophen-mediated hepatotoxicity *in vivo* by ameliorating the glutathione levels [22]. The isoflavones protect against fatty liver disease (FLD) through multiple cellular pathways involving the  $\beta$ -oxidation of fatty acid, biosynthesis of lipids, and modulation of reactive oxygen species (ROS). Moreover, aldose reductase (AR)/polyol pathway leads to the development of FLD by modulating the production of fructose in liver, peroxisome proliferator-activated receptor PPAR- $\alpha$  protein, cytochrome P450 (CYP)2E1 expression, and inflammatory factors expressed by certain endotoxins released by the gut flora. The isoflavones have been reported as potent AR inhibitors and hence reduce the onset of FLD [23]. The presence of complex compounds such as biochanin A, calycosin, daidzein, genistein, kakkalide, and tectorigenin in isoflavones made it a vital plant compound bearing various pharmacological properties. Herein, we will elaborate on the updated pharmacological activities of those isoflavones being applied in DILI.

## 2. Pathophysiology of DILI

The nature of DILI is highly complex pathogenesis work in a sequence of effects or simultaneous effects through series of mechanisms along with numerous risk factors, which has not been yet fully explained yet. During drug metabolism, drugs arrive in liver cells via blood circulation, and hence initial drug transport into the hepatocytes begun via influx transporters [24]. The drug in the form of the parent drug is metabolized by phase I and II drug-metabolizing enzymes (DMEs) and products of many reactive metabolites [25]. Phase I metabolism mainly includes cytochrome P450-1 and P450-2 (CYP1 and CYP2) and flavin-containing monooxygenases (FMO) [26]. Human cytochrome P450 2E1 (CYP2E1) metabolizes various drugs, including anti-tubercular compounds, alcohol, and anesthetics [27]. The mutation in phase I DME genes is a common factor causing the quick incidences of adverse drug reactions (ADRs), which altered the activity of proteins during drug metabolism to induce liver injury [28]. The parent drug, reactive metabolites, and heavier products will then discharge into the bile by efflux transporters [24]. Through phase II DMEs, reactive metabolites with a heavy side chain will be deactivated as toxic compounds [25]. The action of phase II DMEs is to replace the reactive aldehyde and alcohol functional groups with more significant but less reactive functional groups. Conjugated metabolites can be produced and lead the drug to get out in excretion and toxicity via the efflux transporters. In the meantime, conjugated metabolites can also create specific protein adducts that participate in reactive oxygen species- (ROS-) mediated oxidation to damage the cells. While both phases I and II DMEs can clear the parent drug and drugs metabolic products, the phase II metabolized drugs are the most stable and common form of the drug metabolism, with a general tendency to cause cholestasis and DILI during the clearance [29].

## 3. Potential Damage and Mechanism in DILI

**3.1. DILI and Reactive Metabolites.** During phase I reactions, biotransformation of the parent drug involves necessary steps to complete the subsequent phases of detoxification, which altered the compound highly hydrophilic. The parent drug turned to reactive metabolites in phase I metabolism by adding certain functional groups such as hydroxyl, carboxyl, amino, or thiol groups [25]. These functional groups are said to be highly reactive with proteins compared to the parent drug. ROS and reactive nitrogen species (RNS) that create these reactive metabolites are produced by the interaction of drugs with the proteins and lipid at cellular membranes through oxidative stress [30, 31]. Moreover, they can disrupt the cellular redox homeostasis that leads to lymphocyte-signaled apoptosis [31].

Furthermore, it can also lead to the development of inflammations by releasing proinflammatory cytokines [32]. In addition, the upregulation of AMP-activated protein kinase (AMPK) and the overexpression of Forkhead box O 1 (FoxO1), which was inhibited by drugs, can increase the

synthesis of triglycerides (TG). Fatty acid biosynthesis aids in the occurrence of hepatic steatosis, hepatic fibrosis, and even hepatocellular carcinoma [33].

**3.2. DILI Induces Mitochondrial Hazards.** Mitochondria are cellular energy suppliers, if damaged, resulting in apoptosis and/or hepatic necrosis, even leading to the activation of the apoptotic signaling pathway if the mitochondrial damage exceeds a specific limit [34]. Excessive ROS are produced during the process of DILI. The interaction between ROS and the hepatic mitochondrial membranes is a vital factor of oxidative stress. For example, D-galactosamine/lipopolysaccharide (D-GalN/LPS), a high production level of MDA and an end-product of lipid hydroperoxide (LPO), may lead to decreased membrane fluidity and hence induce severe mitochondrial membranes damage [35]. Few studies have shown that the ethanol treatment can enhance the release of cytochrome C and apoptosis-inducing factor (AIF), restricted to the mitochondria but released into the cytosol [36]. Cytochrome C can trigger caspase-3 activation, which results in apoptosis. At the same time, proapoptotic protein AIF is independent of the caspase pathway and directly induces apoptosis of hepatocytes [31].

Moreover, mitochondrial permeability transition pore (MPTP) plays a significant role in maintaining mitochondrial physiology. In acute severe hemorrhagic shock, ROS sharply increased, leading to the opening of mitochondrial permeability transition pore (MPTP), resulting in the imbalance of  $H^+$  on the inner mitochondrial membrane, destroying membrane proteins, inhibiting ATP synthesis, and causing mitochondrial swelling [37]. All these may exacerbate necrosis or apoptotic cascades, leading to rapid cell death [24, 38].

**3.3. DILI Regulates Hepatic Transporters.** Drug transporter proteins are crucial factors in clearing reactive metabolites in the liver, intestine, kidney, and brain [39]. According to the mechanism of action and location on the hepatocyte cell membrane, hepatic transporter proteins can be classified into the solute carrier (SLC) and the ATP-binding cassette (ABC) transporter family. Generally, SLC proteins are influx transporters, which bring drugs from the plasma into the cell [25, 40], while ABC transporters are efflux transporters, transforming metabolized drugs from the cytoplasm to the cell's exterior in the bile [41].

The transporter protein families in the hepatocytes include organic anion transporting polypeptides (OATPs), organic cation transporters (OCTs), multidrug-resistant proteins (MDRs), bile salt export pump (BSEP), breast cancer resistant proteins (BCRP), and multidrug resistance-associated proteins (MRPs) [41, 42]. It has been found that OATP1B and sodium-dependent taurocholate cotransporter (NTCP) significantly affect drug transport of all the influx transporters [39, 43], while ABC transport protein (ABCC2-4) is essential for liver cells to clear the chemicals and biliary excretion. The drugs induced mutations in ABC transporters cannot metabolize drugs to remain inside the hepatocytes and cause impaired canalicular bile flow. This situation

generally appears as cholestasis and fatty liver disease [44]. Widely, inhibition of BSEP leads to the accumulation of toxic bile salts in hepatocytes, which are correlated with the incidence of cholestatic liver disease [41]. Therefore, drugs, such as troglitazone, ketoconazole, nefazodone, and lapatinib [45], which express inhibitory effects on BSEP, can have hepatotoxic potential [46]. Furthermore, age and race play an important role in the morbidity of ADRs from variations in the expression of transporter genes, leading to decreased expression of these functional transporters [47].

**3.4. DILI Modulates Immunological Response.** The immune response is also indispensable in DILI. Long-term drug exposure may cause inflammations in a healthy liver, drug-induced autoimmune hepatitis (DIAIH), or acute liver toxicity [48, 49]. In the adaptive immune response, the drug and its metabolites act as haptens that bind to liver protein cytochrome p450. The drug-protein adduct is then processed by an antigen-presenting cell (APC), while antigen associates with major histocompatibility complex (MHC) class II molecules. After that, CD4 T-cell is activated, resulting in adaptive immune response, which then triggers CD8 cytotoxic T-cell activation, leading to FasL, TNF- $\alpha$ , and other proteins that mediate cell death [50].

The nuclear factor kappa-light-chain enhancer of activated B cells (NF- $\kappa$ B) is a dimer protein, which plays an essential role in releasing inflammatory cytokines. It is generally composed of two functional subunits (P65 and P50) that bind to its natural inhibiting factor, I $\kappa$ B, preventing NF-particles from entering the nucleus and targeting downstream associated genes. Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88) receptor receives the irritant cytokines, activates the mitogen-activated protein kinases (MPAK) signaling pathway to induce inflammation, and has three subunits (p38, JNK, and ERK) [51]. The activation of the NF- $\kappa$ B signaling pathway can increase the risk of inflammation and cell damage. High-mobility group protein box 1 (HMGB1) is reported to play an essential role in sepsis, and it can activate innate immune cells that result in antigen-presenting cells [52, 53]. Many studies reported that SRT1720 reduces the release of inflammatory cytokines (TNF- $\alpha$  and IL-6) and hence blocks the inflammatory reactions. Additionally, immune-based DILI can also connect with gender, age, race, and current immune state [54].

## 4. Health Benefits of Isoflavones

**4.1. As Antioxidants.** Oxidative stress, caused by imbalanced cellular ROS levels, is a critical phenomenon in chronic diseases, cardiopathy, and hepatotoxicity. Many studies showed that soybean isoflavones (daidzein and genistein) and red clover isoflavones (biochanin A) potentially protect from DILI [55–57]. Isoflavones play an essential role as dietary antioxidants by scavenging free radicals and deactivating detoxifying enzymes [57, 58]. Recently, it has been showing that germinated and fermented soybean extracts (GFSE) effectively inhibit the expression of NADPH oxidase

4 (Nox4), which is responsible for the synthesis of ROS [57–59]. Reduced metabolic activation of drugs by mono-oxygenase (P450 2E1) system depresses the initial formation of ROS and some intermediate toxic products, resulting in reduced lipid peroxidation [60, 61]. These isoflavones treatments were found to increase the mRNA and protein expression level of CYP2E1 and regulate the JNK/CYP7A1 signaling pathway [62, 63]. In addition to CYP450, the inhibition of phase II detoxifying enzymes, such as UDP-glucuronyltransferase (UGTs), can also have a resistance to oxidative stress [64].

Recently, huge reports highlighted the antioxidant defenses of isoflavones, including both the nonenzymatic (mainly GSH) and enzymatic antioxidant defenses (SOD, CAT, GSP, GST, and GR) [58, 60, 65, 66]. Nevertheless, this way has not already been confirmed in the antioxidant protection after GalN administration [67]. Formononetin (FMN) is one of the significant isoflavonoid constituents from red clover, and it showed that the pretreatment of FMN significantly enhanced Nrf2 protein expression, stimulated mRNA expression of antioxidant enzymes, and restored GSH level and cell viability upon APAP exposure [68]. Nrf2 regulates and induces its downstream heme oxygenase 1 (HO-1) enzyme, which is reported to have antioxidant activity. Biochanin A upregulated the expression of Nrf2 and HO-1 in a dose-dependent manner and helped resist LPS/D-GalN-induced acute liver injury [69].

The dose and route of isoflavones have different effects on resisting oxidative stress. It has been suggested that the efficacy of a high dose of biochanin A (BCA) is lower than a medium dose of BCA, and it is metabolized initially into genistein. Nevertheless, excessive BCA, which was metabolized into genistein and daidzein, could be the primary reason for the high dose of BCA, while BCA is lower than the medium dose of BCA [57]. Many phytochemicals, such as kakkalide, make contact with intestinal microflora and change it into irisolidone in the alimentary tract. The reports showed that irisolidone was intraperitoneally administered to mice or kakkalide was orally administered to mice. Both exhibited potent hepatoprotective activity. Nevertheless, intraperitoneally administration of kakkalide did not exhibit hepatoprotective activity [70–72].

**4.2. Antiapoptosis.** Recent studies have shown that high ROS concentrations may contribute to apoptotic cell death and DNA damage. Some studies indicated that puerarin (PR) could inhibit apoptosis due to the suppression of caspase-3 activity and alteration of Bcl-2/Bax ratio, which can alleviate raised lead-induced hepatic dysfunction and histopathologic changes rat liver [73]. Further, a downregulation in Bcl-2 and an upregulation in Bax induced by 7,12-dimethylbenz [ $\alpha$ ]-anthracene (DMBA) treatment were also decreased by daidzein [74]. Genistein treatment, on the other hand, also downregulates Bcl-2 levels [75]. Meanwhile, the metabolite tectorigenin from *Puerariae Flos* (isoflavones tectorigenin and tectoridin) prevents liver injury because of its inhibited ion of  $\beta$ -glucuronidase and apoptosis rather than its antioxidant activity [76, 77]. In addition, overexpression of

GSK-3 $\beta$  activates caspase series to activate apoptosis, but puerarin (PR) may inhibit the GSK-3 $\beta$ -induced apoptosis by attenuating inflammatory responses via regulating the GSK-3 $\beta$ /NF- $\kappa$ B pathway [78].

**4.3. Anti-Inflammatory and Antifibrosis Effects.** With alcohol becoming popular in social life, inflammation is relatively easy to find in most clinical cases, especially alcohol-induced liver damage. The inflammatory responses are mainly linked with the activation of TNF- $\alpha$  mediators and the production of IL-1 $\alpha$ , IL-6, and released hepatic stellate cells (HSC) following activation to recruit cytokine-mediated immunological attack/lesions.

It is further revealed that isoflavones play an essential role in removing inflammation-related issues. A study found that puerarin (PR) treatment significantly downregulated TLR4 and p38 phosphorylation levels in mouse livers to inhibit Ni-induced oxidative stress and inflammatory responses. However, p38 also can regulate inflammatory response by activating cAMP response element-binding protein (CREB). The TLR4/p38/CREB pathway plays a crucial role in activating transcription factor NF- $\kappa$ B, which plays a fundamental role in regulating gene expression of inflammatory mediators such as PGE2, COX-2, IL-6, and IL-8, by activating NF- $\kappa$ B and MAP Kinases [79]. NLRP3 inflammasome is responsible for the processing and secretion of the mature IL-1 $\alpha$ . The BCA inhibits thioredoxin-interacting protein (TXNIP) expression and the interaction between NLRP3 and TXNIP induced by GalN/LPS, which may be due to the reduced expression of TXNIP [69].

Most of the studies showed a strong relationship between the inflammatory processes and fibrosis. Alcoholic liver disease (ALD) can cause a high death rate, which led liver fibrosis, cirrhosis, and hepatocellular carcinoma [80]. Acetaldehyde, the primary metabolic product of alcohol, activates hepatic stellate cells (HSCs) that play a vital role in liver fibrosis. Herbal medicines have been regarded as new and promising drugs to resist liver fibrosis. It is confirmed that isoflavones (genistein) significantly decreased the extraordinarily high level of TGF-1 $\alpha$  and Smad 3, which is the activator of HSCs [75]. Tyrosine kinase, one of the factors of HSC activation, is a crucial factor in the proliferation and activation of HSCs. Another study showed that genistein can prevent the activation and proliferation of HSC by inhibiting tyrosine kinase from reducing acute and chronic inflammation and liver fibrosis [61, 65]. Meanwhile, a study shows that ethyl acetate fraction (Beac) from *Butea monosperma* bark can inhibit thioacetamide-induced liver cancer and fibrosis via suppression of PI3K/Akt/mTOR pathway [81].

**4.4. Antihematotoxicity.** Hematotoxicity referred to the influence of drugs on the formation and function of blood, including the inhibition of red and blood cells, platelet count, and hematopoietic function of bone marrow cells. It is illuminated that daidzein pretreatment in rats had a potential beneficial effect on the hematopoietic system by elevating RBCs, Hb levels, and PCV and increasing platelet count against cisplatin-induced hematotoxicity markers.

TABLE 1: Hepatoprotective effects of isoflavone and extracts.

Isoflavone and extracts	Drugs	Injury	Mechanism	Refs
Biochanin A	Arsenic	Hepato/hematotoxicity	Increasing free radical scavenging properties	[57]
	CCl4	Acute liver injury	Increasing antioxidant	[60]
	LSP/D-GalN	Acute liver injury	Activation of the Nrf2 pathway	[69]
Formononetin	APAP	Hepatotoxicity	Enhancing Nrf2 activity	[68]
	TAA	Oxidative stress	Reducing ROS and expression of CYP2E1	[62]
Calycosin	APAP	NASH	Activating FXR	[85]
	HFD	NAFLD	Activating FXR	[86]
	CCl4	Acute liver injury	Activating FXR/increasing expressions of STAT3, Bcl-xl, and SOCS3	[87]
Daidzein	LSP/D-GalN	Hepatic failure	Suppressing production of TNF- $\alpha$ ; increasing caspase-3 activity	[56]
	D-GalN	Liver injury	Activating PG-liposome-based system	[67]
	DMBA	Liver oxidative injury	Activation of antioxidant enzymes and Bcl-2; upregulation of caspase-3 and Bax	[74]
	Cisplatin	Hepato/hematotoxicity	Increasing free radical scavenging properties; reducing bone marrow suppression	[82]
Puerarin	CCl4	Liver oxidative injury/hyperlipidaemia	Inhibiting JNK/c-Jun/CYP7A1 pathway/ROS generation	[63]
	Alcohol	Acute liver injury	Decreasing activity of oxidant enzyme (MDA)/increasing activity of antioxidant enzymes (SOD and GPX)	[66]
	Lead	Liver oxidative injury/hyperlipidaemia	Reducing ROS production/hepatic metabolism genes expression; increasing activation of antioxidant enzymes	[73]
	Alcohol	Chronic liver injury	Inhibiting GSK-3 $\beta$ /NF- $\kappa$ B pathway	[78]
	Nickel	Liver oxidative stress/immunotoxicity	Inhibiting TLR4/p38/CREB pathway	[79]
	TAA	Liver inflammatory/fibrosis	Inhibiting tyrosine kinase/activation of HSC	[61]
	APAP	Liver injury	Increasing expression of UGTs; inhibiting CYP2E1	[64]
Genistein	Alcohol	Hepatic injury/fibrosis	Increasing activities of ADH and ALDH; downregulating expression of TIMP-1, MMP-2, and Bcl-2	[75]
	Endotoxin	Shock/MODS	Decreasing expression of iNOS and COX-2 protein; attenuating the vascular hyporeactivity to NA; inhibiting the activity of protein tyrosine kinase	[84]
	Fructose	NAFLD	Activating AMPK and suppressing SREBP-1 cleavage processing and de novo lipogenesis in hepatocytes	[88]
Kakkalide	Ethanol	Hepatic injury	Orally administered kakkalide and intraperitoneally administered irisolidone have the protective effect; kakkalide can be metabolized to form the bioactive irisolidone by intestinal microflora	[71, 72]
Tectorigenin	TBHQ	Apoptosis in liver injury	Inhibiting $\beta$ -glucuronidase activity	[77]
	Ethanol	Liver steatosis	Increasing expression of PPAR- $\alpha$ ; ameliorating mitochondrial function	[89]
<i>Flemingia macrophylla</i>	CCl4	Acute hepatotoxicity	Inhibiting ROS generation; preventing lipid peroxidation; strengthening antioxidant systems	[58]
Fraxin isolated from <i>Acer tegmentosum</i>	CCl4	Acute hepatotoxicity	Lowering AST and ALT	[91]
GFSE	TBHQ	Hepatotoxicity	Downregulating NOX4; upregulating the mRNA levels of antioxidant enzymes	[59]
<i>Butea monosperma</i>	TAA	Liver injury	Deregulation of PI3K/Akt/mTOR signaling	[81]

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ADH: alcohol dehydrogenase; ALDH: aldehyde dehydrogenase; APAP: acetaminophen; CCl4: carbon-tetrachloride; CYP2E1: cytochromeP450, family 2, subfamily E, polypeptide1; COX: cyclooxygenase; DMBA: 7,12-dimethylbenz[a]-anthracene; FXR: farnesoid X receptor; GFSE: germinated and fermented soybean extract; GSK-3 $\beta$ /NF- $\kappa$ B pathway: glycogen synthase kinase-3 $\beta$ /nuclear factor kappa-B pathway; HFD: high-fat diet; iNOS: inducible nitric oxide synthase; JNK/c-Jun/CYP7A1 pathway: c-Jun NH2-terminal kinase/c-Jun protein/cholesterol 7 $\alpha$ -hydroxylase pathway; LSP/D-GalN: lipopolysaccharide/D-galactosamine; LPO: lipid peroxides; MMP-2: matrix metalloproteinases; MODS: multiple organ dysfunction syndrome; NASH: nonalcoholic steatohepatitis; NAFLD: nonalcoholic fatty liver disease; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; PI3K/Akt/mTOR: phosphatidylinositol 3-kinase/Akt/mammalian; SOCS3: suppressor of cytokine signaling 3; STAT3: signal transducer and activator of transcription 3; TAA: thioacetamide; TLR4/p38/CREB pathway: Toll-like receptor 4/cAMP response element-binding protein; TIMP-1: tissue inhibitors of metalloproteinases; TBHQ: tert-butyl hydroperoxide.

Therein, enhancement of erythrocyte count by daidzein may be linked to either stimulation of erythropoiesis or prevention of bone marrow cell inhibition or decreasing cholesterol effects [82, 83]. In addition, the antihematotoxicity protective effect of isoflavones can also be related to the dose administered. Fine shreds of evidence claimed that only low-dose BCA had a significant ameliorative effect on arsenic-induced hematopoietic, especially the RBC indices [57].

**4.5. Anticirculatory Failure and Organ Dysfunction Effects.** The progression of anticirculatory failure (shock) to multiple organ dysfunction syndromes (MODS) is related to increased mortality. With the increasing number of organ failures, mortality is also progressively increased. The endotoxic shock in rats was regarded as the anticirculatory failure model. Different kinds of isoflavones have different effects on these models. It was found that genistein attenuated the vascular hyperactivity to noradrenaline (NA), but it did not reduce the hypotension elicited by LPS. Daidzein did not revive the circulatory failures caused by LPS. Additionally, both tyrphostin and genistein improve the liver and pancreatic injuries, hypoglycemia, and lactic acidosis caused by LPS, while daidzein did not prevent organ dysfunction or LPS-mediated lactic acidosis. Genistein reduced the high level of LPS-induced TNF- $\alpha$  and suppressed the expression of iNOS and COX-2 proteins and activity in the lung, but not daidzein [84]. Thus, genistein can be regarded as a novel and effective drug to improve LPS-induced circulatory failures.

**4.6. Antisteatohepatitis.** The risk of steatohepatitis has a rapid increase over the last decade because of the bountiful lifestyles and poor eating habits. Nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis are two widespread types of steatohepatitis in clinic cases. NASH, being the frequent form of chronic liver disease, may be induced from nutritional (high-fat diet and high fructose diet), genetic, and immunologic factors, which cause disorders in lipid metabolism and hepatic fibrosis. It is further reported that calycosin is a main active component isolated from *Radix Astragali* and has strong anti-NASH activity. Calycosin treatment has significantly changed the liver histopathology, hepatocytes apoptosis, liver bile acid overload, and hepatocyte mitosis by inhibiting triglycerides (TG) synthesis, increasing fatty acid  $\beta$ -oxidation, and inhibiting HSCs activation, which helps prevent triglyceride accumulation and fibrosis [85]. It has been shown that calycosin that prevents HFD-induced NAFLD may be attributed to farnesoid X receptor (FXR- $\alpha$  and NR1H4) activation that modulates lipid metabolism and restoration of glucose homeostasis [86].

Furthermore, few studies reported that the protective effects of calycosin are in association with FXR activation and STAT3 phosphorylation. The phosphorylated STAT3 can activate the expressions of Bcl-xl and suppressor of cytokine signaling 3 (SOCS3), which can reduce NASH by preventing liver apoptosis and hemorrhagic necrosis [87]. In addition, it was also found that the treatment of

sophoricoside, an isoflavone glycoside (genistein-4'-O- $\beta$ -D-glucopyranoside), decreased the hepatic cholesterol and triglyceride levels and serum low-density lipoprotein-cholesterol (LDL) and apolipoprotein-B levels and elevated the serum high-density lipoprotein-cholesterol (HDL) and apolipoprotein-A1 levels [88]. Alcoholic steatosis may progress to hepatitis and fibrosis, which eventually leads to liver cirrhosis. Tectoridin, an isoflavone glycoside from the flower of *Pueraria lobata*, protected against ethanol-induced liver steatosis mainly through decreasing the expression of PPAR $\alpha$  and its downstream target genes and ameliorating mitochondrial functions [89].

**4.7. Antihyperlipidemia.** Puerarin is a potent isoflavone, which seems to be a potential hepatoprotective drug used to inhibit hyperlipidemia, which can decrease serum cholesterol, triglycerides (TG), and LDL and increase HDL level. Hepatic HMGR and hepatic CYP7A1 are peroxisomal enzymes sequentially used in rate-limiting steps during cholesterol biosynthesis and the biosynthesis of bile acids formation. It has been shown that puerarin remarkably inhibited hyperlipidemia by influencing the expression of hepatic lipid biosynthesis and metabolic-related genes, including cholesterol 7 $\alpha$ -hydroxylase (CYP7A1), HMGR, and low-density lipoprotein receptors (LDL-R) in the liver of lead treated rats [90]. Moreover, puerarin could also inhibit hyperlipidemia by regulating the JNK/CYP7A1 signaling pathways [63].

## 5. Conclusions

With the improvement of living standards and lifestyles, diseases, especially chronic conditions, have increased rapidly. Among various reasons, mainly lousy eating habits and DILI have become the common pathogenic factors. Therefore, specific therapeutic methods have been eagerly sought by many researchers. Recently, the traditional medicinal herbs got the attention. In current essays, puerarin, calycosin, and red clover contain isoflavones that have substantial effects on improving liver injury and circulatory system diseases. All the studies are summarized to elucidate the roles of isoflavones (Table 1) reported in the last decade and we hope it can offer help and convenience in the process of searching for drug treatments.

## Abbreviations

ALF:	Acute liver failure
AIF:	Apoptosis-inducing factor
APAP:	Acetaminophen
AMPK:	AMP-activated protein kinase
ADRs:	Adverse drug reactions
ABC:	ATP-binding cassette
APC:	Antigen-presenting cell
BSEP:	The bile salt export pump
BCRP:	Breast cancer resistant proteins
BCA:	Biochanin A
CYPs:	Cytochromes P450

CYP2E1:	Human cytochrome P450 2E1
CYP1 and CYP2:	Cytochromes P450 1 and P450 2
CYP7A1:	Cholesterol 7 $\alpha$ -hydroxylase
CREB:	CAMP response element-binding protein
D-GalN/LPS:	D-Galactosamine/lipopolysaccharide
DILI:	Drug-induced liver injury
DMEs:	Drug-metabolizing enzymes
DLAIH:	Drug-induced autoimmune hepatitis
FoxO1:	Forkhead box O 1
FXR:	Farnesoid X receptor
FMN:	Formononetin
FMO:	Flavin-containing monooxygenases
GFSE:	Germinated and fermented soybean extracts
HDS:	Herbal and dietary supplements
HO-1:	Heme oxygenase 1
HSC:	Hepatic stellate cells
HDL:	High-density lipoprotein-cholesterol
HMGB1:	High-mobility group protein box 1
LPO:	Lipid hydroperoxide
LDL:	Low-density lipoprotein-cholesterol
LDL-R:	Low-density lipoprotein receptors
MDA:	Malondialdehyde
MPTP:	Mitochondrial permeability transition pore
MDRs:	Multidrug-resistant proteins
MyD88:	Myeloid differentiation factor 88
MPAK:	Mitogen-activated protein kinases
MRPs:	Multidrug resistance-associated proteins
MHC:	Major histocompatibility complex
MODS:	Multiple organ dysfunction syndrome
NTCP:	Sodium-dependent taurocholate cotransporter
NA:	Noradrenaline
NASH:	Nonalcoholic steatohepatitis
Nrf2:	Nuclear factor erythroid 2-related factor 2
NF- $\kappa$ B:	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs:	Nonsteroidal anti-inflammatory drugs
OATPs:	Organic anion transporting polypeptides
OCTs:	Organic cation transporters
PR:	Puerarin
RUCAM:	Roussel Uclaf causality assessment method
ROS:	Reactive oxygen species
RNS:	Reactive nitrogen species
STAT3:	Signal transducer and activator of transcription factor 3
SLC:	Solute carrier
SOCS3:	Suppressor of cytokine signaling 3
TG:	Triglycerides
TXNIP:	Thioredoxin-interacting protein
TLR4:	Toll-like receptor 4
UGTs:	UDP-glucuronyltransferase.

## Data Availability

All the data used to support the findings of this study are included in the paper.

## Conflicts of Interest

The authors declare no conflicts of interest.

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