Acupuncture and Herbal Medicine

Safety evaluation of traditional Chinese medicine: new era, new strategy

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Abstract

Today, as the use of traditional Chinese medicine (TCM) becomes widespread globally, TCM is confronted with numerous new safety issues and challenges. In particular, the frequent emergence of safety issues/events such as liver and kidney injury associated with traditionally "non-toxic" TCM has overturned the conventional understanding of the toxicity and safety of TCM. This has also posed significant challenges to the development and internationalization of TCM. So, how should we understand the situation and problems of TCM safety? How can we scientifically solve the problems in evaluation and risk control of TCM? Our team proposes the following: First, we must keep pace with the times and view the issues of TCM safety in a dialectical manner, without exaggeration or underestimation. Second, we must break through the traditional perception that toxicity only came from the medicine itself, and innovate the theories of TCM toxicity. Third, we must establish precise prevention and control strategies for TCM with different types of toxicity, promoting a shift in the management of TCM safety risks from passive response to scientific and proactive control. On this basis, we have put forward the concept and methodological system of the "New Outlook on TCM safety", hoping to provide new theories, strategies, methods, and successful examples for systematically solving the problems in the evaluation and risk control of TCM.

Keywords: Hepatotoxicity, New Outlook on TCM Safety, Risk prevention, Safety evaluation, TCM

Safety is the foremost attribute of any medication. The safety of traditional Chinese medicine (TCM) is not only crucial for public health and the safe use of drugs, but also significantly impacts the development and internationalization of TCM. As the human disease spectrum, constitution spectrum, health demands, and medication behaviors undergo profound changes, the field of TCM safety has encountered a series of new issues and challenges. Notably, frequent reports of safety issues such as liver and kidney injury associated with traditionally "non-toxic" TCM have overturned the traditional understanding of the toxicity and safety of TCM. This poses significant challenges for the evaluation of TCM safety and risk control.

It should be said that Chinese physicians throughout the ages have placed great emphasis on the toxicity and safe use of TCM, accumulating a wealth of theories and experiences regarding the toxicity and safe practices of TCM. These include classifications such as "highly toxic, toxic, slightly toxic, and non-toxic (大毒，有毒，小毒，无毒)," principles such as "medicine is harmless to the body when there is a disease (有故无殒)," and toxic reduction strategies such as syndrome-based detoxication, herbal combination-based detoxication, and processing-based detoxication. However, these theories and experiences are inevitably general and abstract, making it difficult to provide scientific answers and targeted solutions to the new situations and problems of TCM safety that have emerged worldwide today. So, how should we understand the situation and problems of TCM safety? How can we scientifically solve the problems in evaluation and risk control of TCM? These are the questions that TCM scientists and supervisors must seriously consider.

To address the bottleneck issues in TCM safety, we for the first time put forward the concept and methodological system of the "New Outlook on TCM safety", the system provides novel theories, strategies, and methods for the evaluation and risk control of TCM. This article introduces the background in which the "New Outlook on TCM Safety" idea was proposed, its main content, and some research practices in the hope of providing a useful reference and example for solving the difficult problems of TCM safety, risk prevention, and control as well as promoting the supervision standard of TCM safety and that of traditional medicines safety worldwide.

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The historical background of "New Outlook on TCM Safety"

The safety of TCM has gradually become the focus worldwide

With the widespread global use of TCM, issues and incidents related to their safety have increased. Over the past 30 years, many TCM or their components have been reported to cause severe adverse reactions/events, such as Longdan Xiegan wan causing renal failure, *Polygonum multiflorum* (PM) expresses itself differently from other articles causing liver injury, aristolochic acid causing liver cancer, which have attracted high attention both domestically and internationally. The American Journal of Science Translational Medicine published a research paper on the correlation between aristolochic acid and liver cancer and drawn widespread attention[1]. After the World Health Organization (WHO) included traditional medicine originating from TCM in the "International Classification of Diseases" (ICD-11) in 2019, the European Academies' Science Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM) expressed strong doubts and even opposition to WHO's move due to concerns over the safety and efficacy of TCM[2,3]. The aforementioned issues and incidents related to the safety of TCM have aroused widespread public concern and doubt, casting a shadow over the sustainable development and internationalization of TCM.

It is worth emphasizing that the issues and incidents of TCM safety that still occur frequently today are related to not only TCM traditionally considered "toxic" but also those traditionally considered "non-toxic"[4]. The latter have gradually become the "main character" in severe adverse reactions/events of TCM, such as PM liver injury issues and aristolochic acid nephropathy issues, leading some to exclaim that the current issues of TCM safety are in a predicament where "it is easy to dodge an open gun, but hard to defend against hidden arrows."

Objective view of TCM safety issues/events: do not exaggerate, do not underestimate

According to the data obtained by National Center for Adverse Drug Reaction Monitoring in 2019, chemical drugs accounted for 82.0% of all suspected adverse drug reaction (ADR)/events reports, while TCM accounted for 13.0%[5]. Another study focused on drug-induced liver injury (DILI) suggested that according to DILI-related ADR reports from 2012 to 2016, TCM-induced liver injury accounts for 4.5% of all reports[6]. Therefore, the overall safety of TCM is relatively good, and the safety problems of TCM should not be exaggerated.

However, the safety issues of TCM should not be underestimated either, as the proportions of adverse reaction/incident reports for TCM and chemical drugs do not equal the actual incidence rates[7]. The frequency of clinical use of TCM is much lower than that of chemical drugs (approximately 1:4), which contributes to the low reports number of TCM. Therefore, it is not appropriate to conclude that the safety of TCM is much higher than that of chemical drugs based solely on the number of reports. Second, the risk control is weaker in TCM compared with chemical drugs. The majority of adverse reactions for most patent TCM are in a "not yet clear" state, while chemical drugs have detailed information on adverse reactions and precautions in the drug instructions. Therefore, the safety risks of chemical drugs are more predictable and controllable than those of TCM. Third, in terms of the risk-benefit ratio, chemical drugs are generally superior to TCM. The risk-benefit ratio of chemical drugs is often favorable. For example, although chemotherapy drugs cause serious adverse reactions, such as bone marrow suppression, they are indispensable for clinical treatment. To address the new safety challenges faced by TCM today, novel safety evaluation and risk control theories, methods, and strategies must be put forward.

Basic connotation of "New Outlook on TCM Safety"

To scientifically and effectively address the new challenges and issues related to TCM safety, our team has proposed for the first time the " New Outlook on TCM Safety" concept, which can be summarized as follows: One innovative understanding, two kinds of evaluation modes, tri-element injury hypothesis, four-quadrant risk decision process, and five-level safety evidence body[8]. Below is a brief explanation, combined with examples.

One innovative understanding

It is essential to innovate the theory of TCM toxicity, breaking through the safety evaluation and risk control models that are mainly confined to the cognition of inherent toxicity, which is crucial for the scientific supervision of TCM safety. Conventional toxic theory considered "toxic" mainly according to the inherent or direct toxicity of the medication itself. The classification of toxicity levels, such as highly toxic, toxic, slightly toxic, and non-toxic, is primarily based on the understanding of common, rapid onset, direct, or inherent drug toxicities. Due to scientific and technological limitations at the time, ancient physicians had relatively limited understanding and control strategies for TCM toxicity, with occasional, hidden, cumulative, specific, and indirect characteristics. For example, PM only causes liver injury in a very small number of susceptible individuals, with the latent period ranging from several days to several months[9]; renal-related cancers caused by an *Aristolochia* species (Guanmutong) containing aristolochic acids usually occur after taking the medication for 10 years or even 30 years. These types of toxicity were difficult to discover and recognize in ancient times. To this end, we have proposed for the first time four basic patterns of clinical toxicity formation in TCM (inherent, idiosyncratic, indirect, and mixed types), which provides new theories and strategies for scientifically addressing the safety issues of TCM in the new era of globalization, especially for solving the safety risk control problems of traditionally "non-toxic" TCM with occasional, hidden, cumulative, and large individual differences.

Two kinds of evaluation modes

Current models and methods for evaluating the toxicity of TCM are primarily based on the understanding of inherent toxicity and mainly use normal animal models for routine toxicological assessments (including acute, subacute, and long-term toxicity tests). Routine toxicological tests are well-suited for detecting, identifying, and evaluating the inherent toxicities of drugs. However, idiosyncratic and indirect toxicities of TCM are significantly influenced by factors such as individual-specific constitution, genetic background, underlying diseases, disease state, and the use of combined or paired medications. Consequently, conventional toxicological tests struggle to objectively and truly reflect the clinical safety of drugs, and the evaluation results cannot guide precise and safe clinical medication use.

Notably, for TCM, attention should be paid to individual differences and the impact of disease states on the efficacy and safety of medications. As early as in the "*Inner Canon of the Yellow Emperor·Suwen* (黄帝内经·素问)," the idea "medicine is harmless to the body when there is a disease (有故无殒)" for syndrome (disease)-based medication to control toxicity was proposed. To this end, our team has inherited and innovated the syndrome-based medication concept of TCM and has taken the lead in proposing and establishing a TCM safety evaluation model and method associated with clinical disease syndromes—Disease-Syndrome-Based Toxicology (DSBT)[10]. This approach is based on real-world clinical settings or uses animal models that combine diseases and syndromes to study the differences and patterns in the body's response to the toxic effects of drugs under normal and various disease syndrome states. This allows for a more comprehensive and realistic examination of drug safety and guides the development of targeted safety risk control strategies. When clinical cases are used as carriers, it is called clinical disease syndrome toxicology, and when animals or *ex vivo* biological materials are used as carriers, it is called experimental disease syndrome toxicology. Utilizing the theories and evaluation methods of disease syndrome toxicology can effectively clarify the dose-time-toxicity-efficacy relationship of drugs with inherent toxicities under different disease (syndrome) states, thus establishing a safe therapeutic window for drugs aimed at different disease syndromes[11]. Theories and evaluation methods of disease syndrome toxicology are also helpful in identifying populations susceptible to idiosyncratic drug toxicity and related disease syndromes, or combined/paired medications that can produce indirect toxicity.

The tri-element injury hypothesis

Recent research revealed that idiosyncratic liver injury caused by PM is the result of a synergistic effect between the body's immune stress state, immune-promoting substances (trans-resveratrol glycosides), and potentially liver-damaging substances (cis-resveratrol glycosides, *rhein anthrone* glucosides, etc). Based on this, the "Tri-Element Injury Hypothesis" of TCM-induced idiosyncratic liver injury was also proposed for the first time, which is also referred to as the "Firewood-Oil-Spark" hypothesis. That is, when the body's immune system is in a state of over-activation (firewood), the immune-promoting substances in TCM (oil) can further intensify the immune response, increasing the sensitivity of the liver to substances that can cause liver injury (sparks), leading to the injury of liver parenchymal cells and the overexpression of inflammatory factors, thereby inducing immune idiosyncratic liver injury[12]. The "Tri-Element Injury Hypothesis" has been validated in research on the mechanisms of liver injury caused by a series of related preparations containing *Psoralea corylifolia*, *Epimedium brevicornu*, *Sophora subprostrata,* and other species.

The "Tri-Element Injury Hypothesis" closely integrates the characteristics and risk factors of clinical liver injury caused by TCM, fully considering the impacts of individual factors, drug factors, and the medication environment on the susceptibility to TCM-induced liver injury. It has changed the long-standing traditional pattern of "toxicity only based on drug components" in the safety research of Chinese herbal medicines, providing new strategies and methods for the evaluation and mechanism research of idiosyncratic and indirect toxicities. Based on the "Tri-Element Injury Hypothesis," a systematic prevention and control strategy and related measures for the risk of drug-induced injury from TCM can be established from three aspects: identification of susceptible populations, personalized and precise medication, as well as quality and safety control of TCM.

The four-quadrant risk decision process

It is particularly important to note that the severity of a drug's adverse effects does not equate to its safety. The side effects of a drug are the natural attribute of the drug itself, while the safety of a drug is a matter of human cognition and judgment. When measuring and assessing the safety of a drug, the following should be considered: First, the magnitude of the drug's side effects; Second, the probability of toxic injury; Third, whether the risk of injury is predictable and controllable; Fourth, the risk-benefit ratio related to the use of the drug.

Generally, chemical drugs have relativity severer side effects, and the probability of injury is also higher; however, the risk is predictable and controllable. Conversely, TCM have fewer side effects and the probability of risk occurrence is lower, but the risks are often difficult to predict and control[13]. For example, chemotherapeutic drugs for tumors often have significant side effects and common injuries, but the risk of injury is predictable and controllable and the risk-benefit ratio is relatively good. Therefore, chemotherapeutic drugs are generally safe and effective. Most patent TCM and related health products do not have severe side effects, and injury occurrence is rare or even extremely rare. However, most adverse reactions are "not yet clear" and are difficult to predict and control, with some products having unclear or insufficient risk-benefit ratios. Although the side effects of TCM are not serious, the difficulty in controlling their safety risks should not be underestimated.

Analysis of the risk-benefit ratio of drug safety is a major challenge for drug safety. For TCM products, owing to their complex composition, diverse effects, and

low content with slow onset, there are limited objectively identifiable indicators, making the analysis of their risk-benefit ratio even more challenging. This study proposes for the first time the use of the four-quadrant method for evaluation and analysis. In the first quadrant, the safety and efficacy of the drug product are both good, and it can be considered to have an optimal risk-benefit ratio and can be recommended for priority use. In the second quadrant, the drug has good efficacy but poor safety and can be considered to have a relatively good risk-benefit ratio. For major difficult and rare diseases that currently have no alternative drug treatments, a priority recommendation for use can be considered with suggestions to strengthen the monitoring of safe medication use. In the third quadrant, the drug has good safety but poor efficacy and can be considered to have an average risk-benefit ratio. Diseases without alternative drug treatments and for special populations, such as pregnant women, children, and the elderly, can still be considered for recommendation. In the fourth quadrant, the drug has poor safety and efficacy and can be considered to have a poor risk-benefit ratio. It is recommended not to use it and even to withdraw it from the market.

The five-level safety evidence body

The hierarchy of evidence for drug safety evaluation methods is as follows (from low to high): Level 1, *in vitro* tests; Level 2, animal experiments; Level 3, case reports; Level 4, randomized controlled trials (RCTs); and Level 5, real-world studies (RWS).

Clinical medical practice is one of the most reliable ways to discover and confirm drug toxicity, and individual case reports are highly noteworthy. It is particularly important to note that RCTs have a more significant advantage in drug efficacy research, whereas RWS have more advantages in the discovery and acquisition of drug safety risks. This is because RCTs are limited by the inclusion criteria, sample size, observation time, and ethical considerations, which make it difficult to comprehensively evaluate drug safety issues. In contrast, RWS can fully reflect real-world medication scenarios and are more suitable for ADR monitoring and clinical safety evaluation.

Some people describe the relationship between RWS and RCTs as follows: RCTs are similar to fishing in an ideal state, such as a fish pond or a net cage, which is a highly controlled artificial environment, whereas RWS are similar to fishing in rivers or lakes, which is an environment without human intervention. Clearly, RWS are not only suitable for identifying drug toxicity risks with multiple occurrences, rapid onset, and other characteristics, but also for identifying risks with occasional, hidden, and delayed onset; they are suitable for identifying not only the inherent or direct toxicity risks of drugs but also the idiosyncratic/indirect toxicity risks.

Combining the above five levels of safety evidence, the research team, taking DILI as a representative, innovatively established a strategy and method for evaluating the causal relationship of drug-induced injury associated with TCM—the "Integrated Evidence Chain" (iEC)[14,15]. This has resulted in a significant shift in the diagnosis of drug-induced diseases from subjective experience exclusion to complete evidence chain confirmation, greatly reducing the misdiagnosis rate of DILI, particularly those caused by TCM.

Construction and application of TCM safety risk assessment and control system: a case study of DILI

DILI is a common ADR in clinical practice. Severe cases can lead to acute liver failure and even death. DILI has become an important reason for the failure of drug development, including the development of TCM, the addition of warnings, and market withdrawal, and has attracted significant attention from the medical community, pharmaceutical industry, regulatory authorities, and the public.

In recent years, our team, taking TCM-related liver injury as an example, has focused on three major questions: "Does the target TCM cause liver injury?" "Why does it cause liver injury? "How can liver injury be prevented?." Innovatively, we have established an integrated technical system for "Causality Evaluation - Mechanism Analysis - Systematic Prevention and Control" of TCM-induced injury. This system has been used as a model for the risk assessment and control of a series of TCM associated with liver and kidney injuries. This technology has radiated to approximately 3,000 Chinese herbal medicine-related products, both domestically and internationally. It has effectively solved several "non-toxic" TCM-induced liver injury issues that have attracted international attention, promoting a shift in the management of TCM safety risks from passive response to proactive control. This provides "scientific escort" for ensuring public safe medication, promoting the healthy development and internationalization of the cause and industry of TCM. Based on preliminary research results, our team took the lead in formulating the "Guidelines for safe use of Polygoni multiflori Radix" by the China Association of TCM[16].

With the iEC method at its core, our team took the lead in formulating the "Guidance for the clinical evaluation of TCM-induced liver injury" by the China Association of TCM[17]. Professor Neil Kaplowitz, former president of the American Association for the Study of Liver Diseases, published a featured review article considering the guidelines to provide an innovative and logical approach for the diagnosis of liver injury related to herbs and dietary supplements (HDS). Invited by the National Medical Products Administration, our team also led the development of the "Clinical Guidelines for Diagnosis and Treatment of Liver Injury Related to Chinese Herbal Medicine"[18]. The review expert group, co-chaired by academicians Zhang Boli and Chen Xiangmei, believed that the guidelines were the significant milestone for strengthening and standardizing the safety supervision of TCM. At the invitation of the Council for International Organizations of Medical Sciences (CIOMS), our team participated in the formulation of the international DILI guidelines and took the lead in the HDS chapter, contributing the "Chinese Solution" to the diagnosis, prevention, and control of liver injuries caused by HDS. This has secured China's leading role in formulating international safety standards for HDS.

Conclusion and prospect

With TCM being included in ICD-11 and China's accession to the international council for harmonisation (ICH), the issue of TCM safety will receive more attention and importance internationally. At the same time, as the food and drug safety supervision has entered the "four mosts" (ie, most stringent standards, strict supervision, severe penalties, and serious accountability) era, the safety and efficacy of TCM products should have higher standards and requirements; otherwise, there is a risk of being eliminated by the market. Therefore some TCM with difficult-to-guarantee quality, safety, or poor risk-benefit ratio have been restricted or even eliminated from the market. Therefore, we must develop the concept of TCM safety, view the situation and problems of TCM safety, and strengthen the research and construction of TCM safety and pharmacovigilance in pace with the times. As long as we spare no effort to improve TCM safety standards and pharmacovigilance, the unique and excellent clinical effect of TCM will make a greater contribution to solving China's medical and health problems, and will also contribute more wisdom and strength to solving the health problems of humanity.

Conflict of interest statement

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

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Author contributions

Xu Zhao and Xiaohe Xiao wrote the manuscript, Xu Zhao and Xiaoyan Zhan collected and summarized the literature, Zhaofang Bai and Jiabo Wang contributed to language modification and content adjustment. Yungchi Cheng and Xiaohe Xiao supervised and revised the manuscript. All authors approved the submitted version.

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.

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