

# Chinese Herbal Medicine-induced Liver Injury

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## Abstract

The widespread use of Chinese herbal medicine (CHM) and the associated adverse reactions has attracted the attention of researchers and physicians. Reports have shown that several types of CHM can cause liver injury, with increasing numbers of cases reported every year. The difficulty in characterizing CHM-induced liver injury stems from clinical manifestations, diagnosis and pathogenesis. The clinical manifestations are varied, but gastrointestinal symptoms are the majority. The Council for International Organizations of Medical Sciences scale is currently the most commonly used method for assessing causality in cases of medicine-induced liver injury with excellent sensitivity, specificity and predictive validity. However, the pathogenesis of CHM-induced liver injury is not well understood. The classic view encompasses a contribution from "toxic metabolites" that either elicit an immune response or directly affect cellular biochemical processes or functions. In addition, poor quality and inappropriate clinical use of CHMs contribute to safety concerns. To ensure the safe use of CHMs and decrease the number of hepatotoxic cases, clinicians, researchers and pharmaceutical companies should share responsibility by regulating clinical use, strengthening basic toxicology research and establishing a strict quality control system.

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## Introduction

For thousands of years, herbs have been used to treat disease in China. Based on the prolonged experience and the original treatment principles, traditional Chinese medicines, which include pharmacy components, are being used in clinics today as an alternative and complementary option to modern Western medicine. Many herbal medicines are commonly used to treat the elderly, pregnant women, and children. Nearly 1.5 million people in the United States have tried herbal treatments, with an annual cost as much as \$1.5

billion.<sup>1</sup> The use of traditional Chinese medicine has been popular in Germany since the 1980s, and more than 58% of the German population use herbal remedies,<sup>2</sup> which are accessible in pharmacies.

Reports involving adverse reactions caused by Chinese herbal medicine (CHM) have gradually emerged. In recent years, clinical cases and laboratory data have shown that CHMs and their preparations may cause varying degrees of liver damage. Therefore, an understanding of herbal hepatotoxicity and rational use of CHM is of great importance. The aims of this review were to discuss clinical cases of liver injury caused by CHM, describe the diagnosis, clinical patterns and mechanisms of hepatotoxicity, explore the common causes of adverse reactions, detail current shortcomings and make suggestions for future prospects.

## Clinical overview

### Reported cases

A comprehensive analysis of Chinese academic journals indicated that of the 9355 total cases of drug-induced liver injury (DILI) reported between 2001 and 2010, approximately 20% of these (1979 cases) were associated with herbs.<sup>3</sup> Another report by Jie *et al.* examining 337 cases of DILI from 2009 to 2012 found that 44.2% of the cases of liver injury were caused by CHM.<sup>4</sup> Although the incidence rates of herbal drug-induced liver injury (HILI) are different among the various regions of China, the percent of CHM-induced liver injury from literature published in 2013 ranged from 26.4 to 49%. These data indicate that CHM-induced liver injury in China is an issue that cannot be ignored. Although there are fewer relevant reviews and case reports of liver injury caused by herbal medicine from other countries, the annual average number of herbal hepatotoxicity-related publications in PubMed has increased from 4.2 in 1990–1999 to 9.9 in 2000–2009. There are currently 185 articles, and nearly 60 kinds of herbs implicated in possible liver damage.<sup>5</sup> Based on available data of DILI cohorts from the US and Europe, herbal products may be a cause of hepatotoxicity in 2–11% of patients with DILI, and in 5–10% of patients with drug-induced acute liver failure.<sup>6</sup>

### Clinical characteristics

In general, compared with Western medicine, liver damage caused by CHM develops slowly with clinical symptoms appearing within one week to one month.<sup>7</sup> The clinical manifestations can be classified as acute hepatitis, sub-acute hepatitis, and cirrhosis. Clinical symptoms such as fatigue

**Keywords:** Chinese herbal medicine; Liver injury.

**Abbreviations:** CHM, Chinese herbal medicine; CIOMS, Council for International Organizations of Medical Sciences; DILI, drug-induced liver injury; HILI, herbal drug-induced liver injury.

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(67.3%), jaundice (60.3%), anorexia (58.0%), nausea (35.9%), and fever (19.3%) are more common, but signs such as rash, pruritus and clay-colored stools have also been reported.<sup>8</sup> CHM-induced liver injury can also develop into liver failure. A study of 418 patients with DILI by Teng *et al.* reported 81 cases of liver failure, 19.4% of which had clinical manifestations similar to those caused by viral or alcoholic hepatitis.<sup>8</sup> Investigations regarding HILI also suggest that women are more susceptible,<sup>4,9</sup> especially for those 60–65 years of age.<sup>10</sup> The susceptibility may be due to age- and sex-related differences in hepatic microsomal enzyme activity.

### Diagnosis

Because of the variety of clinical features and time of onset, there is no gold standard for diagnosing DILI or CHM-induced liver injury. The Council for International Organizations of Medical Sciences (CIOMS) scale is the most commonly used method for assessing causality in cases of DILI<sup>11</sup> and HILI,<sup>12</sup> and is currently considered as the best causality assessment method. For physicians treating a patient with suspected DILI or HILI, the CIOMS scale can be used to prospectively collect all necessary parameters without requiring an expert panel.<sup>13</sup> Compared to other assessment methods, including the Maria-Victorino scale,<sup>14</sup> Aithal and Day method,<sup>15</sup> Aithal, Rawlins, and Day method,<sup>16</sup> and Takikawa, Takamori, and Kumagi scale,<sup>17</sup> the CIOMS scale offers excellent sensitivity, specificity and predictive validity (based on cases with positive re-exposures).<sup>18</sup> Due to the complexity of Chinese medicinal ingredients, it is difficult to determine the reference data on herbal hepatotoxicity, and thus misdiagnoses and missed diagnoses are more likely to occur. Therefore, the clinical diagnosis of liver injury caused by herbal medicine focuses more on medical and medication histories. Physicians should first make a comprehensive comparison of clinical manifestations and related enzymology indices before, during and after treatment, followed by a diagnosis of exclusion. The important conditions to exclude are hepatitis A, B, and C, alcoholic liver disease, biliary obstruction, and liver injury due to ischemia or other medications.<sup>19</sup> Although causality assessment methods, such as the CIOMS scale, are better approaches for reaching the correct diagnosis of DILI and HILI than liver histology,<sup>20</sup> liver biopsy should still be considered as a final diagnostic approach in rare instances of diagnostic uncertainty.

### CHM that have been linked to hepatotoxicity

The following CHMs reportedly can cause liver injury: *Dioscorea bulbifera*, *Gynura segetum*, *Fructus xanthii*, *Polygonum multiflorum*, *Tripterygium wilfordii* Hook F, *Folium artemisiae argyi*, *Occidentalis*, *Atractylodes lancea*, trichosanthin, *Loranthaceae*, *Cyrtomium fortunei*, cattail pollen, ephedra, *Bupleurum*, *Folium senna*, centipede, *Albizia julibrissin*, clove, *Fructus toosendan*, *Brucea javanica*, *Ilex pubescens*, castor beans, *Veratrum nigrum*, *Salvia miltiorrhiza*, *Papaver somniferum*, *Rhizoma Pinelliae*, *Alisma orientalis*, rhubarb, *Polygonum cuspidatum*, groundsel, Menispermaceae, *Dysphania ambrosioides*, nutmeg, *Phytolacca acinosa*, antipyretic *Dichroa*, chaulmoogra, cinnamon, *Rafetus swinhoi*, pangolin, *Scutellaria*, valerian, aconite, and ginkgo.<sup>21</sup> The known hepatotoxic components in CHM can be divided into five categories according to their chemical structures: alkaloids, terpenoids, glycosides, toxic proteins,

and tannins.<sup>22</sup> Some of the most common CHMs that cause hepatotoxicity are shown in Table 1.

### The pathogenesis of liver injury caused by CHM

Although little is known about the pathogenesis of CHM-induced liver injury, there are various theories on the pathogenesis of DILI, including the participation of “toxic metabolites” that either elicit an immune response or directly affect cellular biochemical processes or functions.<sup>23</sup>

#### Direct toxicity

Drugs are generally safe when given at recommended doses. However, the intrinsic toxicity of a drug at higher doses is a major cause of acute liver failure and transplantation.<sup>24</sup> DILI is initiated by direct hepatotoxic effects of a drug or its reactive metabolites.<sup>25</sup> Hepatocyte death, which can be either apoptotic or necrotic,<sup>26</sup> is the primary outcome, although bile duct epithelium or sinusoidal endothelial cells may also be involved in liver injury.<sup>27</sup> *Dioscorea bulbifera* L. presents a classical example of direct liver injury.<sup>28</sup> It has been shown that diosbulbin from *Dioscorea bulbifera* L. causes excessive exhaustion of liver glutathione amounts, and reduces levels of normal liver antioxidants, resulting in oxidative stress injury.<sup>29</sup> The reactive oxygen species produced during oxidative stress can modify and inactivate lipids, proteins, DNA, and RNA, and thus lead to apoptotic or necrotic cell death.<sup>30</sup>

#### Idiosyncratic reactions

The majority of adverse liver reactions are idiosyncratic, occurring in most instances 5–90 days after the causative medication was last taken. Such idiosyncratic reactions can be divided into metabolic and immune idiosyncrasy. Metabolic idiosyncrasy is often associated with genetic polymorphisms of cytochrome P450. Electrophilic and free radical metabolites are produced by the activation of cytochrome enzymes, and levels of intermediate metabolites, protein-DNA complexes and other metabolites are increased, which can form toxic metabolites that cause liver damage.<sup>31</sup> In this mechanism, the alkaloids mentioned above produce toxic metabolites resulting in liver toxicity. Pyrrolizidine alkaloids in *Sedum aizoon* and *Senecio* are transformed by cytochrome P450 into unstable toxic metabolites, which damage sinusoidal endothelial cells and cause blood disorders.<sup>32</sup>

Immune-mediated idiosyncratic liver injury can be seen as an immune response. Drugs or their metabolites act as haptens and are processed by immunocompetent cells and converted to new antigens. These antigens then stimulate the body to produce antibodies that can induce an immune response and cause liver damage. It has been shown that *Tripterygium wilfordii* can cause unpredictable liver injury, which has a certain relationship with the activation of Kupffer cells in the liver and the release of large amounts of tumor necrosis factor and carbon monoxide.<sup>33</sup> Because liver injuries caused by idiosyncratic reactions frequently have a long incubation period and are unpredictable, timely detection of liver damage and treatment is difficult, which results in adverse prognoses.

**Table 1. Most common Chinese herbal medicines with hepatotoxicity**

Chinese name	Scientific name	Family	Hepatotoxic components	Intended use	Most common form of hepatotoxicity
Ai Ye <sup>43</sup>	<i>Artemisia argyi</i>	Asteraceae	Volatile oil <sup>44,45</sup>	Malaria, hepatitis, cancer <sup>46</sup>	Hepatocellular <sup>45</sup>
Bi Ma Zi <sup>47</sup>	<i>Ricinus communis</i>	Euphorbiaceae	Toxic proteins (ricin) <sup>48</sup>	Ulcers, cancers, tumors, warts <sup>49</sup>	Hepatocellular <sup>50</sup>
Cang Er Zi <sup>51</sup>	<i>Xanthium</i>	Asteraceae	Glycosides (kaurene), diterpenoids, toxic proteins <sup>52</sup>	Asthma, allergies, nasal diseases <sup>53</sup>	Hepatocellular <sup>54</sup>
Chang Shan	<i>Dichroa febrifuga</i> Lour	Hydrangeaceae	Alkaloids (dichroine) <sup>55</sup>	Malaria, cancer, fibrosis, inflammatory diseases <sup>56</sup>	Hepatocellular <sup>57</sup>
He Huan Pi	<i>Albizia julibrissin</i>	Fabaceae	Glycosides (saponin) <sup>58</sup>	Insomnia, anxiety, depression <sup>59</sup>	Hepatocellular <sup>54</sup>
He Shou Wu <sup>60</sup>	<i>Polygonum multiflorum</i>	Polygonaceae	Anthraquinones <sup>61</sup>	Baldness, hair loss <sup>62</sup>	Hepatocellular <sup>63</sup>
Huang Yao Zi <sup>64</sup>	<i>Dioscorea bulbifera</i> L.	Dioscoreaceae	Glycosides(steroid, diosgenin), <sup>65</sup> diterpenoid-lactones (bafoudiosbulbins A and B) <sup>66</sup>	Thyroid diseases, tumors <sup>67</sup>	Hepatocellular <sup>68</sup>
Ku Lian Zi <sup>69</sup>	<i>Melia azedarach</i>	Meliaceae	Glycosides (tetranortriterpenoids) <sup>69</sup>	Skin diseases <sup>69</sup>	Hepatocellular <sup>69</sup>
Lei Gong Teng <sup>70</sup>	<i>Tripterygium wilfordii</i> hook F	Celastraceae	Glycosides (tripterygium), diterpenoid-lactones, <sup>71</sup> alkaloids (pyrrolizidine) <sup>71,72</sup>	Immune inflammatory diseases <sup>73</sup>	Hepatocellular <sup>74,75</sup>
Qian Li Guang <sup>76</sup>	<i>Senecio scandens</i>	Asteraceae	Alkaloids (pyrrolizidine) <sup>77</sup>	Inflammatory diseases <sup>78</sup>	Hepatocellular <sup>75</sup>
Shang Lu <sup>79</sup>	<i>Phytolacca acinosa</i> Roxb.	Phytolaccaceae	Alkaloids (phytolaccine), glycosides (phytolaccatoxin, esculentoside A) <sup>80,81</sup>	Human immunodeficiency, viral diseases <sup>82</sup>	Hepatocellular <sup>81</sup>
Xiang Si Zi	<i>Abrus Precatorius</i>	Fabaceae	Toxic proteins (abrin) <sup>83</sup>	Cancers <sup>84</sup>	Hepatocellular <sup>85</sup>

## Factors contributing to CHM-induced liver injury

### Misunderstanding of CHM

The most frequent factor involved in CHM-induced liver injury is a misunderstanding of CHM. The public generally regards CHM as "natural" and "safe". However, the earliest Chinese medical classic "The Inner Canon of Huangdi" classifies CHMs as having high, moderate, or low toxicity, or as being nontoxic. Furthermore, recent toxicologic studies found that some chemical compositions of the herbs classified as nontoxic can cause liver toxicity.<sup>34</sup>

### Misuse, abuse and overdose

Liver injury caused by the misuse or abuse of CHM and some folk remedies is common. Clinical data showed that of the 427 cases of liver injury at the Beijing Ditan Hospital that were caused by CHM, two cases were due to accidental ingestion, and in 62 cases, the medications were taken without a prescription.<sup>35</sup> In another 25 cases of HILI caused by *Fallopia multiflora*, excessive dosage was the suspected cause in ten patients.<sup>36</sup>

### Poor quality

The quality of the drug is one of the most important factors affecting CHM safety. CHMs are likely contaminated during the process of growth, collection, storage, transportation and manufacture.<sup>37</sup> Uncontrolled processing can also result in the production of toxic components. For example, cocklebur is usually stir-fried before use in the clinic. Both reduced frying time and uneven heating can lead to toxicity by incomplete degeneration of the toxic protein.<sup>38</sup>

### Improper compatibility of medicines

Compatibility means that two or more kinds of herbs can be used in any combination to achieve the most effective and safe treatment through the interactions among them. On the other hand, incompatibility can not only reduce the effectiveness, but also increase toxicity. The compatibility can significantly reduce the extent of liver cell damage via the antagonism of *Angelica* against *Dioscorea bulbifera* L. on mRNA expression levels of CYP2E1 and CYP1A2.<sup>39</sup>

These situations can be improved by increasing public awareness, precise diagnosis and treatment, and strict quality supervision. However, the adverse reactions due to differences in sensitivity, reactivity, and tolerance of individuals still may not effectively be controlled.

### Future improvements and prospects

The growing number of clinical case reports and laboratory research results clearly shows that some Chinese herbs have a certain liver toxicity. Studies on the diagnosis, treatment and mechanism have not kept pace. Not only doctors and researchers, but also the media and pharmaceutical companies, should share the responsibility to avoid CHM-induced liver injury and to use herbs safely. These issues deserve attention in future studies.

## Limitations of diagnosis

Due to the lack of specific diagnostic criteria, there exists a certain degree of difficulty in diagnosing liver injury caused by CHM, resulting in misdiagnoses or missed diagnoses, as well as delays in treatment.<sup>40</sup> On the other hand, because of the limitation in the diagnosis, in some clinical reports, a past medical history of CHM is sometimes the only clue to the diagnosis.<sup>41</sup> The European Medicines Agency assessed 31 spontaneous cases of assumed HILI by black cohosh reported from countries within the European Union. Following the application of the CIOMS scale, only one case of suspected HILI from black cohosh remained, equivalent to 3% of the reported cases.<sup>42</sup> Therefore, the establishment of diagnostic criteria is a top priority, and for doctors, the knowledge and understanding of the pathogenesis, clinical manifestations and treatment will also assist in detecting liver injury and administering timely and effective treatment.

## Development of toxicology studies

Toxicology studies on CHM are still limited, and further research is needed. The focus of future studies should be on determination of toxic doses, and limiting of doses, providing important reference for rational herbal medicine use.

## Dissemination of the standardized application of CHM

The public awareness of CHM also needs to be improved. This is the responsibility of the public media and the government. Public media needs to educate the public on the rational use of medicinal herbs, and national regulatory authorities should monitor the quality of the herbs, strictly regulate the doses of medicine, and make regulations to forbid non-prescription remedies.

## Conclusions

With the popularity of traditional Chinese medicine in the global market, adverse reactions caused by CHM are increasing. CHM-induced liver injury presents many clinical patterns and clinical manifestations. There is still no gold standard for diagnostic criteria. Advances in the understanding of the frequency, the clinical manifestations and the pathogenesis can improve the accuracy of diagnosis and improve the safety of CHM.

## Conflict of interest

None

## Author contributions

Writing the article (XM), polishing the manuscript (YYH), polishing and organizing the manuscript, revising the manuscript and replying the reviewer's advice (JHP).

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