Review

Herbal Medicine-Induced Liver Injury in China

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Key Words

Herbal medicine · Liver injury · Traditional Chinese Medicine

Abstract

Herbal medicine (HM) has been widely used to prevent and treat diseases for thousands of years. However, recent increasing evidence shows that HM-induced liver injury (HILI) is not something to be ignored. In fact, herbal toxicity has always been recognized and emphasized in the long history of Traditional Chinese Medicine. In this article, we analyzed the situation of HILI in China and its risk factors in detail. In addition, the legal regime of the HM industry in contemporary China is introduced. Recently, the mechanisms of HILI have been widely studied, and epidemiological investigations into HILI have been conducted. In the future, a comprehensive platform for research and communication could help facilitate the development of strategies to predict and prevent HILI.

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Patterns, Regulations and Safety Assessment for Herbal Medicine

In China, herbal medicine (HM), the main part of Traditional Chinese Medicine (TCM), has been used for the treatment of various diseases for more than 3,000 years. Most Chinese people have experiences with using HM to prevent and treat diseases, in the form of herbal slices, herbal extracts, fractions or active ingredients in order to meet the different patient

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needs. Various kinds of Chinese HM are used in the clinic, such as traditional decoctions, granules, tablets, capsules, pills, injections and others.

The World Health Organization (WHO), the specialized agency of the United Nations that is concerned with international public health, published quality control methods for medicinal plant materials in 1998 in order to support WHO member states in establishing quality standards and specifications for herbal materials, within the overall context of quality assurance and control of HM. In China, a wholesome legal regime for the HM industry has been established. The China Food and Drug Administration (CFDA), an important government agency, is responsible for drafting the laws and setting up the regulations as well as the rules and policy plans for the administration and supervision of TCM. Directly affiliated to the CFDA, the Chinese Pharmacopoeia Commission is responsible for drafting and revising the Chinese Pharmacopoeia and its addendums. Seventy toxic herbs have been listed in the Chinese Pharmacopoeia 2010 edition with respective standards and precautions; it is thus a systematic guideline for the use of HM [1]. Additionally, the State Administration of TCM plays a key role in the formulation of strategies, plans, policies and relevant standards for the development of TCM and ethnic medicines.

Similar to chemical or biological drugs, the registration and safety assessments of Chinese patent medicine undergo a strict procedure. In order to register a Chinese patent medicine, manufacturers are required to prove the safety and efficacy of their product and to provide a large number of files and research data which include general information as well as data on pharmacology, pharmaceutics, toxicology, clinical trials and more. Additionally, postmarketing surveillance of the safety of Chinese patent medicine is conducted by China's National Center for Adverse Drug Reaction Monitoring [2], which operates as a system of passive surveillance, to which doctors or the general public can voluntarily report adverse reactions to drugs.

The Situation of HM-Induced Liver Injury

From the earliest records of the use of medicine until today, the toxicity of certain substances has been described. In fact, herbal toxicity has always been recognized and emphasized in the long history of TCM. Shannon's Herbal Classic, China's earliest (from the Han dynasty) medical monograph of TCM, recorded 365 herbs divided into three grades: top, middle and lower grade. The lower-grade herbs included 125 mostly toxic species for the treatment of fever, infections as well as tumors; these should be used with caution and never for a long period. Lately, the Chinese Pharmacopoeia 2010 edition has recorded 70 toxic herbs in total, including 10 species with high toxicity, 42 with middle toxicity and others with low toxicity [1]. Since TCM has become more popular in the Western world, there are increasing concerns about the potential toxicity of plants, animal parts and minerals included in TCM. In recent years, more and more cases of HM-induced liver injury (HILI) have been reported. A multicenter investigation has revealed that the drugs most commonly causing drug-induced liver injury (DILI) are TCM (21.5%) and antituberculosis drugs (21.2%) [3]. Another comprehensive article conducted by Zhou et al. [4] concluded that 18.6% of cases of drug-induced liver damage were attributed to Chinese HM. In addition, the systematic analysis report has listed Chinese patent medicine related to DILI, such as *Xiao He Pian* or *Zhuang Gu Guan Jie Wan*. Hepatotoxicity has been reported with products containing *Polygonum multiflorum* (*He Shou Wu*), *Senecio* (*Qian Li Guang*), *Symphytum* (*Xi Men Fei Cao*), *Dictamnus dasycarpus* (*Bai Xian Pi*) and others [5]. Although the hepatotoxicity of most HM could be confirmed, none of the currently used causality assessment tools were developed specifically for HM [6].

Establishing a causal relationship between the use of HM and liver injury is challenging. However, several risk factors have been associated with HILI. A systematic review [7] has shown that adulteration and contamination of HM is a very common phenomenon, especially in the cases of *Herba ephedrae* (*Ma Huang*), *Fructus Aristolochiae* (*Ma Dou Ling*), *Glycyrrhizae radix et rhizoma* (*Gan Cao*), and others. It may reduce the effectiveness but increase the harmfulness of HM for humans. Besides, inappropriate processing and extraction of materials may also lead to liver injury. For the nonclinical study factor, species differences between humans and animals bring great pressure for monitoring clinical trials and the toxicity of new drugs after being released for sale. Prediction of the drug metabolism in humans based on animal experiments is less persuasive. Otherwise, the improper use of herbs can cause liver damage, including prolonged duration, overdosing and drug combination. Due to genetic variations, environmental and interindividual differences, people who suffer from allergies and chronic liver disease (i.e. viral hepatitis or autoimmune hepatitis) have a higher risk of HILI.

Perspective on the Research of HILI

In China, where there is an increase in the attention to DILI, the regulations and provisions of Chinese HM have been updated and modified. The Chinese Pharmacopoeia 2015 edition further improved the drug safety guarantee, formulated standards for sulfur dioxide residues in TCM and set up standard safety limits for harmful elements in marine drugs such as pearl and seaweed [8].

Efforts must be taken to avoid liver injury in clinical trial design and application evaluations. For the trial design and premarketing evaluation, all toxicological experiments must be carried out in a laboratory with Good Laboratory Practice [9], and researchers should try to establish animal models that replicate the human disease, design a multiphase trial to evaluate drug safety and monitor drug hepatotoxicity by shortening the test intervals or increasing the parameters of liver function. The toxicity of herbal substances, their metabolic pathways and mechanisms have been extensively studied in recent years in China; one good example are the herbs containing hepatotoxic pyrrolizidine alkaloids such as *Senecio*. Prof. Wang's team [10, 11] found that the pyrrolizidine alkaloids could cause sinusoidal obstruction syndrome, macrocytosis and fibrosis. Drug-drug interactions may become an important new area for future research, in particular between herbal products and biochemical drugs. Our research team [12] has shown that Fuzheng Huayu combined with entecavir (ETV) has an advantage in the prevention and treatment of liver fibrosis and inflammation over ETV monotherapy with no effect on the safety and pharmacokinetics of ETV. In order to strengthen postmarketing safety surveillance, the administrative department should encourage more phase IV clinical trials. It is necessary to update the instruction information of HM drugs and the bulletin safety reports about adverse drug effects. Once safety problems occur, the products on the market must be recalled and the drug production suspended.

Facing this harsh situation, the Chinese Government has agreed to set up a committee or teams to develop related research on epidemical investigation, early warning, clinic diagnosis and treatment, toxic substances and the mechanisms of HILI in China. Moreover, some comprehensive platforms for the research and communication of HILI have been established in recent years, such as HepaTox (<http://www.hepatox.org>), the China DILI website, launched in 2014 in order to identify, enroll and characterize cases of DILI. Further, the Shanghai Symposium about HILI was successfully held in April 2015, aiming to set up TCM association related to DILI and to use HM more safely and efficiently. Despite these difficult conditions, Chinese doctors and scientists will take ongoing efforts to investigate and cope with the

difficult problem of HILI. In future, they aim to achieve tremendous breakthroughs with the prediction, diagnosis and prevention of HILI due to the progress of science and the multi-center, multidisciplinary collaborations.

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