Acupuncture and Herbal Medicine

# Discovery, evaluation, prevention, and control of liver injury risk by Polygoni Multiflori Radix

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**Abstract**

In recent years, adverse reactions and events associated with traditional Chinese medicines (TCM) and herbal medicines (HM) have frequently occurred. In particular, with regard to the safety of newly discovered TCM that have been deemed "toxic," providing a scientifically based answer and developing effective solutions is challenging. Owing to the complexity of TCM/HM products and lack of systematic research, our understanding of the potential causes of TCM/HM-induced liver injury is limited. Therefore, significant advancements in understanding the toxicity of TCM and preventing and managing safety risks are urgently needed to address the safety concerns associated with TCM/HM. Using Polygoni Multiflori Radix (PMR) hepatotoxicity as a typical example, we evaluated the "integrated evidence chain" based on the causality evaluation of TCM-induced liver injury, and confirmed the objective authenticity of PMR hepatotoxicity. Furthermore, we first proposed and established a disease-syndrome-combined toxicology model that was applied to the material basis and analysis of the mechanism of PMR-induced hepatotoxicity. The mechanism hypothesis of "three-factor-induced toxicity" of idiosyncratic hepatotoxicity of TCM was proposed and confirmed. Based on this, the disease characteristics of the population susceptible to PMR idiosyncratic hepatotoxicity were elucidated, and various biomarkers were screened and identified, including the genetic marker HLA-B*35:01 and immunological and metabolomic markers. Finally, the study explored and established a safe medication strategy and method for "host-drug-use" three-dimensional risk prevention and control based on identifying susceptible individuals, controlling susceptible substances, and clinical precision medication. This study provides a foundation for comprehensively understanding the scientific implications of TCM/HM toxic side reactions and establishing scientific and effective risk prevention and control strategies.

**Keywords:** Causality evaluation, Liver injury, Mechanism, Polygoni Multiflori Radix, Risk prevention and control

**Graphical abstract:** http://links.lww.com/AHM/A117.

## Opportunities and difficulties in the development of traditional medicine

For millennia, traditional medicines, including traditional Chinese medicines (TCM) and herbal medicines (HM), have been widely used to prevent and treat various human diseases, especially in East Asia and other regions[1–4]. However, despite the growing demand for traditional medicine worldwide, the attention to these products and research on their safety has lagged far behind that of conventional drugs. In recent years, the frequent occurrence of adverse drug reactions (ADR) and events related to TCM/HM, particularly safety reports represented by drug-induced liver injury (DILI), has become a critical and challenging issue contributing to global public health security[5–15]. According to data from the Drug-Induced Liver Injury Network in the United States, herbal and dietary supplements (HDS) rank second among the causes of DILI in the United States, with their involvement percentage increasing from 7% in 2005 to 19% in 2012[16]. The LiverTox database of the National Library of Medicine in the United States contains >30 types of HM known to cause liver injury[17]. The risk of liver damage may also increase further in Asia, where traditional medicines are widely used[18]. In a prospective study of 307 cases of DILI in Japan, HDS and TCM accounted for 9% and 6% of the cases, respectively[19]. In 2019, a large-scale retrospective epidemiological study on DILI in mainland China reported that DILI caused by HDS accounted for 26.81% of the cases[20]. The National Medical Products Administration (NMPA) in China also reported the risk of liver injury caused by several types of TCM, such as Polygoni Multiflori Radix (PMR), Psoraleae Fructus, and Epimedii Folium[21–23]. Furthermore, the joint statement issued by the Federation of European Medical Schools and the Scientific Advisory Committee of the European Academy of Sciences questioned the safety of traditional medicine therapy, thereby sparking a global debate on

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the safety of traditional medicines. This issue has become a matter of great concern, as it has negatively impacted the healthy, sustainable development, and internationalization of traditional medicines[24,25].

## Complexity of the causes of liver injury caused by traditional medicine

Herbal-induced liver injury (HILI) refers to liver injury caused by TCM/HM and/or their metabolites, which can lead to acute liver failure or even death in severe cases. Owing to the complex nature of TCM/HM and the complexity of the drug combinations used in clinical practice, numerous factors contribute to HILI. Moreover, the substances responsible for the toxicity and their mechanisms of action remain unclear. The toxic effect occurs relatively slowly; thus, HILI is often undiagnosed and is associated with a high misdiagnosis rate. Furthermore, the lack of targeted theoretical guidance on TCM, irrational drug use, including unjustified drugs, off-label drugs, overcourse of treatment, drug overdose, and differences in the regulatory measures for TCM/HM in China and worldwide are obstacles to the accurate diagnosis of HILI (Figure 1).

### *The complex system of traditional medicine*

There are instances of homonyms, synonyms, and plants that originate from multiple sources resulting in TCM/HM varieties. In some cases, the original plant nomenclature has been misused because of incorrect translations of names or aliases in different countries or regions. For example, Gynura Segetum is an herb that is often misused as the TCM "Notoginseng Radix et Rhizoma (San Qi)." The TCM contains unsaturated pyrrolizidine alkaloids that have been linked to hepatic sinusoidal obstruction syndrome/hepatic veno-occlusive disease[26,27]. Aristolochiae Manshuriensis Caulis can be confused with Akebiae Caulis (Mu Tong) of the family *Lardizabalaceae*[28]. It contains aristolochic acid and aristolochic amide, which can cause necrosis of renal tubular epithelial cells and result in acute renal failure when used in clinical practice[29–31]. TCM/HM products can become contaminated or deteriorate owing to interference related to growth, fabrication, processing, transportation, storage, and other links, which may lead to excessive pesticides, heavy metals, and microbial toxins in these products. These harmful exogenous substances are hepatotoxic, and long-term use of contaminated TCM/HM products may cause liver injury[32–37].

### *Irrational use of traditional medicine in clinical practice*

The widespread use of TCM/HM may cause liver injury owing to various modes of use worldwide. These products are widely used as dietary supplements in foreign countries and are considered weight-loss health products for long-term use[38–43]. For example, Ephedrae Herba has traditionally been used for weight loss in the United States and has been reported to be related to liver injury in Western literature[44–46]. However, according to theory, Ephedrae Herba (Ma Huang) does not cause hepatotoxicity and can be used for short-term treatment of influenza[47,48]. Green tea extract, which is also used for weight loss in Western countries, has recently emerged as a research hotspot for inducing liver injury[49]. HM is consumed as a daily drink in China and Southeast Asian countries, with no concerns regarding hepatotoxicity[50,51].

In addition, with the popularity of TCM and the development of TCM industrialization, Chinese patent medicines have become one of the main forms of clinical applications in TCM. However, owing to the lack of targeted theoretical guidance for TCM, cases of irrational drug use (misuse and abuse), such as unjustified drug use, off-label drugs, treatment overcourse, and drug overdoses, are common. Moreover, the prevalent traditional belief that TCM is pure and natural and has no toxicity or side effects, as well as the belief in the so-called "folk prescription" has led to cases of disease-free abuse and overdose, inevitably increasing the risk and preventing the safe use of TCM therapy in clinical practice.

### *Differences between Eastern and Western regulatory systems for traditional medicine*

The most significant difference in the use of traditional medicines in China and Western countries is reflected in the drug regulatory systems[52]. In China, the NMPA is responsible for approving and overseeing the production

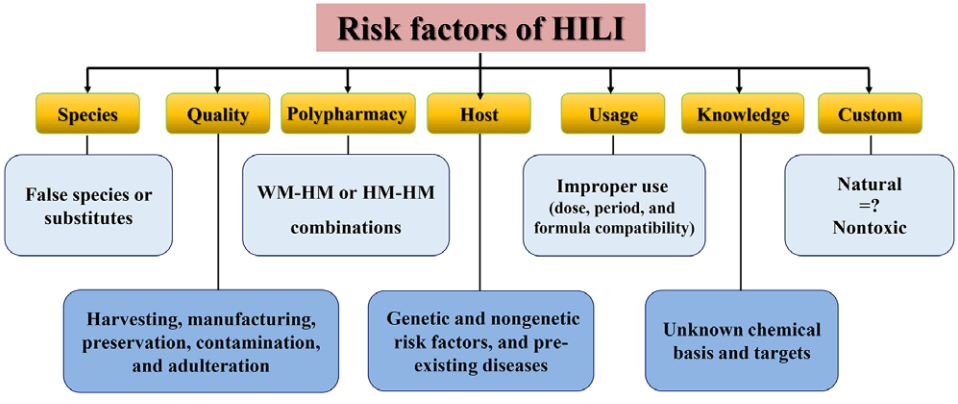


**Figure 1.** Complexity of the causes of HILI. HILI: Herbal-induced liver injury; HM: Herbal medicine; WM: Western medicine.

and use of new TCM, encompassing the entire process including approval, application, and postmarketing evaluation to ensure that its lifecycle is supervised. However, in Western countries, HM are not included in the drug regulatory system, and are not subjected to the same rigorous supervision process as conventional drugs. HM can be marketed without the need for preclinical and clinical toxicological safety or effectiveness studies using clinical trials[53] and approval from regulatory authorities is not required. Consequently, the source, content, and quality of HM are not guaranteed, which may result in worse liver injury outcomes than those of conventional drugs[54–57].

### *Toxicity types and characteristics of liver injury caused by traditional medicine*

TCM places great importance on its safety, and systematic studies have been conducted to investigate the acute and direct toxicity of TCM, resulting in a wealth of knowledge and theoretical understanding of safe medications in TCM. However, in recent years, safety concerns associated with TCM/HM have become a growing concern. Frequent reports of liver injury caused by traditional "non-toxic" TCM have raised global concern. Currently, the global understanding of the types of drug toxicity has evolved significantly and can be categorized into three types: direct, idiosyncratic, and indirect[58–62]. It is recognized that the current cognitive theory and research models of TCM toxicity present certain limitations, and the existing "toxicity" research model is no longer adequate to provide an objective, accurate, and comprehensive understanding of "toxic" TCM. In terms of the "toxicity" characteristics of TCM, most toxic TCMs are related to direct toxicity, whereas the traditional "non-toxic" TCM are primarily associated with idiosyncratic or indirect toxicity related to the body or disease and syndrome factors. According to a study by our research group based on data from the National Center for ADR Monitoring, using DILI as an example, the proportion of liver injury caused by TCM that is known to cause hepatotoxicity was only 14.0%, whereas the proportion of liver injury caused by newly discovered TCMs with hepatotoxicity was as high as 86.0%. This indicates that the proportion of liver injury caused by traditional "non-toxic" TCMs has significantly exceeded that of traditional "toxic" TCM in clinical practice[63]. However, the types of liver injury caused by traditional "non-toxic" TCM are mainly due to idiosyncratic and indirect toxicity, which have not been previously recognized. To summarize, the cognitive theory of "toxicity" of TCM has proven inadequate in addressing new clinical challenges. Hence, innovations and breakthroughs are urgently needed in this area, particularly with respect to the types of "toxicity" associated with TCM. It is important to recognize that TCM has not only direct toxicity but also idiosyncratic and indirect toxicities that are increasingly common, yet often overlooked in clinical practice. These idiosyncratic and indirect toxicities are the primary causes of adverse reactions when TCM is used in clinical practice (Figure 2).

### *Limitations of causality assessment on HILI*

Currently, no normative standard for HILI diagnosis is established[64]. The Roussel Uclaf Causality Assessment Method (RUCAM) is currently the primary evaluation method for DILI, with the score serving as the basis for the evaluation of the correlation strength, which is primarily used for correlation diagnosis. The complexity of the composition of TCM/HM presents challenges that limit their usage, and existing DILI diagnostic standards in China and worldwide are often difficult to meet in clinical practice, resulting in insufficient objective evidence. Thus, accurately diagnosing diseases is challenging, leading to inaccurate diagnoses. For example, "drug hepatotoxicity warning signs," the hepatotoxicity from the use of traditional "non-toxic" TCM such as PMR and Psoraleae Fructus can be described as "it is easy to dodge a spear in the open, but hard to guard against an arrow shot from hiding." A safety warning is usually not presented on the TCM/HM label, and the total score on the RUCAM scale may be reduced. Because only a few studies have reported the hepatotoxicity of TCM, the score for "known hepatotoxicity of drugs" in the RUCAM scoring system is usually 0. Consequently, the

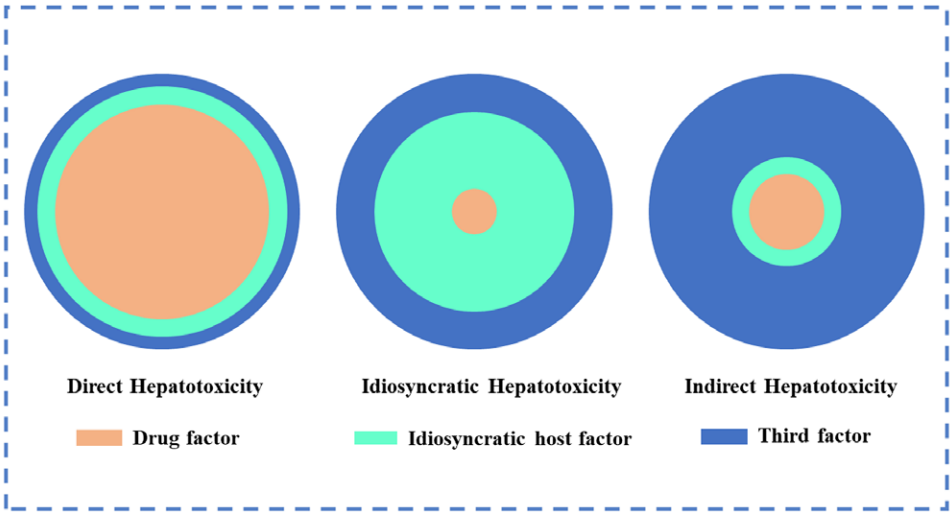


Figure 2. Toxicity types and characteristics of TCM/HM hepatotoxicity. HM: Herbal medicine; TCM: Traditional Chinese medicine.

RUCAM score has limited use in determining the causality of hepatotoxicity from TCM/HM. In addition, "quality problems" and "risk factors" (such as age and alcohol consumption) have limitations in the diagnosis of HILI and may not be consistent in practice[65–67]. Therefore, the use of RUCAM to score HILI has certain limitations and the diagnosis of HILI is more difficult than that of DILI. Therefore, the RUCAM score, which is widely used in clinical practice, does not accurately or objectively reflect the association between TCM and liver injury. Hence, developing a HILI-diagnostic system adapted to the characteristics of TCM/HM is urgently needed.

## Construction of safety evaluation guidelines of TCM/HM-induced liver injury based on the integrated evidence chain-based causality identification algorithm

RUCAM scoring is commonly used to assess the causality of DILI; however, it is not well-suited for evaluating the complexities of TCM/HM use and risks. The hepatotoxicity associated with TCM/HM differs from that of Western medicines, as it is influenced by factors such as the quality of TCM/HM, changes in compatibility, clinical dosage and usage, syndrome differentiation, physical differences, genetics, and other factors, which can make it difficult to diagnose HILI. Currently, no specific causality evaluation scale is available for HILI. Subtle differences related to TCM/HM may interfere with causality assessment methods. Therefore, the RUCAM score, which is widely used in clinical practice, does not accurately or objectively reflect the relationship between TCM and liver injury. Therefore, developing a diagnostic system for HILI that is adapted to the characteristics of TCM is an urgently needed.

To this end, in 2016, the China Association of Chinese Medicine (CACM) issued the first diagnostic and therapeutic technical standard specific to HILI, namely the *Guidelines for diagnosis and management of herb-induced liver injury*[68]. This standard proposed a diagnostic process based on an integrated evidence chain-based causality identification algorithm. Based on the possibility of a RUCAM score of >3, links such as the investigation of the combination of TCM and Western medicines, traceability of Chinese crude drugs, and detection of biomarkers have been introduced to emphasize the objectivity and accuracy of HILI diagnosis[69]. This approach transforms the subjective exclusion method of diagnosis into an objective chain of evidence and further transforms the correlation diagnosis into deterministic diagnosis. The HILI-integrated evidence chain is divided into nine criteria, and the length of the evidence chain is determined according to the number of criteria satisfied. The more complete the evidence chain, the higher is the probative value and credibility of the diagnosis. It is divided into three diagnostic levels: "suspected, clinical, and confirmed" diagnosis.

Considering the complexity of liver injury caused by TCM/HM, with the main focus on strengthening risk management throughout the lifecycle of drugs, the NMPA issued the *Guidance for the clinical evaluation of traditional Chinese medicine-induced liver injury* in 2018[70]. This guideline elaborates on the identification and collection of risk signals for new Chinese medicine drugs, as well as causal relationship assessment, which can significantly reduce the failure rate and clinical use risk of new Chinese medicine drugs. The primary goal of this guidance is to assist relevant institutions and personnel in formulating targeted measures for the prevention and control of DILI in TCM, and to promote the healthy and sustainable development of China's TCM industry.

Furthermore, HDS products are complex and lack research; therefore, our understanding of the potential causes of HDS-induced liver injury is limited[71]. To provide a balanced and global perspective on HDS-DILI detection, susceptibility factors, and outcomes, and advise on causality assessment tools, monitoring, and management during drug development and postmarketing phases, the World Health Organization-Council for International Organizations of Medical Sciences (WHO-CIOMS) working group drafted *a consensus on drug induced liver injury* in 2020 (*Chapter 8: liver injury attributed to herbal and dietary supplements*) (Figure 3). This international consensus effectively addressed the issue of objective evaluation and clinical diagnosis of liver injury caused by TCM/HM and won the right to formulate the diagnosis and prevention standards for HDS-induced liver injury.

## Causality evaluation and research on the mechanism of HILI based on the integrated evidence chain: a case study of PMR

### *Current state of PMR-related liver injury*

In recent years, the number of reports of adverse reactions and events related to TCM has increased. In particular,


**Figure 3.** The core technique for the clinical diagnosis of HILI applied to the "Association-National-International" guidelines for liver injury related to TCM/HM. HILI: Herbal-induced liver injury; HM: Herbal medicine; TCM: Traditional Chinese medicine.

some TCM (PMR, Psoraleae Fructus, Epimedii Folium, etc) that are traditionally considered "non-toxic" have also presented safety concerns, with those exhibited by PMR being the most prominent[72–74]. Liver injury has been reported in raw and processed PMR, compound preparations containing PMR, and patented Chinese medicines and health foods. It is also one of the most common single varieties of TCM and is currently known to cause liver injury in clinical practice. PMR-induced liver injury has been reported previously and in other countries[75]. To date, more than 30 countries, including the United States, South Korea, and Japan, have reported liver injuries caused by PMR and its preparations. The LiverTox Hepatotoxic Drug Database, published by the National Institutes of Health, has a special record for PMR[17]. Drug regulatory authorities in the United Kingdom, Australia, and Canada have successively issued warnings related to PMR-induced liver injury[76]. In China, reports of ADR related to PMR and related preparations received by the National Center for ADR Monitoring rank at the forefront of TCM categories, with most being liver injury cases. The NMPA also attaches great importance to the safety of PMR and has repeatedly issued risk notifications of adverse reactions related to liver injury, as well as notices revising drug instructions and strengthening supervision for preparations, including Jingwu capsules, Qibao Meiran wan, Xinyuan capsules, Yangxue Shengfa capsules, PMR pills and tablets, and Shouwu Yanshou tablets/granules. The scientific understanding of causality evaluation and the possible mechanism of liver injury caused by traditional "non-toxic" Chinese herbs such as PMR, and formulating risk control measures are challenging yet important for the safety evaluation and supervision of TCM/HM.

### *Causality analysis of liver injury of PMR based on the integrated evidence chain*

#### *Step 1*

A patient exhibits abnormal liver function, meets the biochemical standards for DILI recommended by the integrated evidence chain, and has a history of using suspected liver injury-causing drugs (PMR) before disease onset. Further comprehensive screening for the possible causes of liver injury should be conducted to confirm that the patient has no history of other underlying health conditions. After admission, laboratory examinations should be performed to rule out liver injury caused by viral infection, immunity, genetic metabolism, and blood vessel damage. Alcohol consumption history can be used to rule out the possibility of alcoholic liver injury. Additionally, the patient has a RUCAM score of >3. Therefore, liver injury related to PMR is suspected. In a previous study, we collected data from 12,307 patients with abnormal liver function between 2002 and 2013 at the Fifth Medical Center of the PLA General Hospital and excluded other causes of liver injury (such as genetics, metabolism, viral infections, alcohol use, and immunity). Forty patients were suspected of having PMR-induced liver injury. After diagnosis according to the RUCAM score, only 22.5% (9/40) of the suspected cases of liver injury caused by PMR were highly correlated with PMR (RUCAM score ≥8), and 13 cases were possibly correlated with PMR (RUCAM score of 3–5). These data are insufficient in probative value to determine the correlation with the diagnosis of TCM-related liver injury based on the RUCAM score alone[77].

#### *Step 2*

The patient consumed only PMR; thus, combinations with other drugs known to cause liver injury can be excluded. The remaining PMR drug, packaging mark, place of origin, and batch number are collected and sent to a laboratory for pharmacognostic testing. After identification, if the original drug meets the pharmacopeial quality standards, the possibility of TCM contamination by adulterants and harmful substances can be excluded. The characteristic fingerprints of PMR (2,3,5,4'-tetrahydroxy stilbene-2-O-β-D-glucoside [SG]) in the samples is analyzed, and if detected, these findings are consistent with the clinical diagnosis of PMR-related liver injury. In the early stages, our research group used pharmacognostic methods to analyze the remaining six batches of medicinal materials collected from patients with liver injury suspected to be caused by PMR, of which five batches were authentic and one was counterfeit. In addition, heavy metal, mycotoxin, and pesticide levels were determined in PMR samples collected from clinical patients. None of the compounds exceeded the safety limits stated in the Chinese Pharmacopoeia or EU standards. Therefore, the possibility of liver injury caused by toxin contamination was excluded. Plasma and urine samples from some patients were analyzed. The most frequently detected metabolites were the glucuronic acid-conjugated phase II metabolite of SG, and emodin glucuronide[77].

#### *Step 3*

It was determined that the patient had previously been diagnosed with DILI after consuming preparations containing PMR in the past. After taking the single-agent PMR preparation again, the patient experienced a positive re-excitation event. Additionally, immune-metabolic markers can be detected in patients susceptible to idiosyncratic PMR DILI (IDILI). Thus, the diagnosis of PMR-related liver injury is confirmed[21,78,79].

### *Analysis of the causes and mechanisms of liver injury caused by PMR*

Scientifically determining the causes and mechanisms of HILI is crucial for mitigating the safety hazards associated with TCM. It also provides a vital foundation for the formulation of traditional pharmacovigilance strategies and measures. Recently, concerns over the safety of TCM that have been traditionally considered "non-toxic" have arisen, and many of these issues do not appear to be related to factors such as drug dosage and duration. Individual differences are occasionally or rarely observed in clinical practice. Therefore, framing a scientific answer or proposing an effective solution for conventional toxicological evaluation is challenging. In fact, DILI caused by most traditional "non-toxic" TCM

is not due to the direct toxicity of TCM but is closely related to physical factors, especially basic diseases and syndromes. Most cases involve idiosyncratic toxicity; however, studies on idiosyncratic toxicity are almost nonexistent in the field of TCM. Evaluation and prediction of idiosyncratic drug toxicity are challenging international problems. Therefore, we have proposed and established a disease-syndrome-combined toxicology model, which is a safety evaluation model and method for associated clinical diseases and syndromes of TCM; that is, the relativity, susceptibility, and controllability of TCM/HM (Figure 4), which is scientifically recognized and accurately evaluated by comparing and studying the susceptibility and tolerance of drug toxicity in normal and disease (pathological) states, as well as the laws on their differences to identify the susceptible population and disease syndrome basis of TCM toxicity[80]. The toxicology of disease syndromes is a powerful research tool for revealing the objectivity and cause of TCM-IDILI.

In view of the difficulties in elucidating the mechanism of PMR-induced liver injury through large-scale clinical retrospective and prospective case analyses, for the first time, PMR-induced liver injuries were confirmed to be rare in clinical practice and that their occurrence had no significant dependence on dosage and treatment course, suggesting that toxicity is idiosyncratic rather than direct[75,81]. Further studies have shown that PMR-induced liver injuries are closely related to factors such as immune status and genetic background. Abnormal activation of immunity or syndrome differentiation of autoimmune diseases in TCM belongs to yin deficiency, fire excess, and damp heat, which constitute the main disease and syndrome basis for individuals susceptible to PMR-induced liver injuries[82]. Using pharmacogenomics, we identified the human leukocyte antigen HLA-B* 35:01 as an important genetic marker for individuals susceptible to PMR-induced liver injuries[83]. Using immunometabolomics, monocyte chemoattractant protein (MCP-1), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, phenyllactic acid, crotonoyl-CoA, and indole-5,6-quinone were identified as the immune-metabolic markers for individuals susceptible to PMR-induced liver injuries (Figure 5)[21,78,79]. Studies on the characteristics of susceptible individuals and their biomarkers have revealed that PMR poses a risk of liver injury in only a few susceptible individuals and is safe for the majority of populations. These findings provide a solid scientific basis for formulating a targeted comprehensive prevention and control strategy for liver injury risk related to PMR and its related preparations and promote the safe and rational use of TCM to a new level of precision medicine. This study is the first to identify a genetic marker for individuals susceptible to IDILI in traditional medicine, making it a successful example of translational medicine research[84].

Based on the above studies, the susceptibility markers and conditional mechanisms of idiosyncratic liver injury by PMR were clarified using the disease syndrome–related idiosyncratic DILI evaluation model in combination with the pioneering "knock-out and knock-in" identification strategy for toxic substances. The study found *cis*-SG and emodin-8-O-β-D-glucoside (EmG) to be the main components of PMR associated with immune-idiosyncratic liver injury[85,86]. Moreover, the study reported that *trans*-SG with immune-promoting effects can further synergistically aggravate the extent of liver injury[87]. Based on this, a hypothesis of the "three-factor-induced toxicity" mechanism of immune-idiosyncratic liver injury in TCM (PMR) (also known as the "Chai-Oil-Mars Seed" theory) has been proposed, which scientifically reveals the biological mechanisms of immune-idiosyncratic liver injury by PMR induced by the immune activation state of the body, immune-promoting substances of PMR, and risk substances for liver injury (Figure 6). When the body is in a state of immune stress, the immune-promoting substances in the PMR (such as *trans*-SG) further aggravate the immune-inflammatory reaction, increasing the sensitivity of the liver to substances that are predisposed to cause liver injury (such as *cis*-SG) and leading to the overexpression of immune-inflammatory factors, thereby inducing immune-idiosyncratic liver injury. In addition, the "three-factor-induced toxicity" hypothesis has also been successfully used to evaluate liver injury caused by other TCM such as Psoraleae Fructus (Bu Gu Zhi) and Epimedii Folium[22], (Yin Yang Huo Ye) revealing that the targeted activation of NLRP3 inflammatory bodies is the common mechanism of immune-idiosyncratic liver injury induced by Psoraleae Fructus and Epimedii Folium, and various chemicals[23,88–91]. The above research enriches and develops traditional medicine toxicology theory and the toxicity cognitive model and provides new ideas and a basis for the scientific prevention and control of HILI.

### *Risk prevention and control strategies to liver injury caused by PMR*

TCM containing toxic ingredients or those exerting toxic side effects are not necessarily unsafe. A series of

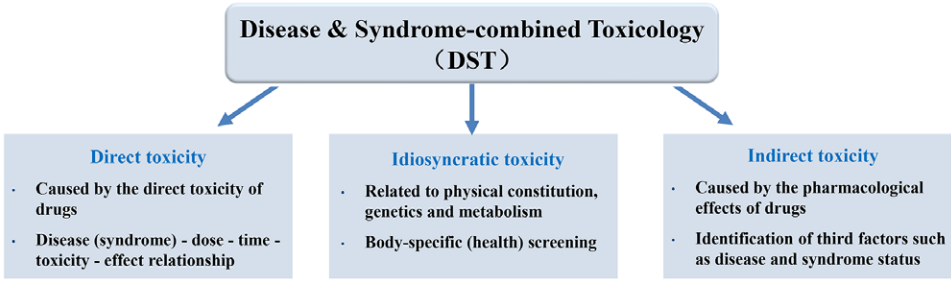


Figure 4. New model and method for safety evaluation of TCM/HM: Disease-syndrome-combined toxicology. HM: Herbal medicine; TCM: Traditional Chinese medicine.

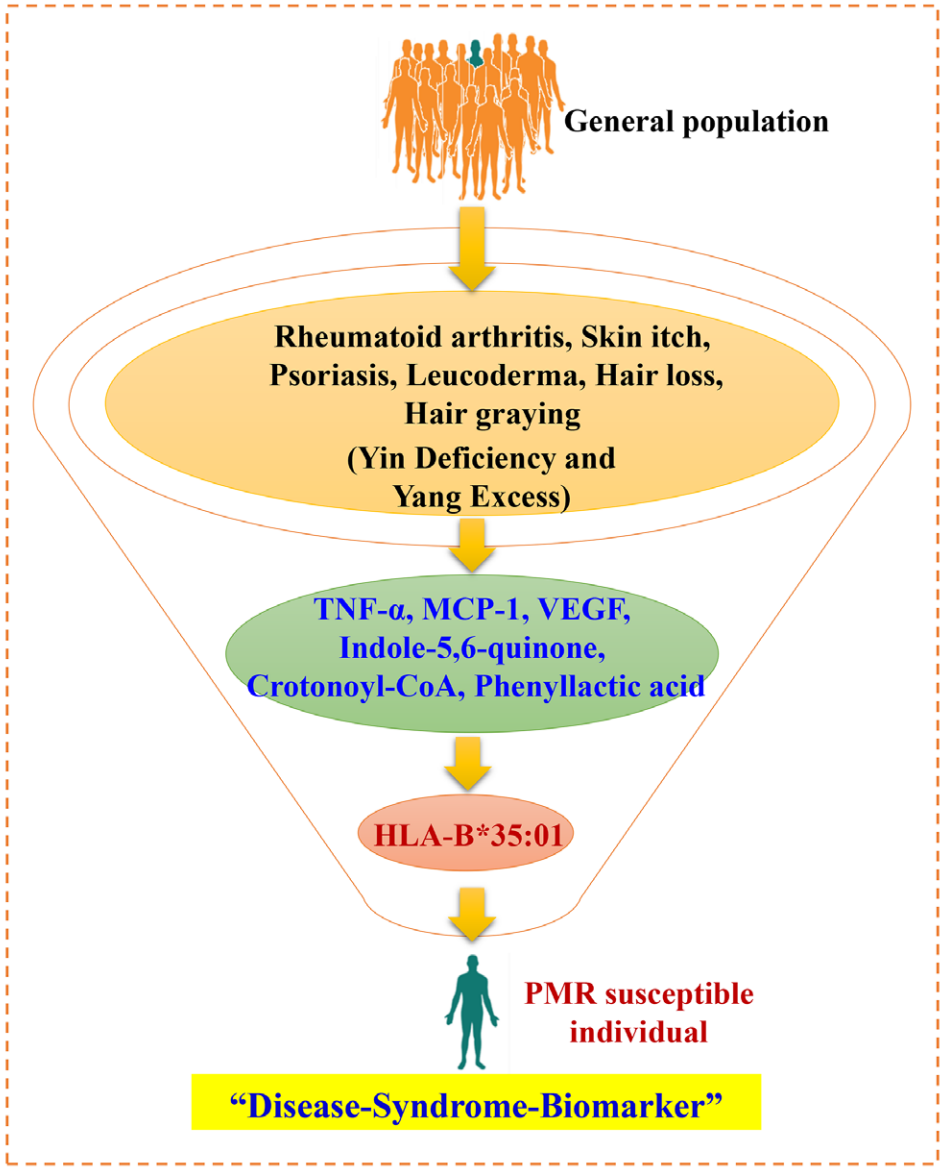


Figure 5. Characteristics of the susceptible population to idiosyncratic liver injuries in PMR based on the "disease-syndrome-biomarker." MCP-1: Monocyte chemoattractant protein; PMR: Polygoni Multiflori Radix; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor.

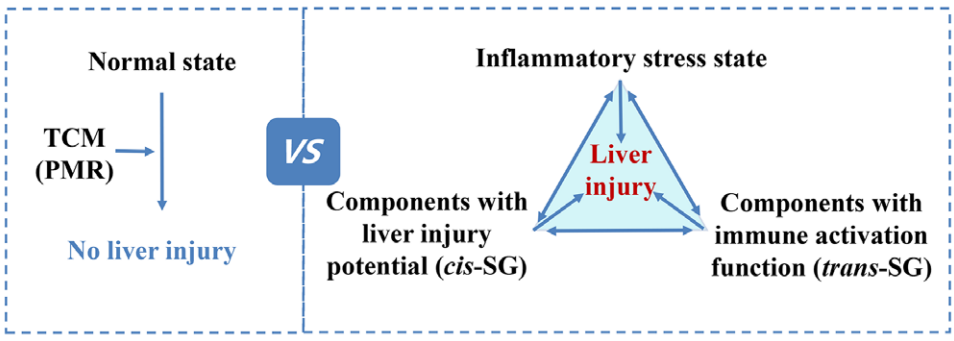


Figure 6. Hypothesis of the "three-factor-induced toxicity" mechanism of immune-idiosyncratic liver injury in PMR. PMR: Polygoni Multiflori Radix; SG: 2,3,5,4'-tetrahydroxy stilbene-2-O-β-D-glucoside; TCM: Traditional Chinese medicine.

studies by our group showed that the safety risks of TCM are relative, conditional, and highly adaptable, and that the rational use of TCM can effectively avoid safety risks. Considering the mechanism and characteristics of different types of liver injuries caused by TCM, the diagnosis of this condition and prescription to avoid toxicity can be achieved by screening susceptible individuals. The ability to reduce toxicity can be guided by

analyzing the mechanism of toxicity. The processing of TCM to reduce toxicity and achieve quality control can be guided by identifying susceptible substances, thereby reducing the risks of TCM from different perspectives and ensuring safe drug use in clinical practice. Therefore, we first proposed and established a "host-drug-use" three-dimensional alert system to identify the safety risks of TCM based on the identification of susceptible individuals, quality control of susceptible substances, and clinical precision medication as comprehensive prevention and control measures.

### *Risk prevention and control strategies and the methods of TCM/HM-induced liver injury based on the identification of susceptible individuals*

A strategy and method for identification and risk prevention in susceptible individuals and control of TCM idiosyncratic liver injury based on disease-syndrome-biomarker sequential screening has been established. Considering the mechanism and characteristics of PMR-induced idiosyncratic liver injury, individuals experiencing inflammation or diagnosed with autoimmune diseases such as yin deficiency, yang excess, and damp heat accumulation by TCM syndrome differentiation should be cautious when using PMR. When required, biomarkers such as the HLA-B*35:01 allele and the inflammatory factors[83] TNF-α, MCP-1, VEGF, phenyllactic acid, crotonoyl-CoA, and indole-5,6-quinone[21,78,79], can be combined to accurately identify susceptible individuals, and the characteristics of "cautious use," "taboo use," and "alternative use" populations and the application scope of PMR can be determined. The above-mentioned prevention and control measures and suggestions have been incorporated into *the Guidelines for the Safe Use of Polygoni Multiflori Radix*[92], a group standard formulated by the CACM, which provides strong support to ensure the safe use of PMR and its related preparations and to promote the healthy development of related TCM industries.

### *Strategies and methods for the accurate evaluation and control of quality and safety of TCM based on the control of susceptible substances*

Oriented toward safety and effectiveness, the strategy and method of multidimensional accurate quality assessment and control of TCM have been established and applied, including high safety risk and complex and unclear effective substances. Considering that *cis*-SG and EmG, which are compounds in PMR capable of causing liver injury, processing technology has improved, and limits for control standards and biological toxicity have been established. Based on the traditional experience of the *Thunder God Processed Treatise*, the "wine immersion and water bleaching method" for the preparation and detoxification of Psoraleae Fructus has been proposed and established, and the content limit standards of coumarin in Psoraleae Fructus that is capable of causing liver injury has been established, thus effectively guaranteeing and improving its quality and safety levels[93]. The *Guidelines for the Quality Evaluation Methods of Traditional Chinese Medicine* issued by the Chinese Society of Traditional Chinese Medicine have been formulated with multidimensional evaluation and control strategies and methods at the core. These provide technical support to solve the problems of disconnection between the quality standards of TCM and clinical efficacy and safety. Relevant technologies are transferred to well-known enterprises to guide the re-evaluation of their relevant products after marketing or to assist with the development of new drug products.

### *Strategies and methods of the precise use of TCM for detoxification are established based on the traditional theory of detoxification and the mechanism of liver injury*

Based on the understanding that immune regulation affects the risk of PMR-induced liver injury, we first confirmed that the combination of *Poria cocos* and PMR could significantly reduce PMR-induced liver injury. A 1:2 ratio of *Poria cocos*:PMR exerts the best detoxification effect[94]. From the perspective of compatibility for detoxification, the modern scientific value of "PMR is used *Poria cocos* as its ingredient" recorded in the Materia medica is explained, and the possible mechanism of *Poria cocos* in attenuating PMR-induced liver injuries by regulating eight biomarkers related to inflammation and immune balance, including sphinganine-1-phosphate and TNF-α, has been confirmed, which provides a scientific basis for reducing PMR toxicity through rational compatibility.

Based on the compounds originally discovered in PMR that can cause idiosyncratic liver injury, the upper limit of quality and safety content control of *cis*-SG and EmG (substances capable of causing PMR-induced liver injury) was established based on the strategy of ingredient knock-out and knock-in, which helps guide the processing of PMR to avoid the risk of liver injury caused by high levels of these harmful compounds[95]. The influence of the processing method and particle size of the pieces used to prepare the decoction on the risk of PMR-induced liver injury has been studied and reported. A new technology for high-pressure steam processing of PMR for detoxification has been established, which is equivalent to the traditional processing of nine steaming and nine drying processes for detoxification, but is simpler and more economical[96]. For the first time, metal ions (especially $Fe^{3+}$ and $Fe^{2+}$) were found to affect the stability of stilbene glycosides in PMR, leading to an increased risk of liver injury. The study revealed the scientific connotation of PMR recorded in Materia medica as "The closer to iron, the stronger the poison"[97].

## Summary and outlook

In this study, we developed the first TCM-related liver injury clinical diagnostic guidelines for HILI and demonstrated that it can effectively reduce misdiagnosis and misjudgment of liver injury related to TCM/HM and can scientifically clarify problems related to TCM/HM-induced liver injuries, such as that caused by PMR. With the integration of the evidence chain as the technical core, we have successfully taken the lead in studying and formulating the "Association-National-International"

guidelines for liver injury related to TCM/HM. These guidelines help to effectively address the issue of objective evaluation and clinical diagnosis of TCM/HM-induced liver injury and facilitate the development of diagnostic, preventive, and control standards for DILI.

Drug-induced diseases, represented by DILI, can cause secondary injury to patients, which not only increases the medical burden on patients but also puts a strain on medical resources. The cognitive innovation theory and strategy method of TCM toxicity we have proposed, taking liver injury caused by PMR as an example, provides a solution to the concerns regarding safety evaluation of TCM at home and abroad and dispels the doubts of international public opinion and the public regarding the safety issues of a series of TCM. By comprehensively revealing the scientific connotation of toxic and side effects of "toxic" TCM, it provides important theoretical guidance and methodological support for scientific evaluation and precise prevention and control of TCM/HM safety risks. Furthermore, the first shared and co-created on-line consulting service platform for safe drug use, "Safe Drug Inquiry" has been successfully developed and established. This platform realizes the transformation and implementation of the integrated response mechanism of "clinical monitoring-scientific evaluation-risk prevention and control" for DILI resulting from the use of TCM. This platform reduces the risk of ADRs among patients by providing free educational and consultation services on drug safety to the public, thereby reducing the medical burden on the public (economic benefits) and promoting beneficial social outcomes by protecting and enhancing public wellbeing.



## Conflict of interest statement

Xiaohe Xiao is editorial board members of this journal. None of the other authors declare any conflicts of interest.

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## Author contributions

Can Tu, Xiaohe Xiao, and Jiabo Wang designed the manuscript; Can Tu and Yuan Gao wrote the manuscript, Zhaofang Bai helped to revise the manuscript. All authors read and approved the manuscript.

## Ethical approval of studies and informed consent

Not applicable.

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## Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## References

[1] Huang K, Zhang P, Zhang Z, et al. Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: efficacies and mechanisms. *Pharmacol Ther* 2021;225:107843.
[2] Gong J, Xie J, Bedolla R, et al. Combined targeting of STAT3/NF-κB/COX-2/EP4 for effective management of pancreatic cancer. *Clin Cancer Res* 2014;20(5):1259–1273.
[3] Lian F, Li G, Chen X, et al. Chinese herbal medicine Tianqi reduces progression from impaired glucose tolerance to diabetes: a double-blind, randomized, placebo-controlled, multicenter trial. *J Clin Endocrinol Metab* 2014;99(2):648–655.
[4] Lam WC, Lyu A, Bian Z. ICD-11: impact on traditional Chinese medicine and world healthcare systems. *Pharmaceut Med* 2019;33(5):373–377.
[5] Lee FY, Wong HS, Chan HK, et al. Hepatic adverse drug reactions in Malaysia: an 18-year review of the national centralized reporting system. *Pharmacoepidemiol Drug Saf* 2020;29(12):1669–1679.
[6] Yousaf MN, Chaudhary FS, Hodanazari SM, et al. Hepatotoxicity associated with Garcinia cambogia: a case report. *World J Hepatol* 2019;11(11):735–742.
[7] Brar HS, Marathi R. Case of cholestatic drug-induced liver injury (DILI) associated with black cohosh. *BMJ Case Rep* 2021;14(5):e240408.
[8] Ferreira GSA, Watanabe ALC, Trevizoli NC, et al. Acute liver failure caused by use of fat burner: a case report. *Transplant Proc* 2020;52(5):1409–1412.
[9] Xia C, Liu Y, Yao H, et al. Causality assessment of skyfruit-induced liver injury using the updated RUCAM: a case report and review of the literature. *J Int Med Res* 2020;48(4):300060520917569.
[10] Shao YM, Zhang Y, Yin X, et al. Herb-induced autoimmune-like hepatitis associated with Xiang-tian-guo (Swietenia macrophylla seeds): a case report and literature review. *Medicine (Baltim)* 2021;100(2):e24045.
[11] Tan Y, Chen H, Zhou X, et al. RUCAM-based assessment of liver injury by Xiang-Tian-Guo (Swietenia macrophylla) seeds, a plant used for treatment of hypertension and diabetes. *Ann Hepatol* 2019;18(2):406–407.
[12] Yeap V, Tan TJY, Loh T, et al. Liver failure associated with mahogany seed extract consumption. *BMJ Case Rep* 2018;2018:bcr2018225382.
[13] Vuppalanchi R, Bonkovsky HL, Ahmad J, et al. Garcinia cambogia, either alone or in combination with green tea, causes moderate to severe liver injury. *Clin Gastroenterol Hepatol* 2022;20(6):e1416–e1425.
[14] Tan R, Hu Z, Zhou M, et al. Diosbulbin B: an important component responsible for hepatotoxicity and protein covalent binding induced by Dioscorea bulbifera L. *Phytomedicine* 2022;102:154174.
[15] Halegoua-DeMarzio D, Navarro V, Ahmad J, et al. Liver injury associated with turmeric-a growing problem: ten cases from the drug-induced liver injury network [DILIN]. *Am J Med* 2023;136(2):200–206.
[16] Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. drug-induced liver injury network. *Hepatology* 2014;60(4):1399–1408.
[17] Navarro VJ, Khan I, Bjornsson E, et al. Liver injury from herbal and dietary supplements. *Hepatology* 2017;65(1):363–373.
[18] Ballotin VR, Bigarella LG, Brandão ABM, et al. Herb-induced liver injury: systematic review and meta-analysis. *World J Clin Cases* 2021;9(20):5490–5513.
[19] Aiso M, Takikawa H, Tsuji K, et al. Analysis of 307 cases with drug-induced liver injury between 2010 and 2018 in Japan. *Hepatol Res* 2019;49(1):105–110.
[20] Shen T, Liu Y, Shang J, et al. Incidence and etiology of drug-induced liver injury in Mainland China. *Gastroenterology* 2019;156(8):2230–2241.e11.
[21] Tu C, Niu M, Wei AW, et al. Susceptibility-related cytokine panel for prediction of polygonum multiflorum-induced hepatotoxicity in humans. *J Inflamm Res* 2021;14:645–655.
[22] Gao Y, Wang ZL, Tang JF, et al. New incompatible pair of TCM: Epimedii Folium combined with Psoraleae Fructus induces idiosyncratic hepatotoxicity under immunological stress conditions. *Front Med* 2020;14(1):68–80.
[23] Wang ZL, Xu G, Wang H, et al. Icariside II, a main compound in Epimedii Folium, induces idiosyncratic hepatotoxicity by enhancing NLRP3 inflammasome activation. *Acta Pharm Sin B* 2020;10(9):1619–1633.
[24] Melchart D. A joint statement for "tighter regulation" of traditional Chinese medicine issued by the federation of European

academies of medicine (FEAM) and the European academies' science advisory council (EASAC): scare stories or obstruction of access? *Complement Med Res* 2020;27(1):3–5.
[25] Eigenschink M, Dearing L, Dablander TE, et al. A critical examination of the main premises of traditional Chinese medicine. *Wien Klin Wochenschr* 2020;132(9-10):260–273.
[26] Wang Y, Qiao D, Li Y, et al. Risk factors for hepatic veno-occlusive disease caused by Gynura segetum: a retrospective study. *BMC Gastroenterol* 2018;18(1):156.
[27] Zhu L, Zhang CY, Li DP, et al. Tu-San-Qi (Gynura japonica): the culprit behind pyrrolizidine alkaloid-induced liver injury in China. *Acta Pharmacol Sin* 2021;42(8):1212–1222.
[28] Wu L, Wang B, Zhao M, et al. Rapid identification of officinal Akebiae Caulis and its toxic adulterant Aristolochiae Manshuriensis Caulis (Aristolochia manshuriensis) by loop-mediated isothermal amplification. *Front Plant Sci* 2016;7:887.
[29] Qiu Q, Liu ZH, Chen HP, et al. Long-term outcome of acute renal injury induced by Aristolochia manshuriensis Kom in rats. *Acta Pharmacol Sin* 2000;21(12):1129–1135.
[30] Zhou Q, Pei J, Poon J, et al. Worldwide research trends on aristolochic acids (1957-2017): suggestions for researchers. *PLoS One* 2019;14(5):e0216135.
[31] Yang B, Xie Y, Guo M, et al. Nephrotoxicity and Chinese herbal medicine. *Clin J Am Soc Nephrol* 2018;13(10):1605–1611.
[32] Prozialeck WC, Edwards JR, Lamar PC, et al. Evaluation of the mitragynine content, levels of toxic metals and the presence of microbes in kratom products purchased in the western suburbs of Chicago. *Int J Environ Res Public Health* 2020;17(15):5512.
[33] Li C, Su X, Feng WH, et al. Simultaneous determination of 12 mycotoxins in polygoni multiflori radix by UPLC-ESI-MS/MS combined with modified QuEChERS. *Zhongguo Zhong Yao Za Zhi* 2016;41(23):4368–4374.
[34] Arroyo-Manzanares N, García-Campaña AM, Gámiz-Gracia L. Multiclass mycotoxin analysis in Silybum marianum by ultra high performance liquid chromatography-tandem mass spectrometry using a procedure based on QuEChERS and dispersive liquid-liquid microextraction. *J Chromatogr A* 2013;1282:11–19.
[35] Han Z, Zheng Y, Luan L, et al. An ultra-high-performance liquid chromatography-tandem mass spectrometry method for simultaneous determination of aflatoxins B1, B2, G1, G2, M1 and M2 in traditional Chinese medicines. *Anal Chim Acta* 2010;664(2):165–171.
[36] Abdullah R, Diaz LN, Wesseling S, et al. Risk assessment of plant food supplements and other herbal products containing aristolochic acids using the margin of exposure (MOE) approach. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2017;34(2):135–144.
[37] Zhou Y, Huang W, Liu X, et al. Interannual variation and exposure risk assessment of lead in brick tea in Hubei, China. *Sci Total Environ* 2020;745:141004.
[38] Hatami B, Saffaei A, Jamali F, et al. Glutamine powder-induced hepatotoxicity: it is time to understand the side effects of sports nutritional supplements. *Gastroenterol Hepatol Bed Bench* 2020;13(1):86–89.
[39] Bastola S, Kc O, Khanal S, et al. Hepatitis-associated aplastic anemia from workout supplement: rare but potentially fatal entity. *SAGE Open Med Case Rep* 2020;8:2050313X20901937.
[40] Richards JR, Scheerlinck PH, Owen KP, et al. Bodybuilding supplements leading to copper toxicity, encephalopathy, fulminant hepatic failure and rhabdomyolysis. *Am J Emerg Med* 2020;38(11):2487.e1–2487.e5.
[41] Villavicencio Kim J, Wu GY. Body building and aminotransferase elevations: a review. *J Clin Transl Hepatol* 2020;8(2):161–167.
[42] Andueza N, Giner RM, Portillo MP. Risks associated with the use of Garcinia as a nutritional complement to lose weight. *Nutrients* 2021;13(2):450.
[43] Bessone F, García-Cortés M, Medina-Caliz I, et al. Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI network. *Clin Gastroenterol Hepatol* 2022;20(3):e548–e563.
[44] Woo HJ, Kim HY, Choi ES, et al. Drug-induced liver injury: a 2-year retrospective study of 1169 hospitalized patients in a single medical center. *Phytomedicine* 2015;22(13):1201–1205.
[45] Nadir A, Agrawal S, King PD, et al. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. *Am J Gastroenterol* 1996;91(7):1436–1438.
[46] Neff GW, Reddy KR, Durazo FA, et al. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. *J Hepatol* 2004;41(6):1062–1064.
[47] Kuchta K, Cameron S, Lee M, et al. Which East Asian herbal medicines can decrease viral infections? *Phytochem Rev* 2022;21(1):219–237.
[48] Ma JX, Xiao X, Zhou KF, et al. Herb pair of Ephedrae Herba-Armeniacae Semen Amarum alleviates airway injury in asthmatic rats. *J Ethnopharmacol* 2021;269:113745.
[49] Hoofnagle JH, Bonkovsky HL, Phillips EJ, et al. HLA-B*35:01 and green tea-induced liver injury. *Hepatology* 2021;73(6):2484–2493.
[50] Hu J, Webster D, Cao J, et al. The safety of green tea and green tea extract consumption in adults—results of a systematic review. *Regul Toxicol Pharmacol* 2018;95:412–433.
[51] Dekant W, Fujii K, Shibata E, et al. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. *Toxicol Lett* 2017;277:104–108.
[52] Low EXS, Zheng Q, Chan E, et al. Drug induced liver injury: East versus West—a systematic review and meta-analysis. *Clin Mol Hepatol* 2020;26(2):142–154.
[53] Gandhi D, Ahuja K, Quade A, et al. Kratom induced severe cholestatic liver injury histologically mimicking primary biliary cholangitis: a case report. *World J Hepatol* 2020;12(10):863–869.
[54] Zheng E, Sandhu N, Navarro V. Drug-induced liver injury secondary to herbal and dietary supplements. *Clin Liver Dis* 2020;24(1):141–155.
[55] Woo SM, Davis WD, Aggarwal S, et al. Herbal and dietary supplement induced liver injury: highlights from the recent literature. *World J Hepatol* 2021;13(9):1019–1041.
[56] Lu H, Sheng R, Zhang C, et al. Comments regarding "Hepatotoxicity by combination treatment of temozolomide, artesunate and Chinese herbs in a glioblastoma multiforme patient: case report review of the literature.". *Arch Toxicol* 2017;91(6):2493–2494.
[57] Kaur P, Shergill R, Mehta RG, et al. Biofunctional significance of multi-herbal combination against paracetamol-induced hepatotoxicity in Wistar rats. *Environ Sci Pollut Res Int* 2021;28(43):61021–61046.
[58] Hoofnagle JH, Bjornsson ES. Drug-induced liver injury—types and phenotypes. *N Engl J Med* 2019;381(3):264–273.
[59] Pan X, Zhou J, Chen Y, et al. Classification, hepatotoxic mechanisms, and targets of the risk ingredients in traditional Chinese medicine-induced liver injury. *Toxicol Lett* 2020;323:48–56.
[60] Fontana RJ, Bjornsson ES, Reddy R, et al. The evolving profile of idiosyncratic drug-induced liver injury. *Clin Gastroenterol Hepatol* 2023;21(8):2088–2099.
[61] Allison R, Guraka A, Shawa IT, et al. Drug induced liver injury—a 2023 update. *J Toxicol Environ Health B Crit Rev* 2023;26(8):442–467.
[62] Carpenter S, O'Neill LAJ. From periphery to center stage: 50 years of advancements in innate immunity. *Cell* 2024;187(9):2030–2051.
[63] Wang JB, Song HB, Ge FL, et al. Landscape of DILI-related adverse drug reaction in China Mainland. *Acta Pharm Sin B* 2022;12(12):4424–4431.
[64] Yu YC, Mao YM, Chen CW. Guidelines for the management of drug-induced liver injury. *J Prac Hepatol* 2017;20(2):257–274.
[65] Lucena MI, Andrade RJ, Fernández MC, et al. Determinants of the clinical expression of amoxicillin-clavulanate hepatotoxicity: a prospective series from Spain. *Hepatology* 2006;44(4):850–856.
[66] Molleston JP, Fontana RJ, Lopez MJ, et al. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. *J Pediatr Gastroenterol Nutr* 2011;53(2):182–189.
[67] Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology* 2009;49(6):2001–2009.
[68] Wang JB, Zhu Y, Bai ZF, et al. Guidelines for the diagnosis and management of herb-induced liver injury. *Chin J Integr Med* 2018;24(9):696–706.
[69] Wang JB, Li CY, Zhu Y, et al. Integrated evidence chain-based identification of Chinese herbal medicine-induced hepatotoxicity and rational usage: exemplification by Polygonum Multiflorum (He Shou Wu). *Chin Sci Bull* 2016;61(9):971–980.
[70] Xiao XX, Tang JY, Mao YM, et al. Guidance for the clinical evaluation of traditional Chinese medicine-induced liver injury-Issued by China food and drug administration. *Acta Pharm Sin B* 2019;9(3):648–658.
[71] Philips CA, Theruvath AH, Ravindran R, et al. Complementary and alternative medicines and liver disease. *Hepatol Commun* 2024;8(4):e0417.
[72] Guo ZJ, Li P, Wang CG, et al. Five constituents contributed to the Psoraleae Fructus-induced hepatotoxicity *via* mitochondrial dysfunction and apoptosis. *Front Pharmacol* 2021;12:682823.

[73] Tu C, He Q, Li CY, et al. Susceptibility-related factor and biomarkers of dietary supplement Polygonum multiflorum-induced liver injury in rats. *Front Pharmacol* 2019;10:335.
[74] Zhang ML, Zhao X, Li WX, et al. Yin/Yang associated differential responses to Psoralea corylifolia Linn. In rat models: an integrated metabolomics and transcriptomics study. *Chin Med* 2023;18(1):102.
[75] Rao T, Liu YT, Zeng XC, et al. The hepatotoxicity of Polygonum multiflorum: the emerging role of the immune-mediated liver injury. *Acta Pharmacol Sin* 2021;42(1):27–35.
[76] Tu C, Jiang BQ, Zhao YL, et al. Comparison of processed and crude Polygoni Multiflori radix induced rat liver injury and screening for sensitive indicators. *Zhongguo Zhong Yao Za Zhi* 2015;40(4):654–660.
[77] Wang J, Ma Z, Niu M, et al. Evidence chain-based causality identification in herb-induced liver injury: exemplification of a well-known liver-restorative herb Polygonum multiflorum. *Front Med* 2015;9(4):457–467.
[78] Zhang L, Niu M, Wei AW, et al. Clinical correlation between serum cytokines and the susceptibility to Polygonum multiflorum-induced liver injury and an experimental study. *Food Funct* 2022;13(2):825–833.
[79] Zhang L, Niu M, Wei AW, et al. Risk profiling using metabolomic characteristics for susceptible individuals of drug-induced liver injury caused by Polygonum multiflorum. *Arch Toxicol* 2020;94(1):245–256.
[80] Wang JB, Cui HR, Bai ZF, et al. Precision medicine-oriented safety assessment strategy for traditional Chinese medicines: disease-syndrome-based toxicology. *Yao Xue Xue Bao* 2016;51(11):1681–1688.
[81] Tu C, Ge FL, Guo YM, et al. Analysis of clinical characteristics and medication rationality of Polygonum Multiflorum Thunb. and its preparation-related liver injury. *Chin J Pharmacov* 2019;16(5):270–276.
[82] Guo YM, Tu C, He Q, et al. Safety administration strategy for Heshouwu (Polygoni Multiflori Radix) based on properties and actions of Chinese medicine. *J Tradit Chin Med* 2018;59(9):721–724.
[83] Li C, Rao T, Chen X, et al. HLA-B*35:01 allele is a potential biomarker for predicting Polygonum multiflorum-induced liver injury in humans. *Hepatology* 2019;70(1):346–357.
[84] Aithal GP. Of potions, poisons, Polygonum, and pre-emptive polymorphism. *Hepatology* 2019;70(1):8–10.
[85] Zhang L, Liu X, Tu C, et al. Components synergy between stilbenes and emodin derivatives contributes to hepatotoxicity induced by Polygonum multiflorum. *Xenobiotica* 2019;50(5):515–525.
[86] Li C, Niu M, Bai Z, et al. Screening for main components associated with the idiosyncratic hepatotoxicity of a tonic herb, Polygonum multiflorum. *Front Med* 2017;11(2):253–265.
[87] He L, Yin P, Meng Y, et al. Immunological synergistic mechanisms of trans-/cis-stilbene glycosides in Heshouwu-related idiosyncratic liver injury. *Science Bulletin* 2017;62(11):748–751.
[88] Qin N, Xu G, Wang Y, et al. Bavachin enhances NLRP3 inflammasome activation induced by ATP or nigericin and causes idiosyncratic hepatotoxicity. *Front Med* 2021;15(4):594–607.
[89] Gao Y, Xu G, Ma L, et al. Icariside I specifically facilitates ATP or nigericin-induced NLRP3 inflammasome activation and causes idiosyncratic hepatotoxicity. *Cell Commun Signal* 2021;19(1):13.
[90] Wang Z, Xu G, Zhan X, et al. Carbamazepine promotes specific stimuli-induced NLRP3 inflammasome activation and causes idiosyncratic liver injury in mice. *Arch Toxicol* 2019;93(12):3585–3599.
[91] Wang Z, Xu G, Gao Y, et al. Cardamonin from a medicinal herb protects against LPS-induced septic shock by suppressing NLRP3 inflammasome. *Acta Pharm Sin B* 2019;9(4):734–744.
[92] BCPM CACM, BHD CACM, CCCP CPA, et al. Guidelines for safe use of Polygoni Multiflori radix. *Zhongguo Zhong Yao Za Zhi* 2020;45(5):961–966.
[93] Song D, Chen SS, Li PY, et al. Attenuating the potential hepatotoxicity of Psoraleae Fructus by pre-processing: the alcohol soaking and water rinsing method. *Yao Xue Xue Bao* 2020;55(2):276–282.
[94] Gao D, Pang JY, Zhang CE, et al. Poria attenuates idiosyncratic liver injury induced by Polygoni Multiflori radix praeparata. *Front Pharmacol* 2016;7:386.
[95] Han T, Xu W, Wang X, et al. Emodin-8-O-β-D-glucopyranoside-induced hepatotoxicity and gender differences in zebrafish as revealed by integration of metabolomics and transcriptomics. *Phytomedicine* 2024;128:155411.
[96] Gao D, Li XF, Yin P, et al. Preliminary study on hepatotoxic components in Polygoni Multiflori radix based on processing and toxicity-decreasing. *Chin Tradi Herb Drugs* 2017;48(10):2044–2050.
[97] Li RY, Feng WW, Li XF, et al. Influence of metal ions on stability of 2,3,5,4'-tetrahydroxy stilbene-2-O-β-D-glucoside contained in Polygoni Multiflori radix. *Yao Xue Xue Bao* 2016;51(1):116–121.