Acupuncture and Herbal Medicine

Guidelines for safe use of Polygoni Multiflori Radix

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Abstract

Polygoni Multiflori Radix (He Shou Wu) is a Chinese medicine widely used in clinical treatment and preventive healthcare. However, recently there have been frequent reports of liver injury caused by Polygoni Multiflori Radix and its related preparations, and some patients have serious adverse outcomes, attracting wide attention worldwide. The risk of liver damage caused by preparations containing Polygoni Multiflori Radix or Polygoni Multiflori Caulis has been repeatedly reported by the Chinese Food and Drug Administration. Fortunately, substantial progress has recently been made in revealing the basic properties, main causes, material basis, and molecular mechanism of Polygoni Multiflori Radix-related liver injury. The basic characteristics and biomarkers of susceptible people have been identified, indicating that Polygoni Multiflori Radix has the risk of inducing liver injury only in a few specific populations and is safe for most populations. This study provides a scientific basis for a correct and objective understanding of liver injury caused by Polygoni Multiflori Radix, and a reasonable formulation of safe medication measures for Polygoni Multiflori Radix and related preparations. The China Association of Chinese Medicine organized experts in relevant fields across the country to draft and formulate the "Guidelines for Safe Use of Polygoni Multiflori Radix" with the aim of helping the public and relevant institutions at home and abroad to scientifically understand, evaluate, and avoid the risk of liver injury; guide the rational use; protect the health rights and interests of consumers; and promote the healthy and sustainable development of Polygoni Multiflori Radix and related preparations. These guidelines were issued by the China Association of Chinese Medicine (No. T/CACM 1328-2019).

Keywords: Drug safety, Liver injury, Polygoni Multiflori Radix, Rational use, Traditional Chinese medicine

Introduction

Polygoni Multiflori Radix is a Chinese medicine widely used in clinical treatment and preventive healthcare. However, recently, there have been frequent reports of liver injury caused by Polygoni Multiflori Radix and its related preparations, and some patients have serious adverse outcomes, attracting wide attention worldwide. Recently, substantial progress has been made in the study of liver injury caused by Polygoni Multiflori Radix. The "Guidelines for safe use of Polygoni Multiflori Radix" (hereinafter referred to as "Guidelines") is designed to help medical and pharmaceutical professionals and the public recognize, assess, and avoid the risk of liver injury; guide the rational use; protect the health rights and interests of consumers; and promote the healthy and sustainable development of Polygoni Multiflori Radix and related preparation.

With the development of modern science and technology and the continuous deepening of research on the safety and rational application of Polygoni Multiflori Radix, these "Guidelines" will include relevant research progress in time, and continue to supplement, revise, and improve.

Scope

These "Guidelines" are applicable to Polygoni Multiflori Radix and the related preparations, and can be referenced for safe use of Polygoni Multiflori Caulis and the related preparations, mainly intended for use by medical services, drug research and development, administrative supervision, and other institutions and staff.

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Standardization of reference document

The following documents are essential for the application of these "Guidelines." For dated citations, only this version applies to these "Guidelines." For undated references, the most recent version (including all amendment orders) applies to these "Guidelines." Including: The 2015 edition of "Chinese Pharmacopoeia," "Guidance for the Clinical Evaluation of Traditional Chinese Medicine-Induced Liver Injury" issued by China Food and Drug Administration in 2018, "Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury" issued by China Association of Chinese Medicine in 2016, "Chinese Herbal Medicine Quality Evaluation Methodology Guidance" issued by China Association of Chinese Medicine in 2017, and "Guidelines for the Management of Drug-Induced Liver Injury" issued by Chinese Medical Association in 2015.

Terms and definitions

Drug-induced liver injury (DILI) is induced by drugs and their metabolites. It is a common adverse drug reaction that can lead to acute liver failure, and death in severe cases.

The basic information of Polygoni Multiflori Radix

Source and medicinal parts

Polygoni Multiflori Radix is the dried tuber of *Polygonum multiflorum* Thunb. The dried caulis of *P. multiflorum* Thunb., named Polygoni Multiflori Caulis, can also be used as a medicine.

The source of Polygoni Multiflori Radix is single, but there are still a few mixed counterfeits on the market, including *Stephania cepharantha* Hayata, *Polygonum cilinerve* (Nakai) Ohwi, *Pteroxygonum giraldii* Dammet Diels, and *Cynanchum auriculatum* Royle ex Wight. In addition, with the intention of selling hype, some business plant Polygoni Multiflori Radix or other plants in the humanoid mold, so that they grow to the so-called male and female Polygoni Multiflori Radix, humanoid Polygoni Multiflori Radix, which should be considered.

Processing method

According to the "Compendium of Materia Medica," the ancient processing methods of Polygoni Multiflori Radix were mainly "nine steaming and nine drying" or "nine steaming and nine exposing." The main purpose was to change the medicinal properties, increase the curative effect, and reduce the toxicity. Currently, different processing methods have been developed, which are mainly divided into black bean juice steaming and methods using atmospheric- and high-pressure steaming.

Medicinal properties, functions, and indications

Raw Polygoni Multiflori Radix is bitter, sweet, astringent, and mild; acts on the liver, heart, and kidney channels; detoxifies; disperses abscesses; interrupts malaria; and moistens the bowel. It is used to treat diseases, such as sore abscess, scrofula, rubella pruritus, chronic malaria, and intestinal dryness constipation.

Radix Polygonum Multiflorum Preparata is bitter, sweet, astringent, and mild; acts on the liver, heart, and kidney channels; nourishes the liver and kidney; invigorates blood; blackens hair; and strengthens bones and muscles. It is used for diseases and conditions, such as blood vacuity, yellowing, vertigo, tinnitus, premature graying of hair, sore waist and knee, limb numbness, uterine bleeding, and morbid leukorrhea.

Polygoni Multiflori Caulis is sweet and mild; acts on the heart and liver channels; with the effect of nourishing the heart and calming the mind, dispelling wind, and removing obstruction in the meridians. It is used to treat diseases and conditions, such as insomnia, dreaminess, blood deficiency, body pain, skin numbness, rheumatic arthralgia, and rubella pruritus.

Chemical components

Polygoni Multiflori Radix (He Shou Wu) components include stilbenes, anthraquinones, flavonoids, and phospholipids. The chemical composition of Polygoni Multiflori Caulis is similar to that of Polygoni Multiflori Radix; however, the stilbene and anthraquinone contents are lower than those in Polygoni Multiflori Radix.

Pharmacological action

Polygoni Multiflori Radix can decrease serum lipids, prevent atherosclerosis and aging, enhance immunity and neuroregulation, protect the liver, prevent inflammation, and promote hematopoietic cell formation. Polygoni Multiflori Caulis exhibits sedative, hypnotic, hypolipidemic, and anti-atherosclerotic activities.

Adverse reactions and safety evaluation of Polygoni Multiflori Radix

Analysis of ancient documents

There are 42 ancient medical documents recording Polygoni Multiflori Radix, 19 of which do not mention its toxicity, 20 of which report *P. multiflorum* as non-toxic, and three of which report *P. multiflorum* as toxic[1].

Polygoni Multiflori Radix was first recorded in *Materia Medica of the Kaibao Era* (开宝本草) in Song Dynasty, which stated, "Long-term use can lengthen muscles and bones, benefit the essence, and prolong life." Most medical books from the Tang Dynasty to the Ming Dynasty report that Polygoni Multiflori Radix is non-toxic and suggest that processing can reduce bias. Li Shizhen in the Ming Dynasty recorded in *The Compendium of Materia Medica* (本草纲目) that, "Polygoni Multiflori Radix is tonic medicine, with the effect of strengthening tendons and bones and blacking hair. It is neither cold nor dry, the effect is better than Rehmanniae Radix, Asparagi Radix, and other medicines… Li Su, Emperor Sejong of Tang Dynasty, gave birth to several imperial heirs after taking Polygoni Multiflori Radix. As a result, Polygoni Multiflori Radix has become popular." Li Shizhen's deductive description of the beneficial effects of Polygoni Multiflori Radix made it popular worldwide, which may

also cause its abuse and misuse. However, during the late Ming and early Qing dynasties, physicians began to pay attention to and record the toxicity of Polygoni Multiflori Radix. In the late Ming Dynasty, Ni Zhumo's Treasury of Words on the Materia Medica（本草汇言） recorded that, "Polygoni Multiflori Radix is bitter, warm, and slightly toxic, and further explained that, "Although predecessors have said that Polygoni Multiflori Radix could prolong life and promote fertility, this may not be true. Frequent cases of illness and death caused by Polygoni Multiflori Radix have not been recognized and treated. The reason may be that people take Polygoni Multiflori Radix without being aware of its toxicity"[2]. Chen Xiuyuan in the Qing Dynasty recorded in *Shennong's Materia Medica*（神农本草经） that, "The taste of Polygoni Multiflori Radix is very astringent, and astringent is enough to block the road of malaria and evil... If it is used in the initial stage of malaria, this is like closing doors to expel the aggressors, the harm is unspeakable... I have witnessed a great deal of victims in the past 20 years. As a physician, I am entrusted with the mission of safeguarding the well-being of humanity, and thus I dare not shy away from the honorable pursuit of seeking truth"[3]. In the book *Leng Lu Yi Hua*（冷庐医话）, written by the Qing Dynasty physician, Lu Yitian, there is a recorded case of poisoning caused by Polygoni Multiflori Radix. It states, "Within a few days of taking Polygoni Multiflori Radix, the patient died from diarrhea." The analysis suggests that, "Polygoni Multiflori Radix may be toxic, so one should be cautious when consuming it"[4]. It is evident that the adverse reactions of Polygoni Multiflori Radix were already discovered and documented in ancient times.

Adverse reaction notification

Over the past 20 years, there have been numerous reports, both domestically and internationally, regarding adverse reactions of liver damage caused by Polygoni Multiflori Radix and related preparations. These include raw Polygoni Multiflori Radix, Polygoni Multiflori Radix Praeparata, compound formulations, Chinese patent medicines, and healthcare foods containing Polygoni Multiflori Radix or Polygoni Multiflori Caulis[5–8].

Foreign countries have reported earlier and more frequent cases of liver damage associated with Polygoni Multiflori Radix. Literature reports on cases of Polygoni Multiflori Radix-induced liver injury can be found in countries, such as South Korea, Japan, Singapore, and the United Kingdom[9,10]. The Hepatotoxicity Drug Database LiverTox, issued by the U.S. National Library of Medicine, contains dedicated records of Polygoni Multiflori Radix[11]. In 2006, regulatory authorities in the United Kingdom, Australia, and Canada successively issued warnings regarding liver injury caused by Polygoni Multiflori Radix[12].

In China, reports of adverse reactions related to Polygoni Multiflori Radix and related preparations rank among the top traditional Chinese medicines (TCM), with liver damage being the main concern. The national regulatory authority for food and drug supervision has also attached great importance to the safety issues of Polygoni Multiflori Radix, issuing multiple risk notifications regarding adverse reactions, such as liver damage, revising drug instructions, and strengthening supervision.

In October 2013, "Notice on the Revision of the Instructions of Six Oral Chinese Herbal Preparations Containing Polygoni Multiflori Radix," was issued, which involves Shouwu pill, Shouwu tablet, Baishi pill, Shouwu Yanshou tablet, Shouwu Yanshou granule, and Yangxue Shengfa capsule; the package inserts were revised to include additional safety information[13].

In July 2014, "Notice on Strengthening the Regulation of Health Food Containing Polygoni Multiflori Radix" was issued. It clearly stated that the daily consumption of raw Polygoni Multiflori Radix in health food shall not exceed 1.5 g, and that the daily consumption of Polygoni Multiflori Radix Praeparata shall not exceed 3.0 g. It is required that in the label of health food containing Polygoni Multiflori Radix produced after September 1, 2014, "People with liver dysfunction and family history of liver disease..... should be added to the unsuitable group of people. The precautions should include that, "This food contains Polygoni Multiflori Radix, cannot be taken in excess for a long time, and used in conjunction with hepatotoxic drugs. Please monitor the liver function while taking the food"[14].

In July 2014, "Notice on the Risk of Liver Injury by Peroral Polygoni Multiflori Radix," was issued[15].

In September 2014, "Notice on Matters Related to the Changes About Health Food Containing Polygoni Multiflori Radix," was issued, proposing registration change adjustment rules for reducing the amount of, replacing, or removing Polygoni Multiflori Radix in health food containing Polygoni Multiflori Radix[16].

In February 2018, "Announcement on Revising the Instructions of Four Varieties of Drugs Including Jingwu Capsule," was reported, suggesting that four preparations containing Polygoni Multiflori Radix or Polygoni Multiflori Caulis (Jingwu capsule, Bailemien capsule, Qibaomeiran pill, and Xinyuan capsule) have the risk of liver injury. Meanwhile, instructions for these preparations have been revised, and safety warnings have been added[17].

Clinical epidemiology analysis

According to domestic and foreign literature reports, adverse reaction reports, and clinical case analyses, the following can be found:

The adverse reactions to Polygoni Multiflori Radix and its related preparations are mainly manifested in the hepatobiliary and gastrointestinal systems, with symptoms, including fatigue, nausea, vomiting, loss of appetite, discomfort in the liver area, dry mouth, bitter mouth, itchy skin, yellow urine, yellow eyes, yellow skin, abdominal pain, diarrhea, abdominal distension, occasional rash, fever, and eye pigmentation[18]. Laboratory tests may show abnormal indicators, such as elevated aminotransferase and bilirubin levels.

The dosage and latency spans in patients with liver injury caused by Polygoni Multiflori Radix and related preparations are wide. Among them, the minimum dosage was 1 g/d to 3 g/d and the maximum was more than 100 g/d. The shortest incubation period was 1 to 3 days, the longest was more than half a year, and the median incubation period was approximately 20 days. There was no obvious correlation

between the dosage and duration of Polygoni Multiflori Radix treatment and the occurrence of liver injury, indicating that liver injury caused by Polygoni Multiflori Radix may be idiosyncratic and that a susceptible population may exist.

The proportion of females was slightly higher than that of males, with the ratio of males to females being approximately 1:1.16. The age of patients with liver injury caused by Polygoni Multiflori Radix and its preparations ranges from 8 to 87 years. The majority of male patients were 20 to 49 years old and mostly had diseases, such as alopecia and eczema. The majority of female patients were 40 to 59 years old, mostly with diseases, such as white hair and heart palpitations.

Cases of liver injury caused by Polygoni Multiflori Radix and its related preparations are mostly found in patients with diseases, such as alopecia seborrhea, white hair, eczema, psoriasis, vitiligo, rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus. Most of these are accompanied by immune or autoimmune diseases, suggesting that immune disorders may be an important risk factor for liver injury caused by Polygoni Multiflori Radix and its related preparations[19]. In addition, the prognosis of liver injury caused by Polygoni Multiflori Radix and related preparations is worse in patients with chronic liver disease (especially alcoholic liver disease) and is more likely to progress to chronic DILI and even cause death[20].

Polygoni Multiflori Radix is the Chinese herb with the highest number of reported cases of liver injury. Most patients consume Polygoni Multiflori Radix without a doctor's guidance, and the most commonly used methods include as a powder, tea, wine, and porridge. Most Polygoni Multiflori Radix products were not processed, and the degree of processing was unclear. In cases of liver injury caused by Polygoni Multiflori Radix and related preparations, approximately 20% of the patients received doses exceeding those prescribed in the instructions or pharmacopoeia, suggesting that large doses of Polygoni Multiflori Radix may increase the risk of liver injury.

Modern toxicological research

Routine toxicological studies have shown that no substantial hepatotoxicity has been observed in either raw or processed products or in different extracts within the range of the maximum tolerated dose in animal experiments, suggesting that it is safe to use Polygoni Multiflori Radix for people under normal circumstances[21,22].

Combined with disease-syndrome-based toxicology studies, it has been found that in susceptible animal models mediated by immune stress, Polygoni Multiflori Radix can promote overactivation of the body's immune system and induce liver injury within a range equivalent to common clinical doses[23]. The risk of liver injury induced by Polygoni Multiflori Radix can be reduced when used in combination with TCM, such as Poria and Glycyrrhizae Radix Et Rhizoma[24].

Combined with pharmacogenomic studies, it was confirmed that the liver injury caused by Polygoni Multiflori Radix was related to body factors, especially immune-related genetic differences. HLA-B* 35:01 has been reported to increase susceptibility to liver injury caused by Polygoni Multiflori Radix, indicating that Polygoni Multiflori Radix only poses a risk of liver injury in a very small number of specific populations but is safe for the vast majority of the population[25].

Using constituent knockout and knockin technology, it has been shown that idiosyncratic liver injury caused by Polygoni Multiflori Radix is related to the structure and content of stilbenes and anthraquinones. Under the state of immune overactivation, both cis-stilbene glycoside (cis-SG) and emodin 8-O-β-glucoside (EmG) in Polygoni Multiflori Radix can induce liver injury[26], and trans-SG can synergistically aggravate the hepatotoxicity[27–29]. Processing can reduce the hepatotoxicity of raw Polygoni Multiflori Radix[30], suggesting that strengthening the quality and safety of Polygoni Multiflori Radix is helpful in reducing the risk of liver injury.

Based on various research results, some scholars have proposed the "Tri-Element Injury Hypothesis" hypothesis (also known as the "firewood-oil-spark" hypothesis) to explain the mechanism of Polygoni Multiflori Radix-induced idiosyncratic liver injury. In a state of immune overactivation, immune-boosting substances (such as trans-SG) in Polygoni Multiflori Radix can further promote the body's immune response, making the liver more sensitive to liver injury-causing components in Polygoni Multiflori Radix (such as cis-SG and/or EmG) and inducing the production of inflammatory cytokines, leading to immune idiosyncratic liver injury[31–33].

Clinical manifestation and diagnosis of liver injury caused by Polygoni Multiflori Radix

Clinical manifestation

In general, liver injury caused by Polygoni Multiflori Radix and some related preparations has no specific clinical indices or pathological manifestations compared with most drug-induced liver injuries. The most common clinical type of Polygoni Multiflori Radix-related liver injury was hepatocyte injury (>90%), while cholestasis and the mixed type were relatively rare. The main pathological types are acute and cholestatic hepatitis, whereas chronic hepatitis is rare. Most patients have mild to moderate injury and a good prognosis (>80% of patients can heal themselves after drug withdrawal or recover after treatment). Some patients may progress to chronic liver injury, while others may suffer liver failure or even death[19–21,34–36].

The clinical manifestations of patients with liver injury caused by Polygoni Multiflori Radix and related preparations substantially varied, and some patients showed only abnormal liver biochemical indices without symptoms. Some patients experience symptoms, such as fatigue, loss of appetite, nausea, aversion to greasiness, gastric duct discomfort, liver pain, and abdominal distension. Cholestasis-type patients can have yellow skin and sclera, skin itching, and light-colored stool. A few patients develop symptoms of extrahepatic allergies.

Regarding clinical manifestations, DILI caused by Polygoni Multiflori Radix and its compound preparations are similar, with no substantial difference.

Clinical diagnosis

Owing to the lack of specific indicators, the diagnosis of DILI has always been a difficult problem in the field of hepatology. Liver injury caused by Polygoni Multiflori Radix and related preparations is no exception. Presently, for suspected liver injury induced by Polygoni Multiflori

Radix, the patient's feedback and exclusive diagnosis, excluding other liver diseases and drug-induced liver injuries, are important for the diagnosis of liver injury induced by TCM[37–39].

The clinical diagnosis of Polygoni Multiflori Radix-induced liver injury can be based on the "Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury," issued by China Association of Chinese Medicine, adopting the "integrated evidence chain method," developed by Chinese scholars to evaluate the causality of DILI, making differential diagnoses with other liver diseases, and excluding the influence of other drugs on the diagnostic results. The diagnostic conclusions are divided into "excluded diagnosis" "suspected diagnosis" "clinical diagnosis" and "confirmed diagnosis".

For the clinical trials and post-marketing re-evaluation of new drugs, the causal relationship between patients' liver injury and Polygoni Multiflori Radix and related preparations can be further determined by referring to the "Guidance for the Clinical Evaluation of Traditional Chinese Medicine-Induced Liver Injury," issued by China Food and Drug Administration; the causal relationship is divided into "excluded" "suspicious" "possible" "likely" and "confirmed".

Clinic treatment

For suspected liver injury caused by Polygoni Multiflori Radix and related preparations, the necessary clinical treatment can be performed according to the "Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury." The primary measures include drug withdrawal, drug therapy, and artificial liver support therapy.

Most patients with mild liver injury can return to normal liver function after discontinuing Polygoni Multiflori Radix and related preparations.

For patients with moderate or severe liver injury, after disusing Polygoni Multiflori Radix and related preparations, liver-protecting and anti-inflammatory drugs, including silymarin preparations, glycyrrhizic acid preparations, bicyclol, and antioxidant stress drugs, including glutathione and tiopronin, can be used. Drugs that promote bile secretion, such as ursodeoxycholic acid and adenosine-methionine, can be administered to patients with elevated bilirubin levels.

In addition to drug withdrawal and liver-protecting, anti-inflammatory, and symptomatic treatments, artificial liver support therapy can be considered for patients with severe liver injury or liver failure. Liver transplantation should be considered in patients with acute and/or subacute liver failure.

Risk prevention and control of liver injury induced by Polygoni Multiflori Radix

Liver injury caused by Polygoni Multiflori Radix and some related preparations is mainly related to body factors, and there is no obvious dependence on dose and course of treatment. It is characterized by serendipitous, occult, large individual differences, and is difficult to predict[40], which makes it difficult for ordinary consumers to scientifically and accurately assess and avoid the safety risks of Polygoni Multiflori Radix. According to the users' professional knowledge background and consumption needs, these "Guidelines" formulate targeted prevention and control countermeasures for the safety risk of Polygoni Multiflori Radix-induced liver injury.

Recommendation 1:

The publicity and education on the safe use of TCM, including Polygoni Multiflori Radix, should be strengthened. Consumers should purchase and use Polygoni Multiflori Radix and its products (including Polygoni Multiflori Caulis) under the guidance of doctors and pharmacists.

When Polygoni Multiflori Radix and related preparations are used in clinical treatments, they should be rationally used under the guidance of doctors. Based on the immuno-idiosyncratic properties of liver injury induced by Polygoni Multiflori Radix and the "Tri-Element Injury Hypothesis" mechanism hypothesis, the risk of liver injury induced by Polygoni Multiflori Radix and its related preparations can be avoided or reduced from three aspects: body factors, drug use, and quality control. For patients with susceptibility characteristics, particularly those with susceptibility biomarkers, Polygoni Multiflori Radix should be used with caution. Healthy foods containing Polygoni Multiflori Radix may also pose a risk of liver injury and should be used with caution.

For the research and development of new traditional Chinese drugs containing Polygoni Multiflori Radix, developers should conduct safety risk assessments for liver injuries. After approval, the drug marketing licensor should establish a safety risk-monitoring mechanism and risk control measures for the entire life cycle. For the detection, evaluation, supervision, and minimization of liver injury risk signals, please refer to the "Guidance for the Clinical Evaluation of Traditional Chinese Medicine-Induced Liver Injury," issued by China Food and Drug Administration.

Risk prevention and control recommendations based on body factors

Liver injury caused by Polygoni Multiflori Radix is immune idiosyncratic and mainly related to body factors. For the use of *P. multiflorum* and related preparations, the susceptible individuals could be identified based on basic diseases, immune status, TCM constitution and genetic background[19,25,41], combined with biomarkers[42–47], such as the HLA-B* 35:01 allele; inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF); and endogenous metabolites, including phenyllactic acid, crotonoyl-CoA, indole-5, and 6-quinone, promoting rational medicine use.

Recommendation 2:

The use of Polygoni Multiflori Radix in patients with diseases, such as seborrheic alopecia, white hair, eczema, psoriasis, vitiligo, rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, which are mostly accompanied by immune disorders or autoimmune diseases, is more likely to induce liver damage. It is recommended that Polygoni Multiflori Radix be used with caution for patients with the syndrome of fire excess from yin deficiency and interior dampness-heat. If necessary, it is suggested that, under the guidance of a doctor, nourishing *yin*, clearing heat, and draining dampness herbs should be used together with Polygoni Multiflori Radix to reduce the risk of liver injury.

The use of Polygoni Multiflori Radix should be avoided in, but not limited to, people with the syndrome of fire excess from yin deficiency or interior dampness-heat, HLA-B* 35:01 allele, and other abnormal levels of biomarkers.

Risk prevention and control recommendations based on drug use

Considering the different diseases and individual characteristics of patients, attention should be paid to factors affecting TCM-induced liver injury, such as indications, contraindications, dosage, course of treatment, and route of administration of Polygoni Multiflori Radix.

Recommendation 3:

There are substantial differences in the drug properties, efficacy, and toxicity between raw and processed Polygoni Multiflori Radix. In general, the toxicity of raw Polygoni Multiflori Radix is greater than that of Polygoni Multiflori Radix Praeparata, and the two cannot be combined.

For a small number of susceptible individuals, the higher the dosage and longer the course of treatment, the greater the risk of liver injury. It is recommended to use Polygoni Multiflori Radix according to the prescribed dosage range in the "Chinese Pharmacopoeia," and to monitor liver function with continuous medication for more than 20 days.

Repeated medication leads to dose superposition of Polygoni Multiflori Radix, which may increase the risk of liver injury. Different preparations or herbal decoctions containing Polygoni Multiflori Radix are recommended simultaneously. Polygoni Multiflori Radix should be avoided when used in combination with other medications that may cause liver damage.

Suggestions for risk prevention and control based on drug quality

Liver injury induced by Polygoni Multiflori Radix is related to the structure and content of stilbenes and anthraquinones; therefore, the quality and safety of Polygoni Multiflori Radix can be ensured by improving processing technology and quality control. It is recommended to establish the control methods and standards of cis-SG and EmG, the main susceptible substances causing liver injury in Polygoni Multiflori Radix, which is helpful for reducing the risk of liver injury[48–51]. Safety-oriented methods and standards for quality assessment and control of Polygoni Multiflori Radix and its related preparations can be established by referring to the "Chinese Herbal Medicine Quality Evaluation Methodology Guidance," issued by the China Association of Chinese Medicine.

Recommendation 4:

Improve the processing technology of Polygoni Multiflori Radix according to the quality and safety requirements. High-pressure steaming can be used to reduce the EmG content and improve product quality and safety; the EmG content should not exceed 0.17%.

In the preparation and preservation of related liquid preparations containing Polygoni Multiflori Radix, light should be avoided to prevent the formation of susceptible cis-SG substances, improving product quality and safety. The content of cis-SG should not exceed 0.1%.

Strictly control the pollution of pesticide residues, microorganisms, heavy metals, and foreign harmful substances; prevent the mildew of Polygoni Multiflori Radix during storage and transportation; and avoid fungal toxins, such as aflatoxin.

Perspective

Recently, the safety problems of TCM, including the liver injury induced by Polygoni Multiflori Radix, has aroused widespread concern, increasing people's doubts about the safety of TCM. However, currently, the safety of TCM is generally preventable and controllable. The population, including the government authority, social media professionals, or ordinary consumers, should have a scientific and sober understanding, neither exaggerating nor trivializing the safety of TCM. Additionally, we should vigorously popularize and publicize knowledge on the safe use, scientifically and rationally understand the safety problems, and constantly improve the awareness of safe drug use and self-protection consciousness of clinicians and consumers regarding TCM.

Through the formulation and implementation of this guideline, we hope to provide guidance and suggestions for medical professionals and the public to scientifically understand the objectivity of liver injury induced by Polygoni Multiflori Radix and its related preparations, for their safe use and healthy and sustainable development.

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Conflict of interest statement

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Author contributions

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Ethical approval of studies and informed consent

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Data availability

Not applicable.

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