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FORUM REVIEW ARTICLE

New Insights into Herb-Induced Liver Injury

Zhi-Tao Ma,[1] Zhuo Shi,[2] Xiao-He Xiao,[2] and Jia-Bo Wang[1]

Abstract

Significance: Herbs are widely used worldwide. However, inappropriate use of some of the herbs can lead to herb-induced liver injury (HILI). Intriguingly, HILI incidents are on the rise, and our understanding of the underlying etiologies is in progress, and hence, an update on the current status of incidents as well as our understanding on the etiologies of HILI is appropriate.
Recent Advances: HILI reports due to the use of some herbs that are traditionally considered to be safe are also on the rise. Furthermore, HILI due to the use of certain herbs in combination with other herbs (herb–herb interaction [HHI]) or non-herb components (herb–drug interaction [HDI]) has also been reported, suggesting a potentially important new type of inappropriate use of herbs.
Critical Issues: Updated overviews focus on the epidemiology, etiology, phenotypes, and risk factors of HILI, as well as HDI and HHI, and analysis on several types of newly reported ''toxic'' effects of herbs based on types of hepatotoxicity and the HILI mechanisms.
Future Directions: HILI will continue to be a significant public health challenge in the near future. In the light of the lack of broadly available guidelines and regulations for proper and safe uses of herbs worldwide, raising the public awareness of HILI will remain one of the most effective measures. In particular, it should include a better understanding of the contributing factors; a more detail subclassification and description of HILI, better characterization of the components/substances that could induce HILI; and development of HILI diagnosis based on the Roussel Uclaf Causality Assessment Method (RUCAM). *Antioxid. Redox Signal.* 38, 1138–1149.

Keywords: herb-induced liver injury, hepatotoxicity subtypes, hepatotoxicity-related substance, oxidative stress, Roussel Uclaf Causality Assessment Method

Introduction

Various collections of herbs have been widely used for various perceived effects worldwide. It is generally assumed that historically, the herbs have been largely chosen from the ''non-toxic'' types of materials, a practice that is based largely on the poorly defined human experience. Yet, it has become certain that some of these herbs, while may be safe to use under the proper circumstances, can certainly cause adverse effect to the humans under difference contexts. Furthermore, much of such exercises predate the emergence of modern biomedical sciences and accordingly did not have a solid scientific basis. In particular, with the exception of the situation in modern China, where a specific preparation and usage guideline exists for a selected list of Traditional Chinese Medicine (TCM) herbs, the use of the various types of herbs in most areas of the world is largely executed in the absence of any specific regulations and appropriate safety guidance. As a result, to date, the safe and proper use of herbs cannot be ensured for the most parts of the world. Instead, inappropriate use or misuse is inevitable.

The liver is the main organ responsible for the processing and detoxification of the various components/substances of the various types of herbs once they are ingested, primarily orally, by humans. Accordingly, the liver is also one of the major targets for the adverse effects of many of the herbs with such adverse effects. Such effects are known as herb-induced liver injury (HILI), a specific subtype of liver injury.

[1]Department of Pharmaceutics of Chinese Materia Medica, School of Traditional Chinese Medicine, Capital Medical University, Beijing, China.
[2]China Military Institute of Chinese Medicine, Fifth Medical Center of PLA General Hospital, Beijing, China.

Furthermore, our knowledge on the types of liver injuries induced by these ''non-toxic'' herbs and the related hepatotoxic mechanisms remain limited and incomplete (Gao et al, 2020; Li et al, 2019). In some areas, even fundamental consensual views have yet to be reached (Fugh-Berman, 2000; Jing and Teschke, 2018; Teschke et al, 2020).

In this review, we focus on HILI-causing herbs and conduct a causality assessment using the Roussel Uclaf Causality Assessment Method (RUCAM), with an intention to objectively dissect HILI based on the types of hepatotoxicity and potential mechanisms. Specifically, we briefly analyze the epidemiology, etiology, and risk factors of HILI. Then, we classify hepatotoxic herbs into three subclasses based on the types of toxicities, namely direct toxicity, indirect toxicity, and idiosyncratic toxicity. Moreover, we provide an update on the matter of the ''toxicity-related substance'' (TRS) as well as the related hepatotoxic mechanisms.

Epidemiology of HILI

According to a recent study on the overall cases of drug-induced liver injury (DILI) and HILI carried out in Asian countries, HILI accounts for about 25% of the total incidents of liver injury (Byeon et al, 2019; Shen et al, 2019). Intriguingly, HILI accounts for only 4.5%, whereas those due to chemicals and biological products account for rest (95.5%) of adverse drug reactions in the liver that were reported in China between 2012 and 2016 (Wang et al, 2022b). However, it is noticeable that newly reported toxic herbs and related cases account for 80.6% of all HILI in China (Wang et al, 2022b). *Reynoutria multiflora* (Thunb.) Moldenke (formerly named as *Polygonum multiflorum* [PM] Thunb.), green tea extracts (GTE), *Gynura segetum* (Lour.) Merr., *Tripterygium wilfordii* Hook. F., *Aristolochia debilis* Siebold & Zucc., *Epimedium brevicornu* Maxim. (EBM), *Psoralea corylifolia* Linn. (PCL), and so on, are the most common herbs causing HILI. In recent years, some herbs have been used for weight loss, psychiatric disorders, and pain control (25.6%, 9.2%, and 8.1%, respectively) (Navarro et al, 2014). Jaundice (46.3%), abdominal pain (22.4%), and nausea (17.2%) are the main clinical presentations of HILI (Ballotin et al, 2021). In addition, liver biopsy results indicate that most HILI are hepatocellular, followed by hepatic sinusoidal obstruction syndrome (HSOS), and cholestatic cases (Ballotin et al, 2021). It has been reported that about 82.8% of HILI patients could have a complete recovery. However, 6.6% required liver transplantation, whereas 1.5% of patients developed chronic liver disease. Overall, the mortality rate was 10.4% (Ballotin et al, 2021; Navarro et al, 2014). Meanwhile, another single-center clinical study showed that liver injury induced by herbs and dietary supplements accounted for 52.5% of the overall chronic DILI and HILI cohort (Wang et al, 2022a).

Etiology, Types, and Phenotypes of HILI

In 2019, a new classification of DILI into three subtypes, namely direct, indirect, and idiosyncratic types, was proposed (Hoofnagle and Bjornsson, 2019). Although this classification has not been fully accepted worldwide, it has provided a useful guide for analyzing the underlying mechanisms of both DILI and HILI. The direct hepatotoxicity of HILI is induced by the intrinsic toxic components of herbs (Nunes et al, 2022), often as the result of the inappropriate use including overdose (Hoofnagle and Bjornsson, 2019; Kuna et al, 2018). Accordingly, such adverse effects are often predictable, dose dependent with a short latency period, and easy to reproduce in experiment animals. Injuries that are caused by *T. wilfordii* and *G. segetum* (Table 1) are some of the typical examples for this type of HILI. Acute hepatic necrosis is the most common form of clinically apparent

Table 1. Characteristics of Three Types of Herb-Induced Liver Injury and the Related Herbs

Classification	*Direct hepatotoxicity*	*Idiosyncratic hepatotoxicity*	*Indirect hepatotoxicity*
Dose-related	Yes	No	Probably no or partially
Predictable	Yes	Difficultly	Partially
Reproducible in animal models	Yes	Difficultly	Partially
Latency	Typically rapid	Variable (days to years)	Delayed (months)
Cause	Take high doses of agent	Idiosyncratic metabolic or immunologic reaction, usually related to genetic backgrounds	Indirect action of agent on the liver or immune system
Correlation with individual factors or underlying diseases	Least but possibly different among individuals	Relevant with individual genetic backgrounds	Relevant with individual factors or underlying diseases
Traditional recognition	Traditional toxic herbal medicines	Traditional ''non-toxic'' herbal medicines	Traditional ''non-toxic'' herbal medicines
Implicated agents	*Tripterygium wilfordii* (Hasnat et al, 2019; Wang et al, 2018; Wang et al, 2014; Yuan et al, 2019) *Gynura segetum* (Fu et al, 2004; Teschke et al, 2021)	*Reynoutria multiflora* (Thunb.) Moldenke. (synonyms: *Polygonum multiflorum*) (Li et al, 2019; Yang et al, 2020) Green tea extracts (Hoofnagle et al, 2021)	*Epimedium brevicornu* (Gao et al, 2021; Gao et al, 2020; Wang et al, 2020) *Psoralea corylifolia* (Gao et al, 2020)

direct hepatotoxicity (Hoofnagle and Bjornsson, 2019). Serum enzyme elevations without jaundice constitute the most common pattern of direct hepatotoxicity, with elevations of alanine aminotransferase or alkaline phosphatase levels without hyperbilirubinemia (Hoofnagle and Bjornsson, 2019). HSOS can be induced by herbs such as *G. segetum*, which contains pyrrolizidine alkaloids (PAs) (Nunes et al, 2022; Teschke and Eickhoff, 2015). HSOS is caused by acute injury and loss of intrasinusoidal endothelial cells, resulting in obstruction of sinusoidal blood flow and liver injury. The major diagnostic features of HSOS are abdominal distention and pain, ascites, malaise, hepatomegaly, increased body weight, and jaundice. Jaundice is the most common symptom in case of 84.8% HSOS by *G. segetum* (Gao et al, 2012; Skalli et al, 2007). Idiosyncratic hepatotoxicity is the cause of most HILI in incidents and is induced by herbs of little or no intrinsic toxicity (Hoofnagle and Bjornsson, 2019; Nunes et al, 2022). The prime examples are HILI induced by PM and GTE (EFSA Panel on Food Additives and Nutrient Sources added to Food et al, 2018; Hassan and Fontana, 2018; Navarro et al, 2017). Traditionally, both PM and GTE were considered nontoxic to humans but have been reported to be hepatoxic in recent years. Key characteristics of the DILI caused by idiosyncratic hepatotoxicity include their unpredictable nature and the difficulty in creating proper animal models (Kuna et al, 2018). In addition, they are also known for their variable latency periods (ranging from days to years). Acute hepatocellular hepatitis is the most common manifestation of idiosyncratic liver injury, including the hepatocellular, the cholestatic, or the mixed types (Hussaini and Farrington, 2007).

The pathogenesis of idiosyncratic liver injury has remained poorly defined to date. More recently, genome-wide association studies of large numbers of idiosyncratic cases have resulted in the identification of the association of this type of HILI with several genetic variants, most within the major histocompatibility complex (MHC) region and linked to HLA class I and II alleles. For example, the *HLA-B*35:01* allele has been reported to be associated with susceptibility to PM- and GTE-induced liver injury (Hoofnagle et al, 2021; Li et al, 2019), whereas the rs2476601 variant in the PTPN22 gene was identified as a risk factor for liver injury that is caused by multiple drugs (Cirulli et al, 2019). In addition, this particular variant has also been reported to be a risk factor for autoimmune diseases, which is believed to be involved in the pathogenesis of idiosyncratic DILI.

Indirect hepatotoxicity is a newly proposed type for which the pharmacological action and/or the derivatives of a drug or herb, rather than the parent drug or herb, are the inducer of the toxicity (Hoofnagle and Bjornsson, 2019). To date, however, a unified view on this new proposition has yet to be established. Nonetheless, it has become increasingly clear that an abnormal immune response is often involved in such an injury. This type of HILI is exemplified by those that are caused by *E. brevicornu* and *P. corylifolia*, two herbs that well known for their potency to tonify the immune response system (Alam et al, 2018; Cheung et al, 2009; Chopra et al, 2013; Gao et al, 2021; Wang et al, 2020). Recent studies have shown that although neither of these induce liver injury in normal animals, both could activate NLRP3 inflammasome and induce extensive secretion of proinflammatory cytokines in lipopolysaccharide (LPS) in mild-stimulated animals (Gao et al, 2021; Wang et al, 2020).

Toxicity-Causing Substances

The identification of the toxicity-causing substance or substances in individual HILI-causing herbs is of great value both in understanding the underlying mechanism of toxicity as well as in developing effective mitigation measures. In the past, the screening based on either an *in vivo* or an *in vitro* system has proven effective for identifying the toxicity-inducing component or components for some, but not all HILI-causing herbs. However, such a strategy might be suitable in identifying the toxicity-inducing component or components for the types of herbs with direct toxicity or idiosyncratic toxicity, but not for those with the indirect type of toxicity. Furthermore, with respect to the toxicity that is caused by herbs of indirect toxicity, the specific herb component or components are necessary, but not sufficient for causing the toxicity. Additionally, other factors, including the specific physiological condition of the host, are also required for the manifestation of HILI for a given HILI-causing herb (Hoofnagle and Bjornsson, 2019). Thus, it appears that it is necessary to further define the term of HILI-causing compound as any compounds that, when administered to humans or animals, could cause HILI incidents at a reproducible manner. That is, some, but not all compounds by themselves, are necessary but are not sufficient to cause the adverse effects that ultimately lead to HILI in some but not all individuals. In this regard, we have proposed to use a new term, the toxicity-related substance or TRS, to represent all the compounds that could cause HILI in humans.

With this new terminology, TRS of direct hepatotoxic herbs would be those components that exhibit toxic effects in the liver. For example, diterpenoid and triterpene compounds are the main TRS of *T. wilfordii*. Triptolide (TPL) is the most well-studied TRS of diterpenoids and can induce hepatocellular death in a dose-dependent and course-related manner clinically and in animal models (Wang et al, 2018). Furthermore, PAs are TRS of *G. segetum* and are known to be hepatotoxic in humans and hepatocarcinogenic in mice (Nunes et al, 2022). TRS associated with indirect or idiosyncratic hepatotoxicity would usually be non-hepatotoxic. It is, however, difficult to evaluate their adverse hepatic effects by conventional approaches. Indirect hepatotoxicity would be highly associated with host conditions, such as abnormal immune activation (Hoofnagle and Bjornsson, 2019). For example, icariside I and icariside II, which are TRS of *E. brevicornu*, can significantly increase NLRP3 inflammasome activity under pre-existing immune stress condition in mice, promoting liver injury (Gao et al, 2021; Wang et al, 2020). Furthermore, host genetic background is a significant determinant on the idiosyncratic hepatotoxicity that is caused by some herbs. For example, in rodents, *cis*-2,3,5,4′-tetrahydroxy stilbene-2-*O*-β-glucoside (*cis*-SG) of PM did not cause any obvious acute hepatotoxicity but could lead to liver injury in LPS- or TNF-α-treated animals (Li et al, 2017; Zhang et al, 2022).

Risk Factors Associated with HILI

The potential risk factors involved in the pathogenesis of HILI can be divided into host-related, herb-related, and environment-related factors (Fig. 1) (Tujios and Fontana, 2011). Within herb-related risk factors, the quality of herbal products and inappropriate dosing constitute the major

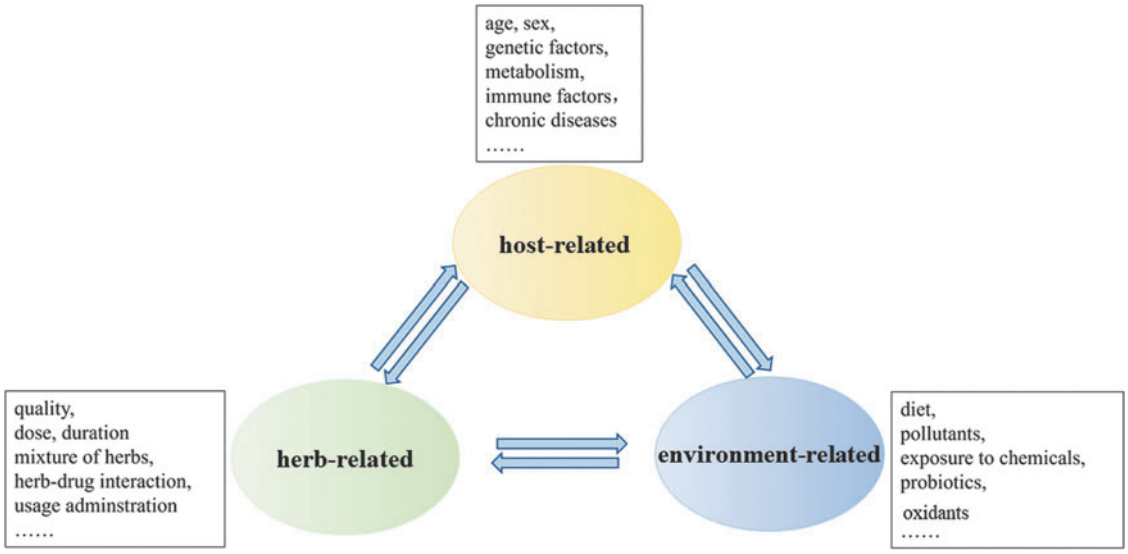

FIG. 1. Potential risk factors associated with HILI. The herb-, host-, and environment-related risk factors involved in the pathogenesis of HILI. HILI, herb-induced liver injury.

contributing factors. In particular, a range of potential variables, including the production of the raw materials, harvesting, manufacturing methods, and the quality control of the final products, can contribute to the quality issue (Nunes et al, 2022; Zhang et al, 2022).

Drug–drug interactions (DDI) may occur when two or more drugs are administered to a patient and one drug interferes with the pharmacological activity of another. DDI may result in decreased effectiveness and/or increased toxicity, even lead to the development of adverse drug reactions, morbidity, hospitalizations, and death. Similarly, while the administration of a given herb in a specific by itself is non-toxic, it could still cause a toxic effect when it is coadministered with another non-toxic drug *via* the so-called herb–drug interactions or another non-toxic herb *via* herb–herb interactions (HHI). Importantly, to date, our understanding on the bases for the toxicity of such interactions remains very limited, and it is not yet feasible to predict which kinds of such combinations could lead to such unique kind of toxic effects (Hoofnagle and Bjornsson, 2019; Nunes et al, 2022). Nonetheless, recent studies have shed lights on the bases of some of such cases. For example, it has been shown that in some cases, an effect on the activity of one or more metabolizing enzymes or efflux transporters is involved (Fugh-Berman, 2000; Skalli et al, 2007). In particular, certain isoforms of members of the cytochrome P450 (CYP) family of metabolic enzymes are particularly vulnerable to modulation by some active constituents of herbs (Wanwimolruk and Prachayasittikul, 2014; Zhou et al, 2003). For example, St. John's wort is a potent inducer of CYP3A4, the most abundant CYP in the liver, which accounts for 30% of the total CYP protein content (Al-Dosari and Parvez, 2018; Moore et al, 2000). Flavonoids, such as quercetin, resveratrol, and naringenin, have been shown to alter the activity of CYP enzymes (Wanwimolruk and Prachayasittikul, 2014). In some cases, even more complex scenarios might be involved. For example, the combination of these *E. brevicornu* and *P. corylifolia*, both potent activators for the NLRP3 signaling pathway, appears to cause a unique synergistic effect on immune modulation and consequently a unique type of HHI (Gao et al, 2020).

Host factors can affect the manifestation of HILI of certain HILI-causing herbs in a manner that can be influenced by a number of variables of the hosts, including sex, genetic factors, immune responses, and certain chronic diseases (Nunes et al, 2022). According to the RUCAM, HILI is more frequent in middle-aged patients aged 55 years or older (Lin et al, 2019; Nunes et al, 2022). Furthermore, some genetic factors have also been reported. For example, *HLA-B*35:01* allele was found to be an important genetic biomarker in the PM-induced liver injury in susceptible population (Nunes et al, 2022; Yang et al, 2020). It has also been recently reported that *HLA-B*35:01* allele was associated with GTE-induced liver injury (Hoofnagle et al, 2021). In addition, certain acquired factors, including the statuses of metabolism and immune homeostasis, have been reported to play roles in HILI susceptibility. For instance, PM-induced liver injury was found to be closely correlated with the perturbation of endogenous metabolites (*e.g.*, sphingomyelin, ceramide, crotonoyl-CoA) (Zhang et al, 2020b). PM-induced liver injury was also clinically found to be closely correlated with several cytokines and chemokines (*e.g.*, TNF-α, CCL2, VEGF) (Tu et al, 2021). A recent pathway enrichment analysis for susceptibility-related endogenous metabolites suggests a close correlation between PM-induced liver injury and TNF-α signaling pathway (Zhang et al, 2022, Zhang et al, 2020b). Hence, either congenital (*HLA-B*35:01* allele) or acquired (metabolism and immune homeostasis) host-related risk factors can affect PM-induced liver injury (Fig. 2). For GTE, both genetic and non-genetic factors have been reported to affect its potency in causing liver injury. For example, GTE-induced liver injury was found to have an increased potential of occurrence in case of dietary restriction of mice characterized by an overactivation of linoleic acid and arachidonic acid oxidation pathways, through metabolomics approach (Shi et al, 2021). This metabolic

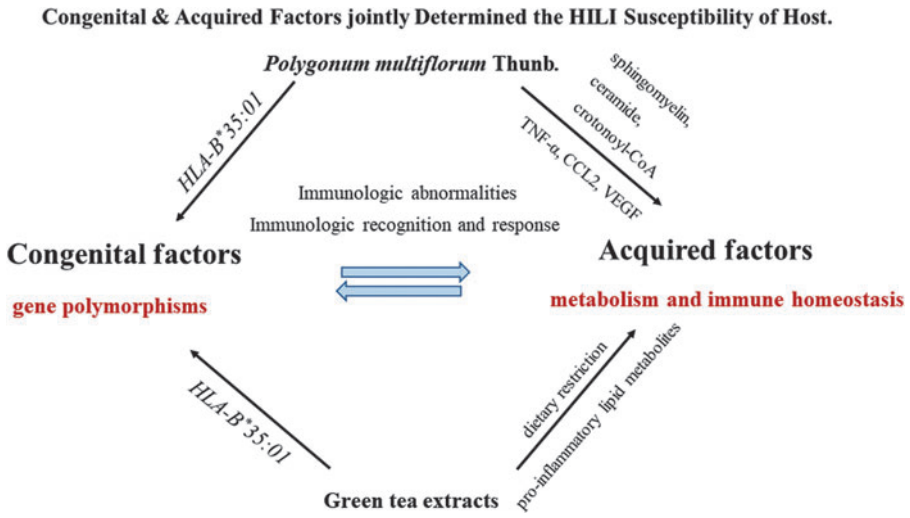

FIG. 2. Congenital and acquired factors jointly used to determine the HILI susceptibility of the host. Recent research indicates that host-related risk factors of HILI involve both congenital (gene polymorphisms) and acquired (metabolism and immune hemostasis) factors.

reprogramming mechanism caused accumulation of proinflammatory lipid metabolites to modulate the potency of GTE in causing liver injury.

In some cases, more complex scenarios of interactions among more risk factors have been reported. For example, a ''firewood-oil-spark hypothesis'' has been proposed for PM-induced liver injury (Zhai et al, 2021). According to this hypothesis, the immune-promoting components in PM or other TRS can enhance immune response but are usually not sufficient to cause overt liver injury. However, such TRS could cause liver injury in certain hosts who are already in an abnormally activated state (*e.g.*, with a mild immune stress) (Li et al, 2017; Zhang et al, 2020a). That is, the pre-existing mild immune stress and the TRS serve as the ''firewood'' and the fire spark, respectively. Yet, this combination alone is not sufficient to trigger a fire. Instead, additional immune component(s) in the PM are required for a fire to be ignited.

Finally, a number of other factors, such as diet, exposure to chemicals, or pollutants, could also affect the onset of HILI. Significantly, such factors can be variable among individual hosts, and their assessments remain challenging to date (Tujios and Fontana, 2011). Specifically, herbal products can be contaminated with toxic elements, such as pesticides, mycotoxins, and heavy metals such as lead, mercury, cadmium, and arsenic (Nunes et al, 2022; Teschke et al, 2000; Vlietinck et al, 2009), whereas many dietary components are rich for substances that can modulate the host responses to some TRSs. For example, epigallocatechin-3-gallate (EGCG), a compound that is rich in many dietary materials, is not by itself a HILI-causing agent, but it can increase the risks of HILI for some herbs (EFSA Panel on Food Additives and Nutrient Sources added to Food et al, 2018; Shi et al, 2021).

Molecular Mechanism of Specific Herbs

HILI-causing herbs can cause liver injury *via* a number of different mechanisms, including oxidative stress, cell death, inflammatory reaction, toxic intermediate metabolite, and disorders of bile acid metabolism. Among them, oxidative stress has been associated with the HILI induced by many herbs (Table 2), and its roles in the etiology of HILI for several herbs are summarized below.

Tripterygium wilfordii *Hook. F.*

T. wilfordii Hook. F. is a herb with potent immunosuppression and anti-inflammatory effects. It has been widely used for centuries in China and some other Asian regions. Its major active components are *T. wilfordii* glycosides (TWG), especially TPL. However, TPL is a well-known poison to possess toxic effects and a potent HILI-causing agent (Fig. 3). Reactive oxygen species (ROS) have been found to be major contributors to the pathogenesis of TPL-induced liver injury (Hasnat et al, 2020; Wang et al, 2018). TPL exposure can enhance the generation of anion superoxide and inhibits the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, which can cause oxidative stress in the liver (Tu et al, 2021).

TPL could cause mitochondrial damage (Fu et al, 2013; Yao et al, 2008), in keeping with the fact that mitochondria are also major target of ROS. Severe ROS-related mitochondrial damage following TPL exposure can further result in cell apoptosis by activating caspases and other components of the apoptotic signaling pathways (Shu et al, 2009; Zhou et al, 2014). In addition, TPL exposure could also cause mitophagy (Hasnat et al, 2019).

TPL is also well known for its immunologic modulation potential, which also plays an important role in TPL-induced hepatotoxicity. For example, in rodents, TPL has been shown to cause liver injury with a time-dependent increase of serum transaminases, NLRP3 inflammasome activation, and neutrophil infiltration (Yuan et al, 2019) and to cause Th17/Treg imbalance in the liver by enhancing the expansion of Th17 cells while suppressing the production of Tregs (Wang et al, 2014).

Gynura segetum *(Lour.) Merr.*

G. segetum (Lour.) Merr. contains a variety of PAs, which are good examples of an intrinsic form of liver injury that is clearly dose dependent, predictable, and preventable (Teschke and Eickhoff, 2015; Teschke et al, 2021). PAs induce HSOS *via* biotransformations through the microsomal CYP isoforms to toxic intermediates (Teschke et al, 2021). The products of these PA transformations can induce acute toxicity, chronic toxicity, and genotoxicity by reacting with cellular proteins and DNA (Fu et al, 2004). For instance, the accumulation of pyrrolic ester metabolite following PA

TABLE 2. HERBS AND THE RELATED TOXICITY-RELATED SUBSTANCES AND HEPATOTOXIC MECHANISMS

Herb	*Toxicity-related substance*	*Mechanism of hepatotoxicity*
Tripterygium wilfordii Hook. F.	*T. wilfordii* glycosides (especially triptolide) (Wang et al, 2018)	Oxidative stress (Hasnat et al, 2020; Wang et al, 2018) Mitochondrial disruption (Fu et al, 2013; Yao et al, 2008) Apoptosis (Shu et al, 2009; Zhou et al, 2014) Mitophagy (Hasnat et al, 2019) Immunologic activation (Wang et al, 2014; Yuan et al, 2019)
Gynura segetum (Lour.) Merr.	Pyrrolizidine alkaloids (Nunes et al, 2022) Pyrrolic ester metabolites (Fu et al, 2004; Teschke et al, 2021)	Metabolic reactivation (Fu et al, 2004; Teschke et al, 2021) Reactive metabolite–protein adducts (Fu et al, 2004; Teschke et al, 2021) Oxidative stress (Chen et al, 2009; Wang et al, 2021) Mitochondria disruption (Chen et al, 2009; Wang et al, 2021) Cell death (Chen et al, 2009; Wang et al, 2021)
Reynoutria multiflora (Thunb.) Moldenke. (synonyms: *Polygonum multiflorum* Thunb.)	*Cis*-2,3,5,4′-tetrahydroxy stilbene-2-O-*β*-glucoside (Li et al, 2017) Emodin-8-*O*-β-glucodise (Zhang et al, 2020a)	*HLA-B*35:01* (Li et al, 2019; Yang et al, 2020) Immune activation (Tu et al, 2021; Zhang et al, 2022) GSH depletion (Dong et al, 2017; Jiang et al, 2017; Wang et al, 2019; Zhai et al, 2021)
Green tea extracts	Epigallocatechin-3-gallate (Shi et al, 2021)	*HLA-B*35:01* (Hoofnagle et al, 2021) Hepatocellular cell death (Shi et al, 2021) Linoleic acid and arachidonic acid (Koonyosying et al, 2018; Shi et al, 2021) Disorders of bile acid metabolism (Koonyosying et al, 2018; Shi et al, 2021)
Epimedium brevicornu Maxim.	Icariside I (Gao et al, 2021) Icariside II (Wang et al, 2020)	Inflammation activation (Gao et al, 2021; Wang et al, 2020) Oxidative stress (Wang et al, 2020) Pyroptosis (Wang et al, 2020)
Psoralea corylifolia Linn.	Bavachin (Wang et al, 2015b) Corylifol A (Wang et al, 2015b) Psoralen (Liu and Flynn, 2015) Isopsoralen (Liu and Flynn, 2015)	Inflammation activation (Gao et al, 2020) Inhibition of UGT1A1 (Wang et al, 2015b) Inhibition of CYP3A4 (Liu and Flynn, 2015)
Aristolochia debilis Siebold & Zucc.	Aristolochic acids (Levová et al, 2011)	Reactive metabolite-mediated DNA mutation (Levová et al, 2011) Oxidative stress (Xu et al, 2021; Yu et al, 2011)

CYP, cytochrome P450; GSH, glutathione; UGT1A1, UDP-glucuronosyltransferase 1A1.

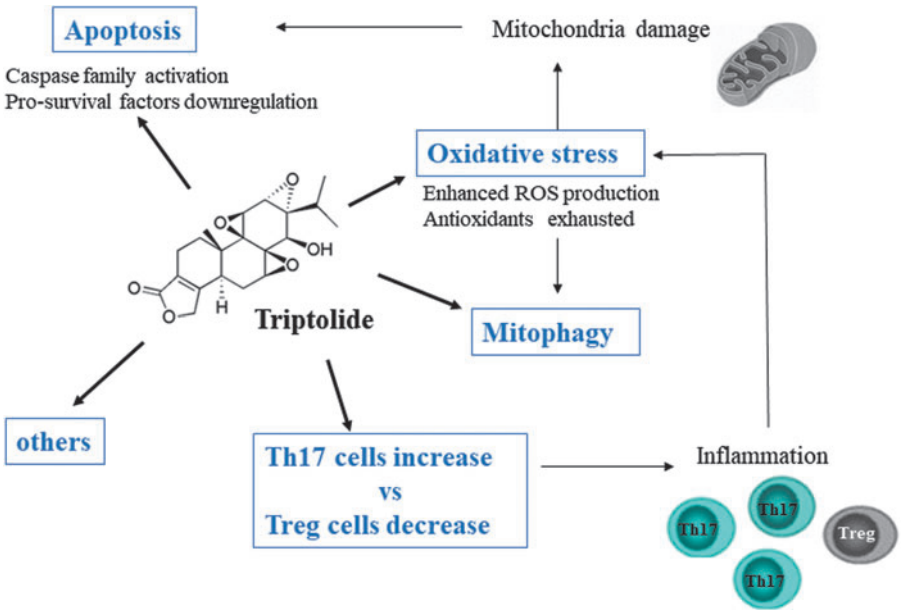

FIG. 3. The molecular mechanisms of TPL-induced liver injury. The main mechanisms include oxidative stress, apoptosis, mitophagy, and Th17/Treg imbalance. These events can influence each other and finally lead to liver injury. TPL, triptolide.

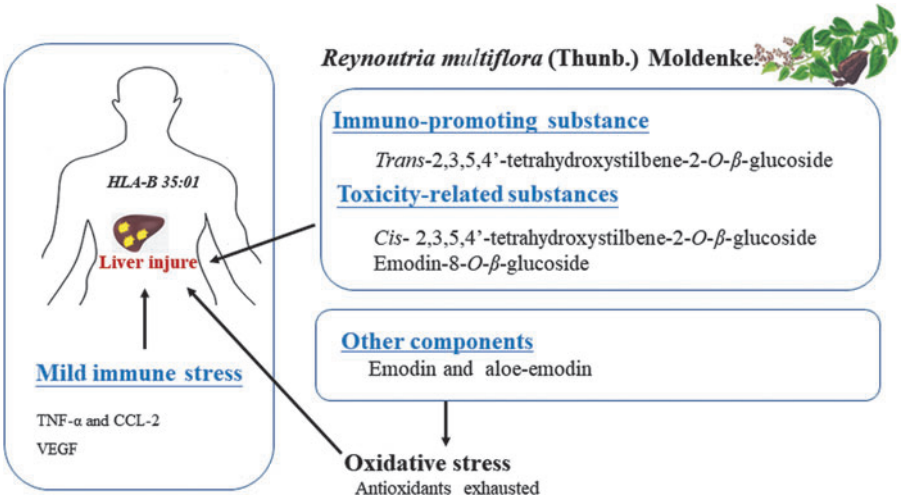

FIG. 4. The molecular mechanisms of PM-induced idiosyncratic liver injury. When the susceptible population is under mild immune stress (such as TNF-α, CCl-2, VEGF upregulation), the immune-promoting components of PM—trans-2,3,5,4′-tetrahydroxystilbene-2-O-β-glucoside, may enhance the body's immune activation, which increases the susceptibility of the liver to the components of PM—cis-2,3,5,4′-tetrahydroxystilbene-2-O-β-glucoside and emodin-8-O-glucoside, and results in liver injury. Furthermore, the components of PM—emodin and aloe-emodin, can exhaust antioxidants, induce oxidative stress, and contribute to PM-induced liver injury. PM, *Polygonum multiflorum*.

transformation can result in the exhaustion of sulfhydryl and glutathione (GSH), leading to the excessive accumulation of ROS, the significant change in the mitochondrial membrane potential, the release of cytochrome c, and cell death (Chen et al, 2009; Wang et al, 2021).

Reynoutria multiflora *(Thunb.) Moldenke. (or* Polygonum multiflorum *Thunb.)*

R. multiflora (Thunb.) Moldenke (PM) is a herb widely used for hair coloration, anti-aging, and neuroprotection. However, there are increasing HILI reports related to PM in recent years. Intriguingly, PM-induced liver injury appears to occur in only a very small population and did so in a manner in which the incident did exhibit a dose-dependent characteristic. Significantly, studies have indicated that *HLA-B*35:01* was a genetic risk factor for PM-induced liver injury (Li et al, 2017; Yang et al, 2020).

Abnormal basal immune response also appears to be an important susceptibility factor for PM-induced HILI (Fig. 4). In particular, it has been reported that 10 cytokines with significant differences were found between the susceptible and tolerant individuals. A PM-HILI susceptibility prediction model based on the combination of TNF-α and CCL-2 or VEGF was built and showed high sensitivity (66.7%) and specificity (83.3%) in predicting PM-DILI-susceptible individuals, respectively (Tu et al, 2021). Susceptible patients who showed high expression of TNF-α had the strongest correlation with ALT level. The correlation coefficient was >0.6, and the area under the receiver operating characteristic curve was >0.8. Moreover, immune perturbation by TNF-α appears to affect the susceptibility to PM-induced liver injury in animal models (Zhang et al, 2022).

GSH depletion has also been reported in PM-related HILI. GSH plays a role in maintaining the normal redox balance and protects the liver from oxidative stress. Reduction of GSH may lead to decreased ability to scavenge oxygen free radicals, resulting in oxidative stress. The components of PM, emodin and aloe-emodin, have been reported to have a role in reducing GSH and contribute to PM-related hepatotoxicity (Dong et al, 2017; Jiang et al, 2017; Wang et al, 2019; Zhai et al, 2021).

Green tea extracts

GTE are known for being rich in various catechins. Such preparations have been widely used for various purposes, including weight loss (Chen et al, 2016; Oketch-Rabah et al, 2020). Yet, EGCG, a catechin in GTE, is highly associated with liver injury (Navarro et al, 2017; Shi et al, 2021). It has been reported that EGCG and GTE are inducers for idiosyncratic toxicity (Hoofnagle et al, 2021).

Dietary status is another crucial factor in EGCG-related liver injury. In particular, it has been reported that a specific dietary restriction regimen could enhance the potency of EGCG-induced HILI in mice (Shi et al, 2021). Furthermore, it has been shown that linoleic acid and arachidonic acid oxidation pathway is involved in this unique effect of dietary restriction (Koonyosying et al, 2018; Shi et al, 2021).

Epimedium brevicornu *Maxim.*

EBM has been reported to induce liver injury *via* the indirect toxicity mechanism (Fig. 5). In particular, it has been reported that *E. brevicornu* could enhance LPS-stimulated IL-1β production and release by activating NLRP3 inflammasomes (Gao et al, 2021) or by enhancing the ATP- and nigericin-mediated activation of NLRP3 inflammasomes (Wang et al, 2020). In addition, mitochondrial ROS have also been reported to contribute to the activation of NLRP3 inflammasomes following PM treatment exposure. The activated NLRP3 inflammasomes mediated IL-1β secretion and subsequently the production of TNF-α, contributing to PM-induced liver injury (Wang et al, 2020).

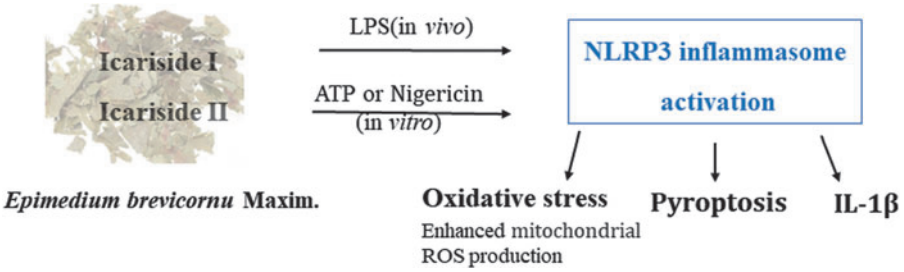

FIG. 5. The molecular mechanisms of *Epimedium brevicornu*-induced indirect liver injury. When maximum nontoxic LPS (*in vivo*), ATP, or nigericin (*in vitro*) exist concurrently, the components of *E. brevicornu*—icariside I or II, can induce NLRP3 inflammasome activation, causing IL-1β production, oxidative stress, pyroptosis, and finally liver injury.

Psoralea corylifolia *Linn.*

P. corylifolia or *P. corylifolia* Linn. (PCL) is a well-known traditional medicinal plant used for treatment of various ailments for both Ayurveda and Chinese medicines (Alam et al, 2018). Recently, the potential hepatotoxicity of PCL has been reported (Cheung et al, 2009; Chopra et al, 2013). The National Medical Products Administration has issued that Chinese patent medicines, such as Zhuang Gu Guan Jie pills (ZGW) and Xian Ling Gu Bao pills, which contain PCL as the main ingredient, may induce liver injury (Gao et al, 2020). Data from *in vitro* and *in vivo* experiments have also supported the contention that PCL extracts have hepatotoxicity (Takizawa et al, 2002).

Interestingly, combined use of PCL and EBM is a common practice, and such a practice has been shown to be associated with a high HILI incident (Gao et al, 2020). Yet, in rodents, neither EBM or PCL alone, nor in combination lead to liver injury. However, EBM or PCL alone can lead to liver injury in LPS-treated rats. Moreover, EBM combined with PCL can induce a greater degree of liver injury than that caused by EBM or PCL alone in LPS-treated rats. PCL alone or in combination with EBM enhanced LPS-stimulated inflammatory cytokine production, implying that PCL induced immune idiosyncratic hepatotoxicity. In addition, the metabolomics analysis results showed that PCL affected more metabolites in glycerophospholipid and sphingolipid metabolic pathway compared with EBM in the LPS model, suggesting that PCL increased the responsiveness of the liver to LPS or other inflammatory mediators *via* modulation of multiple metabolic pathways (Gao et al, 2020).

PCL and some PCL-derived compounds have been shown to have potent inhibitory effects against human UDP-glucuronosyltransferase 1A1 (UGT1A1) *in vitro* and that this effect was associated with PCL-related toxicity (Wang et al, 2015b). Two PCL-derived compounds, bavachin and corylifol A, have been found to be strong inhibitors of UGT1A1 and CYP3A4 enzymes (Liu and Flynn, 2015).

Aristolochia debilis *Siebold & Zucc.*

Aristolochia and related plants, which contain aristolochic acids and similar compounds, have been implicated in multiple cancer types, such as hepatic carcinoma (Ng et al, 2017). *In vivo*, aristolochic acid I (AAI) is reduced to the amino group by cytoplasmic NADH quinone oxidoreductase 1 (NQO1) and CYP1A1/2 and then dehydrated to produce toxic metabolite N-hydroxyaristolactam I (N-OH-ALI). N-OH-ALI can interact with the C7 of adenine in DNA to generate AAI-DNA adducts, which can ultimately lead to adenine (A) to thymine (T) and increase the risk of oncogenic mutations (Levová et al, 2011). Additionally, AAI metabolism can also cause GSH depletion and hence oxidative stress-mediated DNA damage and mitochondrial damage, adding another potential mechanism for contributing to liver injury (Xu et al, 2021; Yu et al, 2011).

Mitochondrial Dysfunction as a Type of Universal Pathogenesis of HILI

Mitochondria are key organelles involved in energy production as well as numerous metabolic processes. There are growing reports of mitochondrial dysfunction in the pathogenesis of HILI, such as oxidative activities, lipid metabolism, and cell death (Han et al, 2013). Alkaloids and flavonoids are frequent constituents of commonly used herbs and are two major biological components associated with liver damage. The oxidative activities seem to be the main pathways involved in damage (López-Gil et al, 2017). PA (a type of alkaloid) metabolism induces ROS production and accumulation *via* the CYP system, leading to the generation of toxic byproducts and radicals such as alkoxyl radical $RO^{\bullet}$ and peroxyl radical $ROO^{\bullet}$. With proteins and phospholipids that undergo peroxidative processes, these radicals are toxic to membrane structures and the constituents of hepatic microsomes. PA metabolism also changes the mitochondrial membrane potential and releases cytochrome c, which induces cell death.

GTE and EGCG (a type of flavonoid) promote the increase of intracellular oxidative stress, genotoxicity, and DNA damage in cellular models (Elbling et al, 2005; López-Gil et al, 2017). EGCG-generated O_2^- is known to mediate pro-matrix metalloproteinase-7 (pro-MMP-7) production in a human colon cancer cell line (Kim et al, 2005). Oxidative stress can induce mitochondrial damage, affect permeability transition, and subsequently cause cell necrosis. Oxidative stress is also a potent contributor to autophagy initiation. Autophagy is a catabolic process involving delivery of damaged organelles (*e.g.*, mitochondria) and long-lived proteins for lysosomal degradation and recycling to maintain cellular homeostasis. It has been found that TPL increases the expression levels of the autophagy-related proteins Beclin1 and LC3II, promotes autophagosome formation, and activates autophagic flux in human normal liver HL7702 cells. These phenomena suggest that TPL upregulates autophagic activity in HL7702 cells (Wei et al, 2019). Overall, mitochondrial dysfunction is critically involved in HILI pathogenesis.

RUCAM and HILI

The RUCAM scale is the most frequently used DILI and HILI causality assessment method (Rockey et al, 2010). The first version of the RUCAM was put forward in 1993 and mainly used in DILI causality analysis by identifying and quantitatively scoring DILI-specific key characteristics (Danan and Benichou, 1993). In 2016, the updated version of the RUCAM scale was published, combining practical experience with emerging new data on DILI and HILI characteristics and few ambiguous questions in domains such as alcohol use and exclusions of nondrug causes (Danan and Teschke, 2015). The updated version of the RUCAM scale has a great progress in HILI analysis and is widely used in HILI causality analysis. Complete identification of all medications is a fundamental element in determining HILI causality. The labeled reactions of the agent and previous publication of hepatotoxicity are important RUCAM components. However, because of the increasing polypharmacy contributed by multiple providers, little clinical records of herbal composition and doses, it is difficult to obtain a high-level accuracy when solely relying on the patients recall. The quality of existing information of herbal medicines is insufficient to fulfill the RUCAM component, which in turn leads to causality underestimation. In addition, 30%–40% of patients do not disclose the use of herbal medicines to their physicians (Verma and Thuluvath, 2007), which can lead to incomplete or incorrect diagnosis (Rockey et al, 2010). Hence, there is a pressing need to gather additional evidence for HILI causality analysis. Disease and pharmacognostic identification may be helpful in discovering fraudulent species or non-declared constituents. *In vivo* phytochemistry identification can provide further evidentiary confidence. HILI diagnosis based on the integrated evidence (iEC) method was developed using the RUCAM as the base (Wang et al, 2015a). The iEC method comprises susceptible population screening, herbal compatibility, and clinical medicine usage analysis, for scientific evaluation of HILI risk, and it has been used to identify PM-related HILI (Wang et al, 2015a).

Conclusions

The use of herbs for various purposes is a popular practice worldwide and will likely to continue or even increase in the future. It has been proven that safe and effective use of herbs is feasible provided that the appropriate guiding information and regulatory measures are in place, for example, the use of TCM under the current TCM system in China. However, by and large, the use of herbs worldwide is largely an exercise that is not based on the appropriate guiding information or regulatory measures. Even in China, inappropriate uses or misuses of herbs appear to be quite common. Yet, it has become clear that some herbs can exert serious adverse effects in humans, often in the form of liver injury. This unique situation is likely to continue into the near future. Consequently, HILI will continue to represent a unique public health challenge in the future. Accordingly, the advance in our knowledge about this unique type of challenge and the educating/informing the public about it will remain one of the effective strategies for dealing with this challenge. With the development of new technologies and big data analysis capacity, new advances are expected in the foreseeable future. The timely update and distribution of such information among the scientific community and to the public will continue to be an important task.

Authors' Contributions

Z-T.M.: writing original draft and conceptualization (leading). Z.S.: writing original draft. X-H.X.: review and editing (equal). J-B.W.: conceptualization (supporting), methodology (lead), and review and editing (equal).

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Address correspondence to:
Prof. Jia-Bo Wang
Department of Pharmaceutics of Chinese Materia Medica
School of Traditional Chinese Medicine
Capital Medical University
Beijing 100069
China

E-mail: jiabo_wang@ccmu.edu.cn

Prof. Xiao-He Xiao
China Military Institute of Chinese Medicine
Fifth Medical Center of PLA General Hospital
Beijing 100039
China

E-mail: pharmacy302xxh@126.com

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Abbreviations Used

AAI = aristolochic acid I
CYP = cytochrome P450
DDI = drug–drug interaction
DILI = drug-induced liver injury
EBM = *Epimedium brevicornu* Maxim.
EGCG = epigallocatechin-3-gallate
GSH = glutathione
GTE = green tea extracts
HDI = herb–drug interaction
HHI = herb–herb interaction
HILI = herb-induced liver injury
HSOS = hepatic sinusoidal obstruction syndrome
iEC = integrated evidence
N-OH-ALI = N-hydroxyaristolactam I
PAs = pyrrolizidine alkaloids
PCL = *Psoralea corylifolia* or *Psoralea corylifolia* Linn.
PM = *Polygonum multiflorum*
ROS = reactive oxygen species
RUCAM = Roussel Uclaf Causality Assessment Method
TPL = triptolide
TRS = toxicity-related substance
UGT1A1 = UDP-glucuronosyltransferase 1A1