



Review Article

Drug-induced liver injury therapy: unveiling the healing potential of natural products from medicinal and food homology plants

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Abstract: Drug induced liver injury (DILI) is an important adverse reaction caused by the use of drugs in clinical practice. In severe cases, it can even pose a threat to life. The commonly reported drugs that cause DILI include non-steroidal anti-inflammatory drugs, antibiotics, and anti-cancer drugs, etc. In recent years, a large number of studies have shown that medicinal and edible plants with their natural products have demonstrated great potential in the treatment of DILI. In animal models, these substances can alleviate DILI by inhibiting oxidative stress and inflammatory responses, activating the antioxidant defense system, regulating the intestinal flora, alleviating endoplasmic reticulum and mitochondrial stress, and regulating autophagy, among other pathways. Furthermore, natural compounds such as glycyrrhizic acid, and silymarin have already shown preliminary improvement effects on DILI in clinical practice. However, it is worth noting that in cases of improper assessment, unreasonable use, or other circumstances, these natural substances can also potentially cause or exacerbate liver damage. Therefore, it is necessary to conduct further assessment of the safety range and potential side effects of the drug during the clinical drug development and application process. Overall, the medicinal and edible plants with their natural products provide new strategies and resources for the prevention and treatment of DILI as well as for drug development.

Keywords: hepatology; liver injury; natural products; oxidative stress; phytotherapy; polyphenolic

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1 Introduction

Drug induced liver injury (DILI) is a ubiquitous clinical health challenge, and the idiosyncratic form of DILI is a significant global health concern for pharmaceutical manufacturers^[1]. Ongoing prospective studies are shedding light on the incidence of DILI in the general population in several countries, including Iceland, the United States, and China. Statistics from Iceland indicate an annual incidence rate of 19 cases per 100,000 persons^[2]. In contrast, the population-based study in the United States reported a significantly lower incidence of 2.7 cases per 100,000 adults^[3]. Meanwhile, the most recent report from mainland China estimates a higher annual incidence of 23.8 cases per 100,000 in

the general population^[4]. Adolescents in China accounted for the majority of children with moderate/severe DILI (65%), and again, adolescents were at significantly higher risk of severe liver injury compared to younger children. Antineoplastics, antibacterials, and herbal medicines were the three most commonly prescribed drugs^[5]. Older adults are particularly susceptible to DILI due to their frequent multimorbidity and polypharmacy^[6].

DILI is a potential adverse effect associated with numerous medications, including acetaminophen (APAP), the world's most widely used analgesic and antipyretic. In particular, in the United States and Europe, APAP has been implicated in 40 to 70 percent of cases of acute liver failure^[7]. A reference hospital study identified the use of anticancer drugs as the primary cause of

DILI^[1]. A recent study by the European DILI Network also highlighted that antibacterials are the most common single class of pathogens, with 40% of cases, followed by antineoplastics and immunomodulating agents with 27%^[8]. Other common drugs that can cause DILI are shown in Fig. 1, and the mechanisms by which they cause DILI are listed in Table 1.

Through meticulous research, scientists have identified treatments for DILI. These include N-acetylcysteine, bicyclol, and ursodeoxycholic acid. N-acetylcysteine with its multifaceted properties including antioxidant, anti-inflammatory, microvessel-dilating and DNA-protective effects, was approved by the U.S. Food and Drug Administration in 2004 as an antidote for a wide range of DILI cases. Bicyclol is approved by Russian clinical guidelines for the treatment of DILI. Ursodeoxycholic acid is commonly used in cholestatic DILI by reducing the cholesterol saturation index of the bile and inhibiting intestinal cholesterol absorption^[9]. While these agents have demonstrated efficacy in mitigating DILI, the current clinical need remains unmet, particularly for personalized treatment approaches. This is due to the heterogeneity of the patient population. The search for a safe and cost-effective treatment strategy is more urgent than ever given the increasing prevalence of DILI and its complications, such as acute liver failure.

Medicinal and edible plants not only have nutritional value, but also due to their presence of effective components such as polyphenols, flavonoids, terpenoids, and alkaloids, they have shown great potential in the prevention and treatment of various disease^[10]. On the other hand, since these types of plants or

components are generally safer and more readily available, the public's acceptance of them is also higher. The research on polyphenols is particularly prominent among these substances. Polyphenolic natural products mainly come from various plants, fruits and vegetables. A large number of studies have shown that polyphenols can protect liver health by regulating oxidative stress, lipid metabolism, insulin resistance, alleviating inflammatory responses and controlling body weight^[11]. More importantly, polyphenols can effectively resist the toxicity caused by drugs by inhibiting cell apoptosis and regulating the expression of antioxidant enzymes^[12]. Therefore, medicinal and edible plants offer a feasible treatment option for DILI.

This work aims to review the effects of medicinal and edible plants with their natural products for the treatment of DILI. It summarized the treatment mechanisms and clinical studies of the liver damages caused by common drugs. It also emphasizes the importance of natural products in the treatment of DILI. Furthermore, we discussed the important issues that should be focused on in the future drug development, providing references for the treatment of DILI and the development of drugs in the future.

2 Molecular mechanisms of drug-induced liver injury

The liver is an important organ for the transformation and metabolism of drugs in the body. It plays a crucial role in the processes of drug absorption, metabolism, excretion and

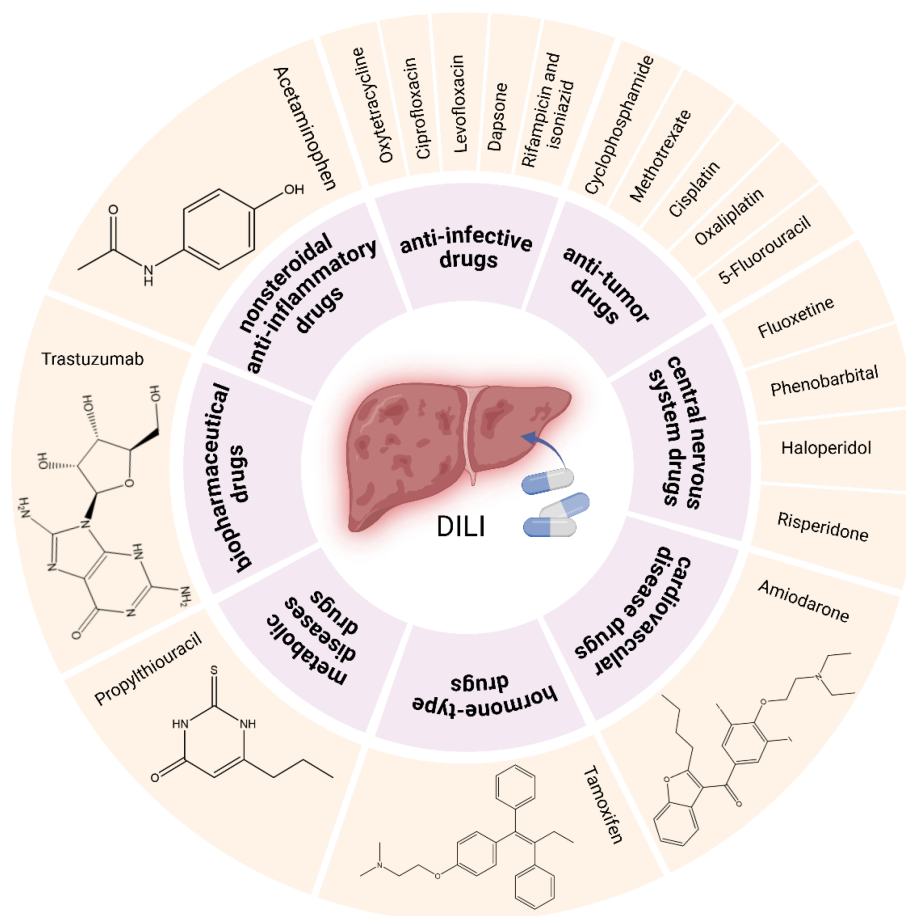


Figure 1 Typical Clinical Drugs Causing DILIs. Eight main classes of drugs cause DILI in the clinic, including paracetamol in nonsteroidal anti-inflammatory drugs, oxytetracycline, ciprofloxacin, levofloxacin, dapsone, rifampicin and isoniazid in anti-infective drugs, cyclophosphamide, methotrexate, cisplatin in antitumour drugs, fluoxetine, phenobarbital in central nervous system drugs, metabolic drugs, biopharmaceutical drugs, hormone type drugs and cardiovascular disease drugs.

Table 1 Classify and describe the mechanism of drugs that may cause liver injury

Typology	Drug	Mechanisms leading to liver injury
Nonsteroidal anti-inflammatory drug	Acetaminophen	Excess APAP in the first metabolism of hepatocytes is metabolised by CYP to NAPQI, a toxic substance that further induces GSH depletion, oxidative stress and activation of complex molecular pathways, ultimately leading to liver injury and subsequent hepatic necrosis
	Oxytetracycline	Causes hepatotoxicity by increasing ROS production and activating the mitochondrial cell death pathway
	Ciprofloxacin	The active metabolite of Ciprofloxacin leads to the release of damage-associated molecular patterns from hepatocytes, which activate inflammasomes, leading to the development of liver injury
Anti-infective drug	Levofloxacin	Levofloxacin causes hepatotoxicity through hepatic GSH depletion and mitochondrial ROS formation
	Dapsone	Dapsone and its N-hydroxylated metabolites cause haemolysis in hepatitis by inducing cholestasis, oxidative stress and hepatic necrosis, leading to hepatic iron overload
	Rifampicin	Rifampicin is converted to toxic metabolites by the enzyme CYP71A1, causing oxidative stress and hepatic cholestasis, as well as activating ER stress leading to liver injury
	Isoniazid	Conversion of isoniazid to toxic metabolites by CYP enzymes induces oxidative stress and leads to damage to the liver
Anti-tumor drug	Cyclophosphamide	Cyclophosphamide is catalyzed by different CYP enzymes to form 4-OHCP and the 4-OHCP isomer aldehyde ALDO, which are converted into toxic metabolites that cause a series of cellular molecular mechanisms that ultimately lead to hepatotoxicity
	Methotrexate	MTX causes liver inflammation by interfering with cellular antioxidant mechanisms, impairing mitochondrial function and leading to the production of ROS. ROS activate the NF- κ B pathway, leading to liver inflammation
	Cisplatin	Cisplatin exhibits hepatotoxicity by attenuating antioxidant defences, activating NF- κ B-induced pro-inflammatory cytokines and inducing pro-apoptotic pathways via Casp9
	Oxaliplatin	Oxaliplatin is hepatotoxic due to mitochondrial oxidative stress, with ROS-mediated lipid peroxidation and protein carbonyls leading to liver injury
Central nervous system drug	Fluoxetine	Fluoxetine exacerbates oxidative stress by increasing superoxide anion levels, which can increase free radical production, decrease hepatic antioxidant capacity and inducing oxidative stress, as well as exacerbating liver injury by aggravating otherwise mild mononuclear cell infiltration, haemorrhage, adipocyte degeneration and apoptosis
	Phenobarbital	Phenobarbital may cause immunoallergic hepatotoxicity
	Haloperidol	Haloperidol Changing hepatic iron metabolism may be a precursor to induced liver injury
Metabolic diseases drug	Propylthiouracil	The mechanisms of propylthiouracil remain not fully elucidated
Biopharmaceutical drug	Trastuzumab	Trastuzumab induces liver damage through a HER2-dependent pathway or by binding to CKAP5 on the surface of the cell, which leads to apoptosis
	Tamoxifen	Tamoxifen causes mitochondrial damage, reducing phosphorylation efficiency, disrupting the mitochondrial membrane and inducing ROS production, resulting in a vicious cycle that ultimately leads to liver injury
Hormone-type drug	Amiodarone	Amiodarone and its major metabolite desethylamiodarone cause hepatotoxicity by generating mitochondrial and oxidative stress and Kupffer cell activation

detoxification. The occurrence of drug-induced liver toxicity involves multiple mechanisms and pathological processes, ultimately leading to liver dysfunction and liver damage. In severe cases, it may even cause liver failure, posing a threat to life and health. After the medication is taken, it first enters the bloodstream and then is transported to the liver through the portal venous system. The organic anion transporting polypeptides (OATPs), organic cation transporting proteins (OCTs), and organic anion carriers (OAT) family are transport proteins located on liver cells^[13]. These transport proteins transport the drugs into the liver cells for their breakdown. The process of drug decomposition within liver cells is a crucial step in determining the toxicity of drugs. According to current research, the process of drugs in liver cells is mainly divided into three stages.

Drugs undergo oxidation/reduction and hydrolysis reactions in the hepatocyte in the initial step and are catalyzed by the enzyme family of cytochrome P450 (CYP) into primary metabolites^[14]. These reactions are able to make some primary metabolites to be more polar and they can eventually be excreted. Nevertheless, detrimental primary metabolites also can covalently react with enzymes of the metabolic process, preventing their functionality and causing cellular responses, including inflammation and oxidative stress. Excessive drug intake into the liver cells and subsequent liver cell accumulation causes hepatotoxicity and damage, further cellular inflammation, and oxidative stress and blockage of enzyme activity.

The second stage of drug metabolism include uridine diphosphate glucuronosyltransferases (UGTs), sulfotransferases (SULTs), N-acetyltransferases, glutathione S transferases (GSTs), amino acid conjugation enzymes, and methyltransferases. The enzymes promote conjugation of the drug or primary metabolite of the drug with a substrate thereby increasing the excretion of the drug of the drug through bile and urine to detoxify. It is worth noting that certain drugs may interact with UGTs to produce acyl glucuronides. Some products formed by the covalent binding of proteins and acyl glucuronides will be recognized by the body as antigens, promoting immune responses within the body and thereby causing DILI^[15]. The third phase involves the translocation of metabolites from hepatocytes, primarily mediated by the ATP-binding cassette (ABC) superfamily of transporter proteins. For example, multidrug resistance proteins (MDRs), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs) facilitate the ATP-dependent transport of toxic substances or metabolic waste products from hepatocytes into bile and blood^[9]. Transporter proteins have been implicated in drug toxicity in the liver, and impaired transporter protein function increases the risk of DILI. Inhibition of the bile salt efflux pump by the products of the above-mentioned metabolic processes prevents the efflux of bile acids into the bile ducts, leading to intrahepatic cholestasis.

Drugs are affected by multiple pathways during their above-mentioned metabolism, and these effects can lead to an imbalance

between toxic metabolite production/activation and detoxification pathways. Enzymes such as UGTs, SULTs, and GSTs play a crucial regulatory role in phase II drug metabolism. Reduced activity of these enzymes can interfere with drug binding, lead to accumulation of active intermediates, or prolong the half-life of toxic metabolites, resulting in liver injury^[16]. OATPs, OATs and OCT are transport proteins responsible for drug uptake. Proteins such as Multidrug Resistance-associated Protein 3 (MRP3), Multidrug Resistance-associated Protein 4 (MRP4), Breast Cancer Resistance Protein (BCRP) facilitate the elimination and transportation of drugs and their metabolites. It causes a direct influence on the efficiency of drug metabolism in case the functioning of these proteins transporters is distorted^[17]. The accumulation of abnormal drugs or their metabolites can induce oxidative stress, mitochondrial dysfunction or DNA damage, ultimately leading to programmed cell death. Moreover, impaired hepatocytes also promote the escape of damage-associated molecular patterns (DAMPs) that mediate the activation of macrophages and natural killer T (NKT) cells in the liver initiating the release of cytokines like tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), and C-X-C motif chemokine ligand 10 (CXCL 10)^[18,19]. Necrosis and apoptosis, is one of the major DILI pathways that result in hepatocyte toxicity^[20].

3 Molecular mechanisms of natural product therapy for DILI

Natural products have attracted attention in recent years due to their roles in regulating cellular responses to stress, enhancing detoxification and repairing cells. The section that follows will discuss the effect of natural products in medicinal and food homology plants in mitigating the DILI caused by different classes of drugs by modulating the biological processes and various targets in the pathways, including the intestinal flora, ER stress, mitochondrial performance, and autophagy.

3.1 DILI caused by APAP

Paracetamol (N-acetylaminophenol, APAP) is a common effectively used drug in fever, pain and inflammation^[9,21]. At therapeutic doses, the cytochrome P450 enzymes metabolize acetaminophen to form N-acetyl-2-benzoxazine imine (NAPQI). NAPQI exerts its detoxifying effect by rapidly combining with glutathione (GSH). However, excessive APAP will lead to depletion of GSH. If the NAPQI that fails to combine with GSH does not get properly detoxified, it will covalently bind to other biological molecules such as proteins in liver cells, thereby interfering with the normal functions of the cells. This will trigger a series of molecular events such as oxidative stress, ultimately leading to liver damage and necrosis^[22,23]. The most recent scientific studies have uncovered that there exists a strong association between the pathogenesis and the therapy of DILI and biological procedures like the intestinal flora, ER stress, mitochondrial stress and autophagy^[24-27]. At the same time, more and more evidence indicates that many natural substances, especially those from medicinal and edible plants, can exert therapeutic and preventive effects against DILI by interacting with these biological processes. Studies have shown that the disruption of the intestinal flora can exacerbate acute liver injury caused by APAP^[28]. However, the gut microbiota can also alleviate the hepatotoxicity of APAP by synthesizing metabolites or regulating an individual's susceptibility to the drug^[29,30]. *Lycium barbarum* L.

is a traditional Chinese medicinal herb and food supplement. It can alleviate APAP-induced liver damage by increasing the abundance of *Akkermansia muciniphila* in the colon of mice and the expression of YAP1 in the liver^[31]. Furthermore, a study demonstrated that the liver-protective effect of *Broussonetia papyrifera* polysaccharides depends on the intestinal microbiota through the depletion of the intestinal microbiota and fecal microbiota transplantation^[32].

Autophagy is one of the crucial self-cleaning machineries of the cells, which take part in various pathological and physiological processes like cell homeostasis, aging, immunity, etc. Autophagy is able to inhibit cell damage caused by APAP by getting rid of NAPQI protein adducts and also broken mitochondria. In addition, autophagy may also inhibit the activity of inflammasomes, which reduces the release of inflammatory factors and inflammatory necrosis caused by APAP^[33]. The phenolic compound ferulic acid that can be found in many plants. Ferulic acid has a protective effect on liver cells by reversing the decline in mitochondrial membrane potential and increasing the adenosine monophosphate-activated protein kinase (AMPK) phosphorylation to induce autophagy^[34]. The essential oil^[35], Schisandrol A^[36] and Schisandrin B^[37] are all derived from *Schisandrae Chinensis* Fructus. They have been reported to reduce the damage of liver which caused by APAP by activating the autophagy.

Mitochondria are important for maintaining the energy of the cell. A number of researches showed that poor mitochondrial function serves as an essential part of the causes of APAP-induced hepatic injuries^[38]. In the liver, a high dose of APAP will react with mitochondrial proteins and form N-acetyl-p2-benzopyronate adducts that will cause mitochondrial superoxide release, JNK activation, and disruption of the mitochondrial membrane potential. It promotes the occurrence of autophagy in mitochondria further. But, when too much APAP is over used in a large quantity, this compensation process can actually be a bad thing by changing the mitochondrial permeability to death^[39]. In addition, mitochondrial biosynthesis of surviving liver cells can also promote liver regeneration and reduce damage, and is involved in liver recovery after APAP-induced liver cell injury^[38,40]. Recent study has shown that medicinal and edible plants with their natural products such as xanthohumol^[41], puerarin^[42], and sinapic acid^[43] can reduce the harm done to liver by APAP through regulation of the mitochondria.

ER is an organelle where is an important part and it stores as well as release calcium and part of proteins folding, processing and transportation too^[44]. Factors such as drugs and toxins that interfere with the normal function of the ER may cause the formation of misfolded proteins, thus triggering ER stress^[45]. The purpose of ER is to repair damage. But if it is excessively further the ER stress may also excite many more lengthy complex cascaded responses which lead to various form of cell prone damage^[46]. ER stress is proven to be part of the cause of liver damage from APAP^[47]. Natural products like oridonin^[48], salidroside^[49] and kahweol^[50] have also been found to be possibly decreasing DILI by reducing the ER stress caused by APAP. In addition, natural products with nanotechnology have been found to be even more advantageous for use as a therapy. Epigallocatechin-3-gallate (EGCG) encapsulated in molybdenum nanoparticles can effectively relieve ER stress, oxidative stress and inflammation, and has become a new approach to treating DILI^[51]. This plan provides a typical case of the combination of traditional Chinese medicine and modern nanotechnology, as well

as the therapeutic value of compounds rich in polyphenols in the treatment of DILI.

A lot of studies on the positive effect of natural products for liver injury caused by APAP. Among them, polyphenolic natural products have become a strong complement to APAP-induced DILI. Polyphenolic natural compounds like puerarin^[42], tangeretin, 4'-demethyltangeretin^[52], xanthohumol^[41], leonurine^[53], and salidroside^[54], which can induce the activation of the antioxidant defense system mediated by nuclear factor erythroid 2-related factor 2 (Nrf2), relieve oxidative stress, and lessen liver injury due to acetaminophen, as seen in Fig. 2. In addition, natural products such as extracts of *Sophora viciifolia*^[55], taraxasterol^[56], pectolinarigenin^[57], confusoside^[57], kaempferol^[58], and anthraquinones like emodin have also shown significant hepatoprotective effects^[59,60]. Furthermore, a variety of other natural products with both medicinal and dietary uses are listed in Table 2, highlighting the breadth of potential sources for liver protection.

3.2 DILI caused by anti-tumor drugs

3.2.1 Cyclophosphamide

Cyclophosphamide is widely used in the treatment of various solid tumors, hematological malignancies, inflammatory diseases and autoimmune disorders. After being metabolized by the liver, cyclophosphamide is converted into 4-hydroxy-cyclophosphamide (OHCP)^[124]. The isomers of phosphamide aldehyde (ALDO) that are in equilibrium with 4-OHCP will form the alkylating metabolite phosphamide mustard (PAM) and the pro-apoptotic aldehyde 3-hydroxypropionaldehyde (HPA) under the action of phosphodiesterase. PAM damages the cell DNA through alkylation, while HPA enhances the apoptotic process

triggered by this damage^[125]. Numerous studies have demonstrated the efficacy of medicinal and edible plants and their natural products in alleviating liver damage caused by cyclophosphamide. Among these plants with both medicinal and edible properties and their natural products, or derivatives of natural products, taxifolin^[89], allicin^[88], arbutin^[90], *Cichorium glandulosum* seed and cynarin^[91] mainly exert protective effects against the oxidative stress, inflammation and hepatotoxicity caused by cyclophosphamide in rats by activating the Nrf2 signaling pathway. Lutein^[82], sinapic acid^[83], magnesium isoglycyrrhizinate^[84], and punicalagin^[85] mainly exert a core anti-inflammatory effect in cyclophosphamide-induced liver toxicity by inhibiting the NF- κ B signaling pathway. *Laminaria japonica* fucoidan can simultaneously alleviate liver and kidney damage caused by cyclophosphamide by regulating the Nrf2/HO-1 and TLR4/NF- κ B signaling pathways^[81]. Similarly, nerolidol can also alleviate cyclophosphamide-induced hepatitis, apoptosis and fibrosis by regulating the Nrf2, NF- κ B p65 and caspase-3 signaling molecules^[87]. Furthermore, ganoderic acid A can also restore the Txnlp/Tx/NF- κ B pathway and the levels of apoptosis-related proteins, thereby alleviating the liver toxicity caused by cyclophosphamide^[86].

3.2.2 Methotrexate

Methotrexate (MTX) is a potent drug commonly used in clinical practice to treat various malignant and autoimmune conditions. However, the widespread clinical use of MTX has led to reports of its adverse reactions and side effects^[126,127]. Although the mechanisms by which MTX induces human toxicity have yet to be fully elucidated, some studies have proposed that it could disrupt cellular antioxidant mechanisms, leading to worsened hepatocyte injury caused by oxidative stress and ER stress^[128].

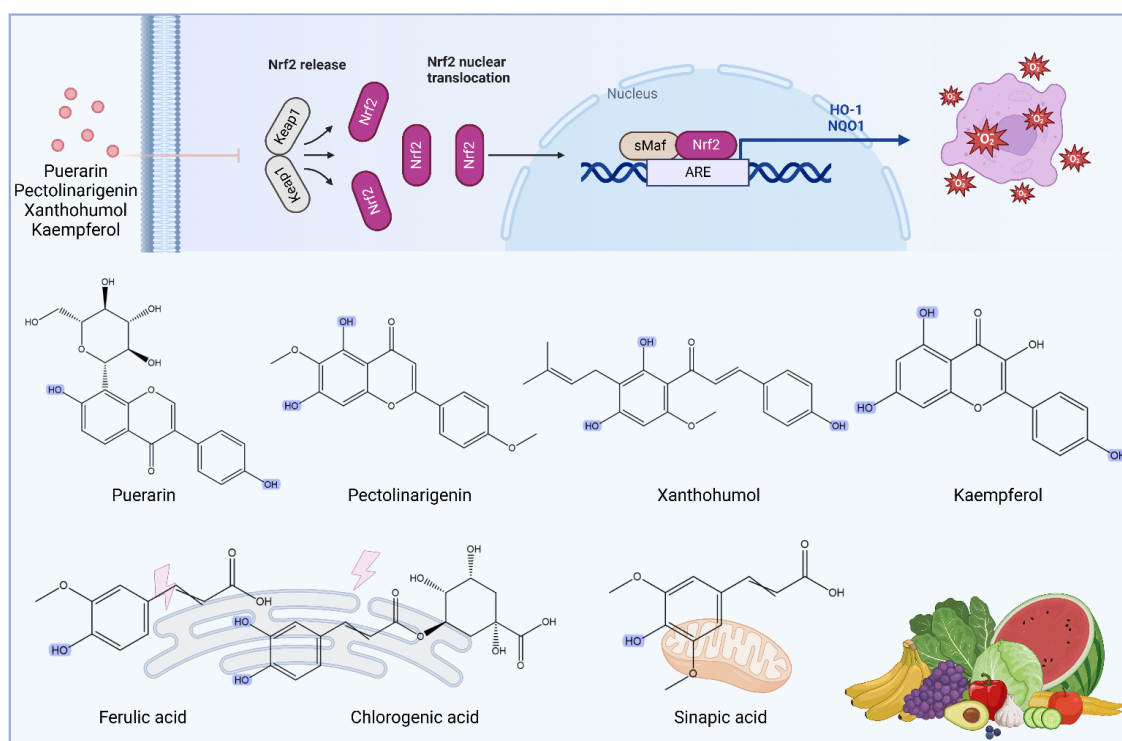


Figure 2 Phenolic medicine and food homology natural products for the treatment of APAP induced DILI. Natural products of polyphenols from medicinal and food homology plants, such as puerarin, pectolinarigenin, xanthohumol, and kaempferol, have the capacity to alleviate APAP induced DILI by acting on the NRF2 pathway, thereby inhibiting oxidative stress. Other phenolic compounds, including ulmic acid, chlorogenic acid, exert their protective effects by suppressing ER stress, while sinapic acid alleviates liver injury by inhibiting mitochondrial damage.

Table 2 Mechanism of action of natural products from medicinal and food homology plants for the treatment of DILI

Drugs that cause liver injury	Doses causing liver injury	Natural product	Source	Dosages	Model	Molecular mechanism	DOI
APAP	300 mg/kg	Puerarin	<i>Pueraria lobata</i>	200, 400, 800 mg/kg	APAP induced acute liver injury in SPF ICR mice	↑Keap1/Nrf2 signaling pathway	[42]
	10 mM			60 µM	APAP induced acute liver injury in HepG2 cell		
	3.6 mM	Tangeretin and 4'-demethyltangeretin	Citrus fruits	2.5-10 µM	APAP induced hepatotoxicity in AML-12 cell	↑Nrf2-related antioxidant pathway ↓CYP2E1	[52]
	400,900 mg/kg	Xanthohumol	<i>Humulus lupulus</i> L.	25, 50 mg/kg	APAP induced acute liver injury in C57BL/6J mice	↑AMPK/Akt/GSK3β/Nrf2	[41]
	300 mg/kg	Leonurine	<i>Leonurus japonicus</i> Houtt.	20, 40 mg/kg	APAP induced acute liver injury in ICR male mice	↑Nrf2, ↑PI3K/AKT	[53]
	10 mM			10 µM	APAP induced hepatotoxicity in MPHs		
	300 mg/kg	Salidroside	<i>Rhodiola</i>	50, 100 mg/kg	APAP induced acute liver injury in C57BL/6 mice	↑Sirt1/Akt/Nrf2 ↓NF-κB/NLRP3	[54]
	10 mM			25, 50 µM	APAP induced hepatotoxicity in L02 cell		
	300 mg/kg	<i>Sophora viciifolia</i> extract	<i>Sophora viciifolia</i>	500 mg/kg	APAP induced acute liver injury in Kunming mice	↓CYP2E1, ↑Nrf2/Keap1	[55]
	300 mg/kg	Taraxasterol	Dandelion (<i>Taraxacum officinale</i> Weber ex F. H. Wigg.)	2.5, 5, 10 mg/kg	APAP induced acute liver injury in Kunming mice	↑Nrf2/HO-1 pathway	[56]
	10 mM			5, 10, 20 µg/mL	APAP induced hepatotoxicity in AML12 cell		
	400 mg/kg	Pectolarigenin	<i>Clerodendrum volubile</i> , <i>Cirsium setidens</i> , <i>Cirsium chanroenicum</i> and <i>Cirsium japonicum</i>	5, 10 mg/kg	APAP induced acute liver injury in C57BL/6 mice	↑Nrf2 and PPARα signaling	[57]
	20 mM			2, 5, 10 µM	APAP induced hepatotoxicity in HepG2 cell lines		
	120 mg/mL	Confusoside	<i>Anneslea fragrans</i>	20, 60 mg/kg	APAP induced acute liver injury in Kunming mice	↑Nrf2 ↓NF-κB/caspase	[61]
	250 mg/kg	Kaempferol	Grapefruit	80 mg/kg	APAP induced acute liver injury in BALB/c mice	↑Nrf2 pathway	[58]
	5 mM			5, 10, 20 µM	APAP-induced hepatotoxicity in L02 cell line		
	300 mg/kg	Emodin	<i>Cassia tora</i>	30 mg/kg	APAP induced acute liver injury in C57BL/6 mice	↑Nrf2 ↓NLRP3, cGAS-STING ↑YAP1	[60]
	300 mg/kg	Wolfberry (<i>Lycium barbarum</i> L.)	<i>Lycium barbarum</i> L.	0.25 g/mice	APAP induced acute liver injury in BALB/c and yap1 knockout mice	↑Akkermansia muciniphila abundance	[31]
	200 mg/kg	Broussonetia papyrifera polysaccharide	<i>Broussonetia papyrifera</i>	100, 200, 400 mg/kg	APAP induced acute liver injury in KM mice	↑intestinal flora structure	[32]
	300 mg/kg	Oridonin	<i>Isodon rubescens</i> (Hemsl.) H. Hara	20 mg/kg	APAP induced acute liver injury in C57BL/6 and Nrf2-/- mice	↑ <i>Bacteroides vulgatus</i> -urea cycle- Nrf2	[62]
	300 mg/kg	Ferulic acid	Grains, pineapple, banana, orange, etc.	50, 100 mg/kg	APAP induced acute liver injury in C57BL/6J mice	↑AMPK-mediated protective autophagy	[34]
	10 mM			12.5, 25, 50 µM	APAP-induced hepatotoxicity in MPH cell		
	300 mg/kg	Schisandra chinensis essential oil	<i>Schisandra chinensis</i>	0.25, 0.5, 1.2 g/kg	APAP induced liver injury in male C57BL/6 mice	↑LC3-II ↓p62	[35]
	50 mg/kg	Echinacea purpurea polysaccharide	<i>Echinacea purpurea</i>	20, 50 mg/kg	APAP overdose induced DILI in C57BL/6 J mice	↑PINK1/Parkin	[63]
	10 mM			0.1–0.5 mg/mL	APAP induced hepatotoxicity in L-02 cell		
	300 mg/kg	Chlorogenic acid	Coffee beans, Tomatoes, Eggplants, etc.	40 mg/kg	APAP induced hepatotoxicity in C57BL/6 Egr1 KO mice	↑EGR1 transcriptional	[64]
	200 mg/kg	Schisandrol A	<i>Schisandra chinensis</i> Turcz. (Baill.)	50 mg/kg	APAP induced DILI in Male ICR mice	↓PNP, MAD, TNF-α, IL-1β	[36]
	200 mg/kg	Schisandrin B	<i>Schisandra chinensis</i> Turcz. (Baill.)	50 mg/kg	APAP induced acute liver injury in ICR mice	↑EGFR/TFEB signaling pathway	[37]
	10 mM			20 µmol/L	Schisandrin B-induced autophagy of HepG2 cells		
	900 mg/kg	Xanthohumol	<i>Humulus lupulus</i> L.	25, 50 mg/kg	APAP induced acute liver injury in Female C57BL/6 J mice	↑AMPK/Akt/GSK3β/Nrf2	[41]

(Continued)

Drugs that cause liver injury	Doses causing liver injury	Natural product	Source	Dosages	Model	Molecular mechanism	DOI
Oxytetracycline	300 mg/kg	Puerarin	Pueraria lobata	200, 400, 800 mg/kg	APAP induced acute liver injury in SPF ICR mice	↑Keap1/Nrf2	[42]
	10 mM			0–60 μmol/L	APAP induced hepatotoxicity in HepG2 cells		
	300 mg/kg	Sinapic acid	citrus fruits, berry fruits, grains, rapeseed, Brassica juncea, etc.	50 mg/kg	APAP induced acute liver injury in Male C57BL/6 mice	↓NF-κB ↑Sirt1/Nrf2/HO-1	[43]
	300 mg/kg	Oridonin	<i>Rabdosia rubescens</i>	25, 50 mg/kg	APAP induced acute liver injury in mice	↓ATF4/PGC-1α pathway	[48]
	500 mg/kg	Salidroside	<i>Rhodiola</i>	100 mg/kg	APAP induced acute liver injury in male C57BL/6 J mice	↑AMPK/SIRT1 pathway	[49]
	400 mg/kg	Kahweol	Coffee	20 mg/kg	APAP induced hepatotoxicity in C57BL/6N mice	↑Nrf2 ↓NF-κB	[50]
	200 mg/kg	Naringenin	Citrus fruits, Grapefruit, Tomatoes, Banana, Coffee, etc.	50 mg/kg	Oxytetracycline mediated oxidative damage in rat	↑VitC, VitE, GSH	[65]
	200 mg/kg	Nigella sativa oil and ascorbic acid	<i>Nigella sativa</i> , fruits	Nigella sativa oil, 200 mL/kg, ascorbic acid 1 mL/kg	Oxytetracycline-induced hepato-renal toxicity in rabbits	↓MDA ↑SOD, CAT, GSH, TAC	[66]
	20 mg/kg	Quercetin	Onion, Apple, Berries, Tea, Citrus Fruits, Broccoli, Spinach, etc.	20 mg/kg	Ciprofloxacin induced liver damage in Wistar albino rats	↓MDA ↑GSH, GPx	[67]
	40 mg/kg	M. oleifera leaf extracts	<i>Moringa oleifera</i>	300 mg/kg	Levofloxacin-induced hepatic toxicity in rats	↓MDA ↑SOD, CAT, GSH, IL-1β, IL-10	[68]
Dapsone	30 mg/kg	Ethanollic banaba leaves extract	Banaba	500 mg/kg	Dapsone-induced liver inflammation in rats	↓TNF-α, TGF-β	[69]
Isoniazid, Dapsone	Dapsone 30 mg/kg, Isoniazid 50 mg/kg	Ethanollic banaba leaves extract	Banaba	EBLE 500 mg/kg, silymarin 100 mg/kg	Isoniazid-and dapsone-induced hepatotoxicity in rats	↓TNF-α, TGF-β, NF-κB, ↑SOD, CAT, GSH	[70]
Rifampicin	200 mg/kg	Tanshinone IIA	<i>Salvia miltiorrhiza Bunge</i>	10, 30, 50 mg/kg	Rifampicin-induced liver injury in mice	↑Nrf2	[71]
Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	isoniazid 39 mg/kg, rifampicin 77 mg/kg, pyrazinamide 195 mg/kg, ethambutol 156 mg/kg	Magnesium isoglycyrrhizinate	<i>Glycyrrhiza glabra</i>	40 mg/kg	Anti-Tuberculosis drug-induced liver injury in BALB/c mice	↓LPS/TLRs/NF-κB Signaling Pathway	[72]
Isoniazid, Rifampicin	INH 150 mg/kg, RIF 150 mg/kg	Gallic acid	Pomegranate, Grape, Hawthorn, Tea, Blackberry, etc.	50, 100 150 mg/kg	Isoniazid and rifampicin-induced liver injury in Wistar Rats	↑Nrf2 ↓NF-κB	[73]
	INH 150 mg/kg, RIF 150 mg/kg	Quercetin	Onion, Apple, Berries, Tea, Citrus Fruits, Broccoli, Spinach, etc.	25, 50, 100 mg/kg	Isoniazid- and rifampicin-induced hepatotoxicity in divided Wistar rats	↑Nrf2 ↓NF-κB/TLR4	[74]
	INH 100 mg/kg, RIF 100 mg/kg	Telfairia occidentalis (Cucurbitaceae) pulp extract	Telfairia occidentalis	125–500 mg/kg	Rifampicin-isoniazid-induced hepatotoxicity in rat	↓MDA ↑SOD, CAT, GSH, GSPx	[75]
	INH 75 mg/kg, RIF 75 mg/kg	Rhus chinensis Mill.	<i>Rhus chinensis</i> Mill.	800 mg/kg	Isoniazid and rifampicin-caused liver injury in mice	↑Nrf2, BSEP, Mrp2 ↓CYP2E1, Bax, Bcl-2	[76]
	INH 100 mg/kg, RIF 100 mg/kg	<i>Crocus sativus</i> L. Extract	<i>Crocus sativus</i> L.	100, 200 mg/kg	Isoniazid- and rifampicin-induced liver injury in Wistar rats	↓TNF-α, COX-2	[77]
	INH 100 mg/kg, RIF 100 mg/kg	Dendrobine	<i>Dendrobium nobile</i> Lindl	50, 100, 200 mg/kg	Isoniazid- and rifampicin-induced liver injury in mice	↓miR-295-5p-mediated CYP1A2 expression	[78]
	INH 100 mg/kg, RIF 100 mg/kg	Yulangsans polysaccharide		100, 200, 400 mg/kg	Isoniazid and rifampicin-induced liver injury in mice	↑SOD, GSH, GSH-Px	[79]
	INH 100 mg/kg, RIF 100 mg/kg	Naringenin	Citrus fruits, Grapefruit, Tomatoes, Banana, Coffee, etc.	50, 100 mg/kg	Isoniazid- and rifampicin-induced hepatic injury in mice	↓Bax, ↑Bcl-2	[80]
	80 mg/kg	Laminaria japonica fucoidan	Laminaria japonica	20, 40 mg/kg	Cyclophosphamide-induced liver injury in ICR mice	↑Nrf2/HO-1 pathway, ↓TLR4/NF-κB pathway	[81]
Cyclophosphamide	80 mg/kg						

(Continued)

Drugs that cause liver injury	Doses causing liver injury	Natural product	Source	Dosages	Model	Molecular mechanism	DOI
Methotrexate	50 mg/kg	Lutein	Spinacia oleracea, Brassica oleracea var. capitata, Brassica oleracea var. italica, etc.	100 mg/kg	Cyclophosphamide induced liver injury in BALB/c mice	↓(ROS)/NF-κB/MAPK pathway	[82]
	200 mg/kg	Sinapic acid	Citrus fruits, Berry fruits, Grains, Rapeseed, Brassica juncea	5, 10 mg/kg	Cyclophosphamide-induced liver toxicity in mice	↓caspase-3, NF-κB	[83]
	2.5 µg/mL	Magnesium Isoglycyrrhizinate	Glycyrrhiza glabra	100, 120, 140 µM	Cyclophosphamide-induced hepatotoxicity in HepG2 cells	↓PI3K/Akt/mTOR/p70S6K/4EBP1 axis-mediated autophagy	[84]
	20 mg/kg	Punicalagin	<i>Punica granatum</i> L.	30 mg/kg	Cyclophosphamide-induced liver toxicity in rats	↓TNF-α, IL-1β	[85]
	200 mg/kg	Ganoderic acid A	<i>Ganoderma lucidum</i>	20 mg/kg	Cyclophosphamide-induced hepatotoxicity in mice	↓Txnip/Trx/NF-κB	[86]
	200 mg/kg	Nerolidol	Ginger, Tea tree, Orange, etc.	200, 400 mg/kg	Cyclophosphamide-induced hepatotoxic in Swiss albino mice	↑Nrf2 ↓NF-κB p65, Caspase-3	[87]
	200 mg/kg	Allicin	<i>Allium sativum</i> L.	10 mg/kg	Cyclophosphamide-mediated hepatotoxicity in rats	↑Nrf2/ARE pathways	[88]
	30 mg/kg	Taxifolin	<i>Allium cepa</i> L., olive oil, grapes, citrus fruits, etc.	25, 50 mg/kg	Cyclophosphamide-induced hepatotoxicity in mice	↑Nrf2/HO-1 signaling	[89]
	150 mg/kg	Arbutin	<i>Pyrus spp.</i>	25, 50 mg/kg	Cyclophosphamide-mediated oxidative and inflammatory reactions and hepatotoxicity in rats	↑Nrf2/HO-1 signaling	[90]
	80 mg/kg	Cichorium glandulosum seed	<i>Cichorium</i>	125, 250 mg/kg	Cyclophosphamide and its metabolite acrolein-induced hepatotoxicity	↑Nrf2 pathway	[91]
	20 mg/kg	Apigenin	<i>Apium graveolens</i> L. var. dulce DC., <i>Chamaemelum nobile</i> , <i>Allium cepa</i> , etc.	3 mg/kg	MTX-induced liver and kidney injury in CD-1 mice	↓Caspase-3, CRP, G-CSF, iNOS	[92]
	40 mg/kg	Glabridin	<i>Glycyrrhiza glabra</i> L.	10–40 mg/kg	MTX-induced liver injury in the Swiss mice	↑Nrf2, Bax ↓NF-κB	[93]
	20 mg/kg	Ferulic acid	grains, pineapple, banana, orange, etc.	25, 50 mg/kg	MTX-induced liver injury in rats	↑Nrf2/HO-1 signaling	[94]
	20 mg/kg	Naringin	Citrus grandis, Citrus paradisi, Citrus sinensis, Citrus limon, etc.	20, 40, 80 mg/kg	MTX-induced liver injury in male albino rats	↓MDA, NO, TNF-α, IL-6	[95]
	12.5–3.2 mM			12.5–3.2 mM	MTX-induced hepatotoxicity in HepG2 cells		
	20 mg/kg	Crocin	<i>Crocus sativus</i> L., <i>Gardenia jasminoides</i> Ellis.	25, 50 mg/kg	MTX-induced liver injury in rats	↓TNF-α, IL-1β	[96]
	20 mg/kg	<i>Ginkgo biloba</i> extract	<i>Ginkgo biloba</i> L.	60 mg(kg-day)	MTX-induced liver injury in Sprague Dawley rats	↓IL-6/STAT3 signaling pathway ↓miRNA-21	[97]
	20 mg/kg	Sinapic acid	Citrus fruits, Berry fruits, grains, Rapeseed, Brassica juncea	20 mg/kg	MTX-induced hepatotoxicity in rats	↑Nrf-2/HO-1 signaling	[98]
	20 mg/kg	Epicatechin	Tea leaves	100 mg/kg	MTX-induced hepatotoxicity in mice	↓MDA, NO	[99]
	20 mg/kg	Naringenin	Citrus fruits, Grapefruit, Tomatoes, Banana, Coffee, etc. <i>Ampelopsis</i>	50 mg/kg	MTX-induced hepatotoxicity in rats	↓MDA, NO, TNF-α, IL-6	[100]
Cisplatin	40 mg/kg	Dihydromyricetin	<i>grossedentata</i> , Grapes and red bayberry, <i>Hovenia dulcis</i>	300 mg/kg	MTX-induced hepatotoxicity in rats	↓TLR4/NF-κB, NLRP3/caspase 1	[101]
	20 mg/kg	Punicalagin	<i>Punica granatum</i> L.	25, 50 mg/kg	MTX-induced hepatotoxicity in mice	↑Nrf2 Signaling ↓NF-κB p65 ↓miRNA-34a	[102]
	5 mg/kg	Betanin	<i>Beta vulgaris</i> L.	100 mg/kg	Cisplatin-induced liver injury in Wistar rats	↑SIRT1/PGC-1α pathway	[103]

(Continued)

Drugs that cause liver injury	Doses causing liver injury	Natural product	Source	Dosages	Model	Molecular mechanism	DOI
	10 mg/kg	Protocatechuic acid	Grapes, Tea, Blueberries, Apples, Legumes, etc.	100, 150 mg/kg	Hepatotoxicity induced by cisplatin in mice	↓iNOS, NF-κB p65, IL-6, TNF-α	[104]
	3 cc/rat	Gallic acid	Pomegranate, Grape, Hawthorn, Tea, Blackberry, etc.	8 mg/kg	Cisplatin-Induced Nephrotoxicity and Hepatotoxicity in Wistar albino rats	↑CAT, SOD	[105]
	7.5 mg/kg	Epigallocatechin gallate and CoQ10	Green tea	Epigallocatechin gallate 15 mg/kg, CoQ10 5 mg/kg	Cisplatin-induced hepatotoxicity in rats	↓cytochrome c efflux, caspase-3	[106]
Oxaliplatin	8 mg/kg	Curcumin	<i>Curcuma longa</i> L.	50, 100 mg/kg	Oxaliplatin (OXA)-induced liver injury in BALB/c mice	↑Nrf2 Pathway, HO-1, NOQ1	[107]
5-Fluorouracil	10 mg/kg	<i>Nigella sativa</i> and Onion Extract	<i>Nigella sativa</i> , Onion	50 mg/Kg	5-Fluorouracil-Induced Hepatic Toxicity in rats	↑Nrf2	[108]
	10 mg/kg	Caffeic Acid Phenethyl Ester	Propolis	10 mmol/kg	Fluoxetine-Induced Hepatotoxicity in rats	↑PON-1, TAC ↓TOS, OSI	[109]
Fluoxetine	10 mg/kg	Olive oil and leaf extract	<i>Olea europaea</i>	Olive oil 1.5 mL/kg, leaf extract 100 mg/kg	Fluoxetine-Induced Hepatotoxicity in rats	↓Bax, Caspase-3 ↑Bcl-2	[110]
	10 mg/kg	Baicalin	<i>Scutellaria baicalensis Georgi</i>	50, 100 mg/kg	Fluoxetine-induced hepatotoxicity in Male albino Wistar rats	↓TNF-α, IL-6, IL-10, IFN-γ	[111]
Phenobarbital	0.05%	Extract of aged garlic	Garlic	5% w/v	dimethylaminoazobenzene and phenobarbital-induced hepatotoxicity in rats	↓ALT, AST	[112]
	0.2 mL/kg	<i>Punica granatum</i> (pomegranate) peel and seed oil extracts	<i>Punica granatum</i> (pomegranate)	2 mL/kg	Diethylnitrosamine and phenobarbital induced hepatic injury in rats	↓Caspase-3, MDA ↑GSH, SOD, GST, t-GPx	[113]
Diethylnitrosamine, Phenobarbital	500 ppm	<i>Punica granatum</i> (pomegranate) juice extract	<i>Punica granatum</i> (pomegranate)	200 mg/kg	Diethylnitrosamine and phenobarbital induced hepatic injury in male rats	↓MDA, DNAF, t-GPx, GSR, caspase-3	[114]
Haloperidol	15 mg/kg	Functional Oil from Black Seed	<i>Nigella sativa</i>	150 mg/kg	Haloperidol-induced Hepatic Toxicity in Rat	↑hepatic ATP ↓ectonucleotidase, aldose-reductase	[115]
Risperidone	2 mg/kg	Resveratrol	<i>Vitis vinifera</i> , <i>Arachis hypogaea</i> , <i>Morus alba</i> , etc.	20, 40, 80 mg/kg	Risperidone-induced liver damage in rat	↓ALT, AST, ALP	[116]
Propylthiouracil	10 mg/kg	<i>Astragalus membranaceus</i> and <i>Laminaria japonica</i> extracts (85: 15 g/g)	<i>Astragalus membranaceus</i> , <i>Laminaria japonica</i>	100, 200, 400 mg/kg	Propylthiouracil-induced hypothyroidism and liver injury in rats	↓ALT, AST	[117]
Trastuzumab	10 mg/kg	Aqueous garlic extract	<i>Allium sativum</i> L.	75 mg/kg	TAM-Induced Hepatotoxicity in Rats	↓TNF-α ↑SOD2, CAT, GPX1	[118]
	1 mg/kg	Allicin	<i>Allium sativum</i> L.	10 mg/kg	TAM induced liver injury in rats	↑SOD, GSH, ↓ALT, AST, ALP, γGT, TNF-α	[118, 119]
	3 μM			5, 10 μM	TAM-Induced Hepatotoxicity in EAC cells		
Tamoxifen	90 mg/kg	Osthole	<i>Angelica</i> , <i>Archangelica</i> , and <i>Citrus</i> species	100 mg/kg	TAM-induced liver injury in mice	↓p38, ALT, AST	[120]
	45 mg/kg	Thymoquinone	<i>Nigella sativa</i>	50 mg/kg	TAM-induced liver injury in female rats	↑SOD ↓TNF-α	[121]
	50 mg/kg	Chlorogenic acid	Coffee beans, Tomatoes, Eggplants, etc.	25, 50 mg/kg	TAM-induced liver injury in rats	↓IL-10, IL-1β, TNF-α, Caspase-3, -9	[122]
Amiodarone	40 mg/kg	Alpha lipoic acid	Spinach, Broccoli, Brussels Sprouts, etc.	100 mg/kg	Amiodarone-induced pulmonary fibrosis and hepatic injury in rats	↓α-SMA, IFN-γ, TGF-β1	[123]

MTX-induced oxidative stress impairs mitochondrial function by inhibiting the mitochondrial electron transport chain complex, resulting in the production of reactive oxygen species (ROS), allowing for the activation of the NF-κB signaling pathway^[129, 130].

The recent studies have demonstrated the potential of a range of natural products in alleviating MTX-induced liver damage. Apigenin, a flavonoid widely distributed in vegetables and fruits, was found to alleviate MTX-induced liver injury in mice by

reducing oxidative stress and apoptosis^[92]. Glabridin, an active ingredient extracted from *Glycyrrhiza glabra*, attenuated MTX-induced hepatotoxicity in mice. This attenuation occurred through the up-regulation of Nrf2, inhibition of NF-κB activation, and up-regulation of Bax, thus ameliorating factors important for oxidative stress, inflammation, and apoptosis^[93]. Ferulic acid, an antioxidant phytochemical, has been proven to prevent MTX-induced hepatotoxicity in rats by activating the Nrf2/HO-1

signalling pathway and PPAR γ , and reducing oxidative stress and inflammation^[94]. More natural medicines that alleviate MTX-induced hepatotoxicity^[95-102] are listed in Table 2.

3.2.3 Cisplatin

Cisplatin (CP) is a common platinum-based anticancer drug. Used to treat 40%–60% of cancer patients, it is one of the earliest and most widely used chemotherapeutic agents in clinical practice^[131]. However, in recent years, a large number of studies have demonstrated that CP has severe hepatotoxicity. CP can cause excessive ROS production and increase its oxidative stress in the liver. At the same time, it decreases GSH and superoxide dismutase (SOD) levels and increases malondialdehyde (MDA) levels, thereby exhibiting a weakened antioxidant defense system^[132].

Recently, an increasing number of natural products have been found to alleviate CP-induced hepatotoxicity. Betanin, derived from beets as a natural red glycoside pigment, successfully attenuated CP-induced liver injury by down-regulating miRNA-34a expression and activating SIRT1/PGC-34 α pathway^[103]. Protocatechuic acid, a widely distributed natural phenolic acid^[133], ameliorates CP-induced liver injury by anti-oxidant, anti-apoptotic and anti-inflammatory^[104]. Moreover, in rats with CP-induced nephrotoxicity, silymarin and gallic acid increased the activities of catalase (CAT) and SOD to alleviate liver injury^[105]. Furthermore, the combination of epigallocatechin gallate and CoQ10 attenuated CP-induced hepatotoxicity and apoptosis by suppressing the activation of proapoptotic proteins and mitochondrion accumulation, upregulating anti-apoptotic

proteins, and inhibiting cytochrome c efflux, caspase-3 activation, and DNA fragmentation through the respective antioxidant effects of epigallocatechin gallate and CoQ10^[106]. Furthermore, it is noteworthy that these natural products mentioned are all derived from plants with the characteristic of being both food and medicine. Of these, protocatechuic acid, arjunolic acid, and epigallocatechin gallate are all phenolic compounds.

3.2.4 Others

Oxaliplatin is a widely used platinum-derived chemotherapeutic agent for the treatment of colorectal cancer. Unfortunately, hepatotoxicity is emerging as one of the major constraints to its use^[134]. The main cause of oxaliplatin hepatotoxicity is mitochondrial oxidative stress, in which ROS-mediated lipid peroxidation and protein carbonyls^[135]. Curcumin, a hydrophobic polyphenol from turmeric, attenuated oxaliplatin-induced liver injury and oxidative stress by activating the Nrf2 pathway and increasing the expression of HO-1 and NOQ1 in mice^[107].

5-Fluorouracil is one of the most commonly used antimetabolite chemotherapeutic agents in recent decades, which can exert anticancer effects by inhibiting thymidylate synthase or interfering with the normal biosynthesis of nucleic acids^[136]. *Nigella sativa* and onion extracts attenuate 5-fluorouracil-induced liver injury through antioxidant, anti-lipid peroxidation, and anti-inflammatory mechanisms^[108].

For the problem of anticancer drug-induced DILI, natural products, especially phenolic compounds derived from medicinal and food homology plants as shown in Fig. 3, have shown their

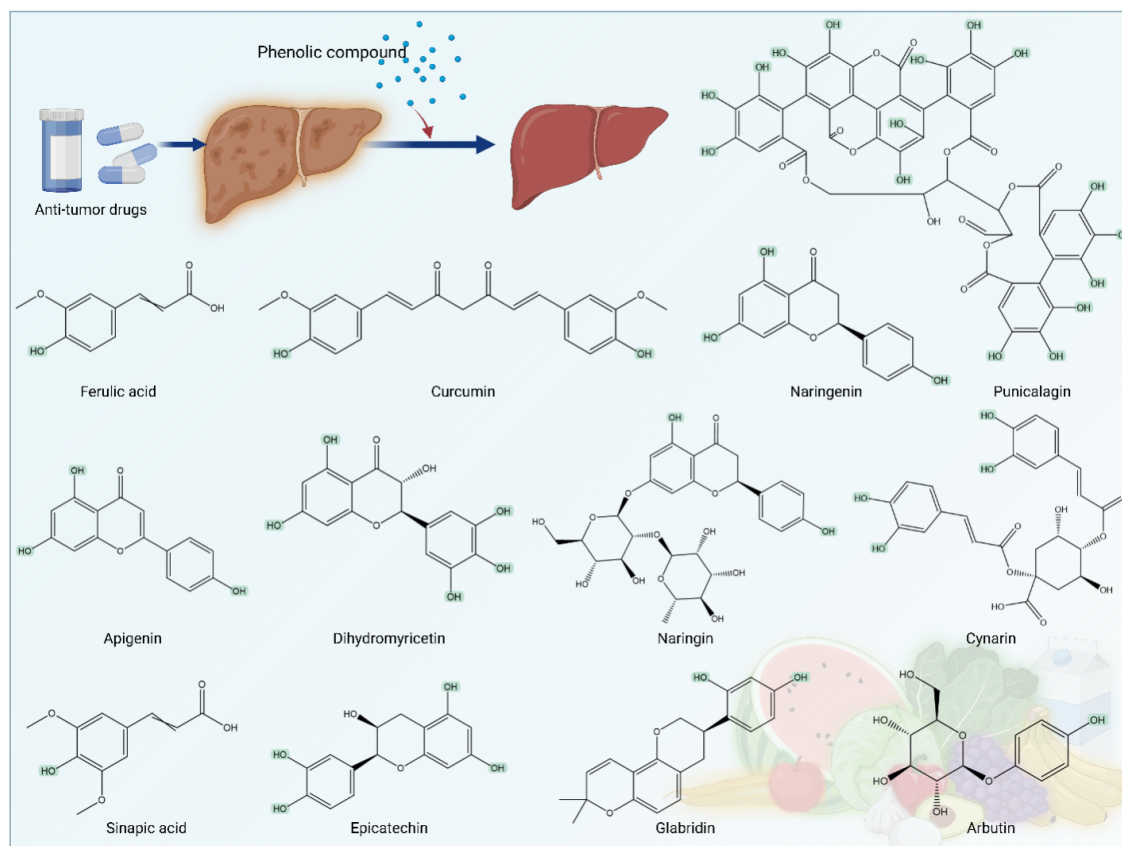


Figure 3 Phenolic natural products for the mitigation of DILI induced by anti-tumor drugs. A rich tapestry of natural polyphenolic compounds, including ferulic acid, curcumin, naringenin, punicalagin, apigenin, dihydromyricetin, naringin, and cynarin, is derived from the bountiful realm of medicinal and food homology plants. These potent phytochemicals have shown promise in their capacity to alleviate the liver injuries induced by antitumor drugs.

importance and potential. In addition to possessing antioxidant and anti-inflammatory properties, these natural products mitigate chemotherapy-induced liver injury through various mechanisms. For example, cynarin from *Cichorium glandulosum* seed, fucoidan from *Laminaria japonica*, apigenin from edible herbs, punicalagin from *Punica granatum*, and ganoderic acid A from *Ganoderma lucidum* have been noted for their remarkable effects in protecting the liver. In addition, polyphenolic compounds such as allicin from garlic, arbutin, chicory seeds, *Ginkgo biloba* leaf extract, epicatechin, nerolidol, dihydromyricetin, etc., have been shown to have the ability to activate the Nrf2 signaling pathway and reduce oxidative stress, thus playing a protective role in hepatotoxicity caused by anti-tumor drugs. These compounds not only have a long history of use in traditional medicine but are also widely used in modern nutritional science. They offer new strategies and hope for liver protection in cancer therapy.

3.3 DILI caused by anti-infective drugs

3.3.1 Oxytetracycline

Oxytetracycline, a widely used broad-spectrum antibiotic, is clinically utilized for various infections. However, oxytetracycline has been reported to cause liver damage and, combined with quinocetone, further increases ROS generation and activates the mitochondrial cell death pathway, leading to hepatotoxicity^[137]. Naringenin, a polyphenolic compound classified within the flavanone subclass, is a significant phytochemical present predominantly in citrus fruits, including grapefruits^[138]. Naringenin has been shown to protect against liver injury caused by oxytetracycline in rats by prior studies. And then to give naringenin resulted in serum marker (AST, ALT, ALP, LDH) and bilirubin levels being reduced along with increased levels of GSH, vitamin C, and vitamin E in the liver^[65]. *Nigella sativa* oil or black seed oil, which is a known Mediterranean food, has consumption of *Nigella sativa* oil is good for human health^[139]. Another study has also shown the hepatoprotective activity of *Nigella sativa* oil and ascorbic acid against liver injury in rabbit due to oxytetracycline, due to the antioxidative property^[66]. Although there are not many studies in the literature on this subject, but some evidence shows that the therapeutic effects of natural products towards oxytetracycline induced liver injury.

3.3.2 Ciprofloxacin

Ciprofloxacin is an antibacterial which interfer with the DNA gyrase. The active metabolite of ciprofloxacin causes the release of damage associated molecular pattern by the hepatocytes and it activates the inflammasome leading to development of the liver injury^[140]. Some researchers speculate that the hepatotoxicity is caused by generation of free radicals causing an oxidative stress of liver. Quercetin treatments on rats in a study also found to reduce hemorrhage, inflammatory cell infiltration and intracellular vacuolization in ciprofloxacin induced liver damage^[67].

3.3.3 Levofloxacin

Fluoroquinolones, a class of broad-spectrum systemic antimicrobials, have been extensively utilized in the treatment of respiratory and urinary tract infections. Among these agents, levofloxacin, a third-generation fluoroquinolone, is commonly prescribed to address mild to moderate respiratory and urinary tract infections caused by susceptible microorganisms^[141]. Nevertheless, recent studies have reported a significant association between levofloxacin treatment and liver damage. Hepatocellular

or mixed damage, jaundice, and in severe cases, liver failure may manifest as sudden symptoms^[142, 142]. Levofloxacin is postulated to cause hepatotoxicity through hepatic GSH depletion and mitochondrial ROS formation^[143]. *Moringa oleifera* is a rich source of polyphenolic natural products; its leaves are edible and have a wide range of bioactivities^[144-146]. *Moringa oleifera* leaf extracts have the potential to mitigate levofloxacin-induced liver injury and inflammation by upregulating IL-10 and IL-1^[68].

3.3.4 Dapsone

Dapsone (4,4'-diaminodiphenylsulfone) is a cornerstone of dermatologic therapeutics, widely used in the treatment of a spectrum of skin conditions. It is the main dynamic component of the World Health Organization (WHO)-endorsed polypharmaceutical regimen specifically designed for the treatment of leprosy^[147]. However, the therapeutic use of dapsone is not without its challenges. Dapsone and its metabolites, particularly the N-hydroxylated form, have been observed to induce hemolysis in the presence of hepatitis. This response can induce cholestasis, oxidative stress, and hepatic necrosis, culminating in hepatic iron overload^[148]. Fortunately, the intersection of traditional medicine and modern research has yielded promising results. A recent study has shed light on the hepatoprotective effects of *Lagerstroemia speciosa* (L.) Pers., a plant whose leaves are traditionally used in herbal medicine. It is colloquially known as banaba, exemplifies natural products serving not only as nutrition but also as therapeutics. Its extract, alongside silymarin, was shown to ameliorate dapsone-induced liver injury and inflammation in rats. This beneficial effect is thought to be mediated by the downregulation of pro-inflammatory cytokines, particularly TNF- α and TGF- β ^[69, 70].

3.3.5 Rifampicin and isoniazid

Isoniazid and rifampicin are primary drugs used in tuberculosis treatment, with liver injury being their primary adverse effect^[149]. In the first metabolic step, rifampicin is induced by the CYP enzyme (CYP7A1) via the pregnane X receptor (PXR) to produce toxic drug metabolites. This leads to oxidative stress and hepatic cholestasis, as well as activation of ER stress^[150]. Similarly, isoniazid metabolites are metabolized by CYP enzymes to toxic substances that induce oxidative stress. However, in the second metabolic process, GSTs detoxify the active metabolites generated by the oxidation of acetylhydrazine and hydrazine, metabolites of isoniazid^[151]. Indeed, the combination of isoniazid and rifampicin is commonly used in clinical practice for tuberculosis therapy. Consequently, this synergistic approach significantly elevated the levels of ALT, AST, ALP, LDH, serum bilirubin, and cholesterol^[152]. Furthermore, prolonged concurrent administration of isoniazid and rifampicin induced hepatic stellate cell activation and hepatic fibrosis^[153].

Recently, there has been a rise in the emergence of potent natural medicines for alleviating liver injury induced by isoniazid and rifampicin. For instance, Tanshinone IIA mitigated rifampicin-induced liver injury through the upregulation of ten-eleven translocation 2 (TET2), which facilitated the DNA demethylation of Nrf2 and subsequently enhanced the expression of bile acid receptors, including bile salt efflux pump (BSEP) and Na⁺/taurocholate cotransporter (NTCP)^[71]. Magnesium isoglycyrrhizinate (MgIG) is a fourth-generation glycyrrhetic acid preparation that consists mainly of the magnesium salt of the 18 α -glycyrrhizin stereoisomer. MgIG alleviated the liver injury induced by both rifampicin and isoniazid by modulating intestinal

flora and suppressing the LPS/TLRs/NF- κ B signaling pathway^[72]. In a similar vein, quercetin and gallic acid alleviated rifampicin- and isoniazid-induced liver injury in rats by activating Nrf2 and inhibiting the NF- κ B/TLR-4 signaling pathway^[73,74]. Furthermore, several plant-derived extracts alleviated liver injury induced by rifampicin and isoniazid in preclinical studies. These include *Telfairia occidentalis* pulp extracts^[75], *Rhus chinensis* fruit extracts^[76], and *Crocus sativus* extracts^[77]. Additionally, Table 2 includes a list of more natural products that alleviate liver injury induced by rifampicin and isoniazid^[78-80].

In summary, plants with both medicinal and dietary uses have demonstrated efficacy in animal and cellular models of anti-infective induced DILI. Among these, naringenin, gallic acid and quercetin stand out as polyphenolic compounds, as shown in Fig. 4. In addition, the above plant extracts such as those from *Moringa oleifera*, ethanolic banaba, *Rhus chinensis*, and *Crocus sativus* L., are rich in polyphenols. In particular, quercetin has the ability to attenuate liver damage induced by a number of drugs used to treat infectious diseases, including ciprofloxacin, isoniazid, and rifampicin.

3.4 DILI caused by central nervous system drugs

3.4.1 Fluoxetine

Fluoxetine, a selective 5-hydroxytryptamine reuptake inhibitor, is commonly used clinically as an antidepressant to treat

depression and a range of neuropsychiatric disorders, including major depressive disorder and anxiety. However, a large body of research now suggests that fluoxetine has inevitable side effects. Fluoxetine exacerbates oxidative stress by increasing superoxide anion levels, which can increase free radical production, decrease hepatic antioxidant capacity and induce oxidative stress, as well as exacerbating liver injury by aggravating otherwise mild mononuclear cell infiltration, haemorrhage, adipocyte degeneration, and apoptosis^[109].

Caffeic acid phenethyl ester is a naturally occurring phenolic compound that plays an important role as a functional component in propolis. It has considerable potential for application in the food, nutritional, and pharmaceutical fields due to its diverse bioactivities. Caffeic acid phenethyl ester mitigated fluoxetine-induced toxicity, a beneficial effect achieved by reducing serum and liver levels of total oxidant status and oxidative stress index, while increasing levels of paraoxonase 1 (PON-1) and total antioxidant capacity (TAC)^[109]. Olive oil and leaf extracts have similarly been noted for their hepatoprotective properties. They have been effective in mitigating fluoxetine-induced liver injury and inflammation, evidenced by decreased levels of TNF- α and IL-1 β , alongside reduced apoptosis indicated by lowered Bax and caspase-3, and elevated Bcl-2. Their mechanism of action involves the reduction of oxidative stress, marked by a decrease in NO and an increase in GSH, SOD, catalase, and GPx^[110]. Baicalin, a flavonoid derived from the

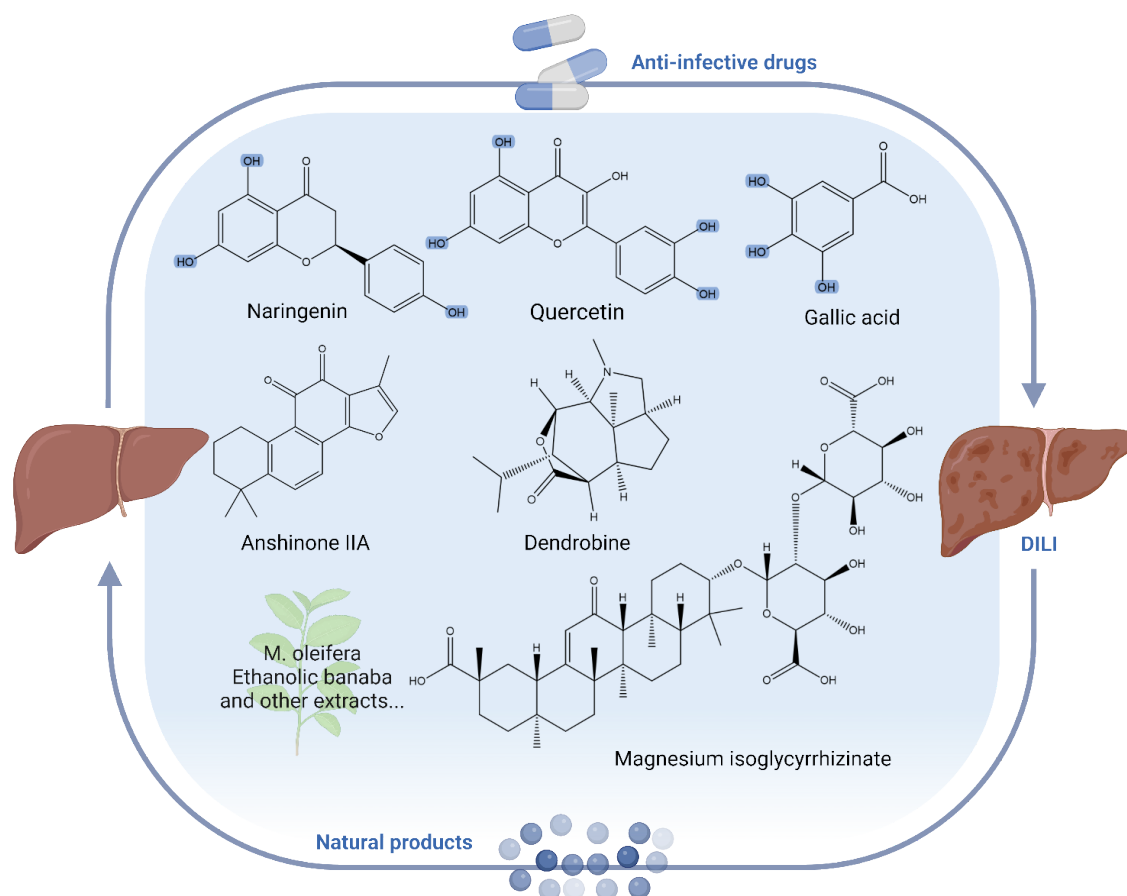


Figure 4 Medicine and food homology natural products for the treatment of anti-infective induced DILI. Polyphenols from medicinal and dietary plants, such as naringenin, gallic acid, and quercetin, show potential in animal and cellular models to mitigate DILI caused by anti-infective drugs. Notably, quercetin can alleviate liver damage induced by medications like ciprofloxacin, isoniazid, and rifampicin. Other plant extracts rich in polyphenols, including *M. oleifera*, ethanolic banaba, *Telfairia occidentalis* (*Cucurbitaceae*) pulp, *Rhus chinensis* Mill. and *Crocus sativus* L., also demonstrate hepatoprotective effects against liver injury from infectious disease treatment.

traditional herbal plant *Scutellaria baicalensis*, is widely used as a functional food in many Asian countries, where it's known to help reduce inflammation^[154]. It attenuated fluoxetine-induced liver injury and hepatotoxicity. This protective effect is mediated through modulation of oxidative stress, characterized by upregulation of antioxidant enzymes such as SOD, CAT, GST, and GSH, while down-regulating the levels of MDA. Furthermore, baicalin exerts anti-inflammatory activity by reducing the expression of pro-inflammatory cytokines, including TNF- α , IL-6, IL-10, and IFN- γ , thereby ameliorating fluoxetine-induced hepatotoxicity^[111].

3.4.2 Phenobarbital

Phenobarbital is a barbiturate psychotropic drug used as a sedative, hypnotic, anticonvulsant, and antiepileptic^[155]. Phenobarbital sodium was included in the FDA Adverse Event Reporting System between 2018 and 2020^[156]. Phenobarbital-induced hepatotoxicity is usually associated with hypersensitivity reaction characteristics^[157].

The extract of garlic is rich in active ingredients such as polyphenols, sterols, and tocopherols, which have antioxidant, hypoglycaemic, and hypocholesterolemic properties^[158]. It reduced levels of biomarkers of p-dimethylaminoazobenzene and phenobarbital-induced liver injury in mice^[112]. In addition, the extracts of pomegranate peel and pomegranate seed oil also exhibited anti-proliferative, pro-apoptotic and anti-inflammatory effects against various types of cancer^[159]. Pomegranate peel and seed oil extracts decreased MDA, DNA fragmentation, caspase-3 and GSR activities, and increased GSH, SOD, GST, and total glutathione peroxidase (t-GPx) activities, attenuating the effects of diethylnitrosamine and phenobarbital in rat liver injury^[113,114].

3.4.3 Others

Haloperidol has been a widely used drug for the treatment of psychiatric disorders^[160]. However, concerns about potential hepatotoxic effects have not been without their use. Recently, a promising intervention has emerged in the form of a functional oil derived from black seed. In a rodent study, this oil demonstrated a protective effect against haloperidol-induced liver toxicity. This protective mechanism is thought to involve the inhibition of aldose reductase and ectonucleotidase activities. This is achieved through the upregulation of cellular energy levels^[115].

Risperidone, recognized as an effective antipsychotic agent, is often preferred for its reduced potential to induce hepatotoxic side effects compared to phenothiazine antipsychotics^[161]. However, there have been documented cases where both risperidone and its metabolites have been involved in hepatotoxicity^[162]. In a positive development, resveratrol mitigated liver injury induced by risperidone in rats. This protective effect is observed through the upregulation of the fatty acid synthase gene expression^[116]. This natural compound is widespread in the plant kingdom and is especially abundant in fruits, which serve as the primary dietary source of resveratrol^[163].

3.5 DILI caused by other drugs

3.5.1 DILI caused by metabolic disease drugs

Propylthiouracil, a conventional antithyroid drug, is associated with the risk of DILI, the mechanisms of which remain not fully elucidated^[164]. *Astragalus membranaceus* and *Laminaria japonica*, traditionally used as both medicinal and dietary plants, have demonstrated protective effects against propylthiouracil-induced hypothyroidism and liver injury. These beneficial properties are

likely due to their abundant content of iodine and ferulic acid, key components that may counteract the DILI associated with propylthiouracil^[117].

3.5.2 DILI caused by biopharmaceutical drugs

Trastuzumab is a drug consisting of the medetanin-like toxin DM1 linked to the humanized monoclonal antibody trastuzumab via a thioether-based chemical linker approved for the treatment of HER2-positive breast cancer^[165]. However, trastuzumab treatment may cause hepatotoxicity through a HER2-dependent pathway^[166]. In addition, DM1 mediates the binding of trastuzumab to CKAP5 on the cell surface, which then initiates cell membrane disruption and calcium influx into the hepatocyte, leading to disruption of microtubule polymerization and apoptosis^[167].

According to the present findings, aqueous garlic extract attenuated trastuzumab-induced hepatotoxicity in rats by upregulating antioxidant enzyme activities (SOD2, CAT, and GPX1), reducing lipid, liver enzyme, and ROS levels, and inhibiting expression of TNF- α ^[118]. A member of the *Allium* genus, garlic is rich in health-promoting compounds, including polyphenols, organosulfur compounds, flavonoids, alkaloids, and polysaccharides. These bioactive constituents not only underscore garlic's role in culinary traditions, but also highlight its potential as a therapeutic ally in the fight against liver toxicity and the support of overall health^[168].

3.5.3 DILI caused by hormone-type drug

Tamoxifen (TMX) is an anti-estrogenic drug with tumor-initiating and tumor-promoting properties and is used for the treatment and prevention of estrogen-dependent breast cancer at all stages of the disease^[169]. However, a large number of clinical studies have demonstrated that TMX has a toxic effect on the liver. It may cause toxic hepatitis, massive hepatic steatosis, multifocal fatty infiltration of the liver, submassive hepatic necrosis, and even cirrhosis in humans^[120]. In addition, high doses of TMX can be a liver carcinogen in rats. Injection of TMX led to impaired fatty acid mitochondrial β -oxidation and overproduction of ROS, which led to mitochondrial damage, making phosphorylation less efficient and ultimately affecting mitochondrial membrane integrity^[170].

Allicin, derived from garlic, has been shown to reduce liver injury in both *in vivo* and *in vitro* TMX-induced liver injury experiments. Pretreatment with allicin not only enhances the antitumor effects of TMX, but also mitigates its hepatotoxicity by preventing oxidative stress and lipid peroxidation, enhancing antioxidant enzyme activity, and reducing hepatic inflammation^[119]. Osthole, a natural coumarin derivative originally isolated from the plant *Cnidium monnieri*, is found in several medicinal and food homology plants, including *Angelica*, *Archangelica*, and *Citrus* species. By inhibiting p38 activation and thereby reducing oxidative damage, it prevents TMX-induced hepatotoxicity^[120]. Thymoquinone, the active ingredient of *Nigella sativa*, reduced TMX-induced hepatotoxicity of female rats by reducing TNF- α ^[121]. Chlorogenic acid has been shown to attenuate TMX-induced hepatotoxicity in rats by reducing levels of pro-inflammatory cytokines (IL-1 β and TNF- α), oxidative stress (MPO and NO), and Casp-3 and -9 activity^[122].

3.5.4 DILI caused by cardiovascular disease drugs

Amiodarone is a potent antiarrhythmic drug that is widely used in clinical practice for the treatment of ventricular and atrial

arrhythmias^[171]. Unfortunately, chronic oral administration of amiodarone can lead to liver disease such as acute liver failure^[172]. The pathogenesis is that amiodarone and its major metabolite desethylamiodarone cause hepatotoxicity by generating mitochondrial and oxidative stress and Kupffer cell activation^[173]. However, previous studies have reported that treatment with the natural product alpha lipoic acid, a natural product found in *Arabidopsis thaliana*, reversed oxidative stress, fibrosis, and inflammatory parameters and reduced α -smooth muscle actin expression, and alleviated amiodarone-induced pulmonary fibrosis and liver injury in rats^[123].

In conclusion, natural products derived from medicinal plants show great potential in treating and preventing multi-drug-induced DILI, particularly in modulating cellular stress response, enhancing detoxification and promoting cellular repair. Among them, polyphenolic compounds offer new strategies and promise for the treatment of DILI. They activate antioxidant defence systems, attenuate oxidative stress and modulate cell signalling pathways. As these natural products continue to be explored, we expect to discover more effective natural products to treat and prevent DILI.

4 Clinical profiles of natural products from medicine and food homology plants for DILI therapy

Extensive research and promising preclinical results highlight the therapeutic potential of natural products derived from medicine and food homology plants to treat DILI. It is with great optimism that we observe certain natural products progressing from the experimental stage to clinical application. In this section, we will highlight examples of proven efficacy and safety in the clinical setting and explore the clinical profile of these natural products for the treatment of DILI.

Nigella sativa, known as black seed, is celebrated both for its culinary uses in baking and food products and for its diverse traditional medicinal applications. Valued across cultures, this plant addresses a variety of health issues, including bacterial infections, dyslipidemia, diarrhea, and inflammation^[174]. A previous clinical trial investigated the therapeutic effect of black seed oil on MTX-induced hepatotoxicity in Egyptian children with ALL. The results suggested that despite the fact that black seed oil treatment failed to decrease TBIL, ALT, AST, and ALP levels and prothrombin time, the treatment group exhibited superiority over the control group in terms of complete remission, relapse, and survival. Therefore, black seed oil was revealed to reduce the hepatotoxicity of MTX and improve survival in children with ALL, which might be used as an adjunct to MTX in the treatment of patients with ALL^[175].

Silybum marianum, it is also a kind of plant, and in the traditional medicine which have a long history, it is more about dealing with the problem of liver and gallbladder diseases in Europe. Also having botanic extracts which can be commonly found and widely used in food, health products, cosmetics, and cosmetics^[176]. From the clinical research that can be found that silymarin can lower the hepatotoxicity brought about by anti-tuberculosis drugs. A study showed us that taking 140 mg/day silymarin has lowered rates at 28% of experiencing hepatotoxicity compared to control groups. This treatment also led to a reduction in the level of SOD^[177]. In addition, silymarin also exhibited efficacy in mitigating hepatotoxicity caused by interferon- β (IFN- β), which is used to treat multiple sclerosis. Research shows that

after 6 months of oral silymarin intake at 420 mg/day, the percentage of Th17 cells and the levels of liver enzymes, IL-17 and IFN- γ were lowered. Conversely, IL-10 and TGF- β levels were raised and IFN- β caused inflammation and DILI were lessened^[178]. In non-metastatic breast cancer: A clinical trial has shown that oral silymarin decreased severity of liver toxicity after 1 month of antineoplastic treatment. A 140 mg dose reduced the indicators of fatty liver disease and total bilirubin more effectively^[179]. However, it should also be pointed out that although silymarin has shown effects under certain circumstances, it is not necessarily more efficacious than other ingredients in every situation. From a clinical trial in 2015 we find out that both folic acid and silymarin were used in the treatment of antiepileptic DILI. The patients of the folic acid group 1 mg/(kg-day) had significantly lower value of ALT, AST and GGT and had a larger percentage of normal value of ALT 30.7% VS 3.4%, AST 42.3% VS 0% and GGT 23.1% VS 0% as compared to the silymarin 5 mg/(kg-day) group. And the result suggests that both treatments can reduce the liver enzyme, but the folic acid look like have more advantage than the silymarin in the treatment of DILI^[180].

Licorice (*Glycyrrhiza uralensis*), a natural botanical resource that has been widely used in China as a food and medicine^[181]. MgIG, from the pharmaceutical compound derived as the magnesium salt of the 18- α glycyrrhetic acid stereoisomer, is a development in the fourth generation of glycyrrhetic acid type drugs, and it has a range of pharmacological effects^[182]. The key study on patients who experienced liver damage by chemotherapy, MgIG demonstrated its hepatoprotective capabilities by lowering ALT and AST levels^[183]. According to the above, a clinical trial in 2019 assessed the efficacy of MgIG compared with thiopronin in acute DILI. According to the results, ALT levels normalized in 84.75% of the 54 patients in the MgIG 100 mg group and 85.71% of the 54 patients in the MgIG 200 mg group at week 4. And it was 3.6 times more likely for ALT normalization in patients of the treatment group compared with control group (200 mg thiopronin). The above result further illustrate MgIG is safe and effective agent and maybe MgIG can be used for the acute DILI in clinic and it might be a new possibility for the future of the treatment for liver injury^[184].

5 Medicine and food homology plants: side effects and safety concerns

According to current research, natural drugs and food-derived plants are promising approaches for treating DILI. However, it should be noted that there is a key limitation in this field. The misuse or improper use of these natural products is associated with hepatotoxicity, as confirmed by some case reports^[185]. To promote the clinical application of these natural products, it is necessary to conduct detailed research to confirm the therapeutic effects of these claims and ensure their safety during the treatment of DILI.

5.1 *Nigella sativa*-induced liver injury

Nigella sativa has both culinary and medicinal value and is widely used in South Asia, Southeast Asia, Africa and the Mediterranean region. *Nigella sativa* possesses properties such as diuretic effect, blood pressure reduction, anti-diabetic action, anti-cancer effect, immune regulation, liver protection, repair and antioxidant function^[186]. Although *Nigella sativa* and its extracts have shown excellent therapeutic effects in inhibiting DILI induced by drugs such as APAP, tamoxifen or 5-

fluorouracil^[66, 108, 121], there are also certain risks involved. According to clinical case reports, the intake of *Nigella sativa* oil can cause acute kidney injury, rhabdomyolysis and liver toxicity, etc.^[187]. The other two case reports indicate that the use of *Nigella sativa* oil as an external agent may cause contact dermatitis^[188, 189]. This suggests that traditional therapies should be treated with caution, and it is crucial to conduct further research on the potential negative effects of these traditional treatments.

5.2 Green tea extract induced liver injury

Over the years, green tea has shown positive effects in treating various diseases, including cancer, heart disease, obesity and insulin resistance. This multi-functional beverage is well-known for its refreshing taste and health-promoting properties. It is also widely used in the food industry. The active components that contribute to its health benefits are catechins and EGCG. These compounds have been proven to be effective in alleviating DILI caused by APAP^[99, 106]. Although EGCG has these advantages, some studies have shown that high doses of EGCG may cause liver toxicity. The direct liver damage effect caused by high doses in rodent models has become the focus of research on the hepatotoxicity of green tea extracts. According to a research report, mice that received a high dose of oral catechin EGCG green tea exhibited liver toxicity, and their survival rate decreased as the time and dose changed^[190]. Furthermore, the comprehensive causal assessment studies conducted between 2004 and 2018 revealed that there were approximately 70 suspected cases of liver damage caused by green tea extract. Among these, 40 cases were directly related to the use of such extracts, which also indicates the need for caution when using such supplements^[191]. Another relatively new study was a phase II randomized placebo-controlled double-blind clinical trial, aiming to explore the possible impact of long-term high-dose oral green tea dosage on liver injury markers. The research results indicate that regular high-dose green tea (approximately 1,300 mg of catechins and 800 mg of EGCG) as a dietary supplement may be associated with mild to severe elevation of liver enzymes in a small number of healthy postmenopausal women^[192]. Furthermore, existing evidence indicates that high doses of EGCG have hepatotoxicity. The A/C genotype of UGT1A4 (rs6755571) may be an important risk factor for menopause and elevated serum transaminase levels in women after taking high-dose GTE^[193]. These results emphasize that when using green tea extract as a medication, individual genetic differences and dosage addition should be fully considered to minimize the risk of liver damage to the greatest extent.

5.3 Turmeric-induced liver injury

Turmeric is a popular spice in cuisines around the world, adding a distinctive flavor and rich golden hue to a variety of dishes. The essential oils and curcuminoid compounds identified in the rhizomes of turmeric are the active ingredients, collectively known as curcuminoids, which are celebrated for their antioxidant, anti-inflammatory, and anti-carcinogenic properties. These compounds are generally considered to be safe and may protect the liver from DILI induced by oxaliplatin^[107]. However, their absorption in the digestive system is limited by the low water solubility of curcuminoids. Interestingly, curcumin's absorption can be significantly enhanced when combined with other compounds such as black pepper or lecithin, with bioavailability increasing up to 20-fold if combined with black pepper^[194]. While increased use of turmeric may have health benefits, it may also increase the risk of liver damage. It is important to note that there

are documented cases linking turmeric to liver damage that need to be taken into account. For example, a 66-year-old African-American woman began taking half a teaspoon of turmeric powder as a dietary supplement from a local herbal shop six months before her medical consultation. She presented with a mixed pattern of hepatocellular and cholestatic liver injury and was also taking long-term medications including metoprolol, amlodipine, hydralazine and lisinopril^[195]. Another case involved a 57-year-old woman with no significant medical history who sought medical attention because of a two-week history of nausea, abdominal distension and jaundice. She denied drinking alcohol or taking paracetamol. She had taken over-the-counter turmeric and black pepper supplements 2,000 mg/day for three months for back pain, and liver biopsy revealed acute hepatitis. In addition, a 53-year-old woman with no reported medical history had abnormal liver function tests during a routine laboratory examination. The woman had been using apple cider vinegar for more than five years and had recently started taking turmeric tablets twice daily, causing abdominal pain and nausea^[196]. Before turmeric is used clinically, a full assessment of its hepatotoxic potential should be carried out.

5.4 Aloe vera-induced liver injury

Aloe vera, known for its calming properties, has demonstrated the ability to improve hepatic histopathology by reducing oxidative stress, attenuating liver damage, and replenishing hepatic GSH to alleviate APAP induced hepatitis^[197]. As a food product, *Aloe vera* is also widely consumed for its health benefits and is often added to beverages and desserts for its subtle flavor and gelatinous texture. Regrettably, *Aloe vera* has been reported to pose a risk of liver injury in several cases^[198, 199]. Aloe emodin, a compound found not only in *Aloe*, but also in plants such as *Cassia occidentalis*, *Rheum palmatum*, and *Polygonum multiflorum* has been associated with hepato and nephrotoxicity^[200]. There is also experimental evidence that the hepatotoxicity of aloe emodin is mediated by activation of the NF- κ B inflammatory signaling pathway and the P53 apoptosis signaling pathway in zebrafish^[201].

In conclusion, natural products from medicinal and food homology plants offer a promising therapeutic tool for the treatment of DILI. However, their incorporation into clinical practice and drug development must be accompanied by rigorous studies to confirm their efficacy and ensure their safety.

6 Discussion

DILI gets a lot of focus on being a key problem for drug development and use in the clinic. As the current trend seems to be that DILI patients can be found all over the world, and more and more people are getting DILI every year. More efficacious therapeutic agents thus need to be developed urgently. Though there were an increasing number of natural products that alleviated DILI in animals, the number of natural products developed specifically for DILI was small. So, we must continue to find more natural products in a hurry, and at the same time, we should pay more attention to further research on these natural products that have already been found to have therapeutic effects.

In the treatment of the DILI model, there are many natural products that can achieve good curative and palliative effects, especially polyphenolic substances such as chlorogenic acid, naringenin, quercetin, gallic acid, etc., which are commonly present in a variety of medicinal and food homology plants. And

because they have structural diversity and activity and have antioxidant, anti-inflammatory and cytoprotective effects and can be used to treat various types of liver diseases including DILI^[202]. Due to these, they show promising prospects for use in treating different types of liver disease like DILI^[203]. For its potential to be fully tapped into we must discover the relations between such molecules and phenolic structures with biological function to build more researched substitutes. In this respect, coupled with some advanced drug delivery systems can be better absorbed and more stable in body. Different kinds of natural medicines that are used to treat DILI may have different effects. So, we personalize clinical drug development for everyone according to their own characteristics. Better outcomes could be possible if someone studied the combination with other drugs or approaches to therapy of these natural products. Comprehensive research and development to open new chapters and better ways to treat DILI.

Also, most of the current natural remedies are simply oxidative stress, metabolite induced-inflammation and ER stress inhibitors from the early stage of drug metabolism. But these agents do not actually attack the toxic metabolites at the root of the problem, so their therapeutic effect is not at its root. Although so, there it is therapeutically recognized and valued. They might be good partners for combination therapies with other DILI treatments as supporting roles. And we have to think whether it is possible in further study that we can know more about how natural product can interact with the enzymes involved in phase 1 and phase 2 of drug metabolism such as CYP enzymes, UGTs, SULTs, GSTs and so on. And try to figure out a way by which we can control those enzymes such that the toxic metabolites get converted to nontoxic products. Or else, by increasing the activity of CYP, we can make sure that there is metabolism of the extra drugs and that they do not build up to harmful levels. Both strategies may be able to solve the problem of DILI. At the same time, we also have to understand that some natural products also show hepatotoxicity when it messes up with metabolic enzymes too much. Therefore, it is necessary to keep a correct understanding that the natural products may be available for detoxification as well as it is also a product of poisoning. We should pay attention to the various effects of natural products, so as to achieve the effect of maximizing the benefit of protecting the liver of natural products and reducing the harm caused by it.

Additionally, while natural products offer a wealth of potential for the treatment of DILI, their use must be carefully calibrated to avoid negative impacts on liver function. Along the way of improvement with DILI therapy, we should form strategies that use its therapy features of natural product treatment. Overall, the potential benefits of the medicine and food homology natural products for the treatment of DILI provide good options for drug discovery.

7 Conclusion

The natural product may have good potential on the treatment of DILI and some compounds which come from the medicines and food homologous plants especially have very good potential. They are exerted in terms of various mechanisms including the reduction of oxidative stress and inflammation, modulation of gut microbiota, reduction in stress of ER and mitochondria, and promotion of autophagy. However, rigorous studies are needed to confirm their efficacy and ensure their safety before they can be incorporated into clinical practice and drug development. In conclusion, the medicinal and edible plants with their natural products also show the possibility of them being used for the

treatment of DILI, and open the door for the future development of drugs.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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