Reflections on the Toxicity and Safety of Traditional Chinese Medicine Combined with the Cases of Nephrotoxicity and Hepatotoxicity

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Abstract This paper analyzes the relationship between toxicity and safety of traditional Chinese medicine (TCM) based on the cases of current nephrotoxicity and hepatotoxicity, and summarizes the literature on hepatotoxicity and nephrotoxicity. It is found that the main reasons for the toxic reaction of TCM are own factors of drugs, irregular administration of medicine and individual difference. However, as long as the "quality" and "quantity" of TCM are guaranteed, the toxicity of TCM can be controlled within the safety range.

Key words Traditional Chinese medicine, Nephrotoxicity, Hepatotoxicity, Cause of toxicity, Safety

1 Introduction

Traditional Chinese medicine (TCM) comes from a wide range of sources and has various properties, including toxic drugs since ancient times. *Sheng Nong's Herbal Classic*, the earliest materia medica classic in China, contains 125 types of TCM, mostly of which are toxic and can not be taken for a long time. National Decree No. 23 *Measures for the Management of Toxic Drugs for Medical Use* also clearly lists 28 types of toxic TCM varieties such as *Datura metel*. Although toxic TCM is poisonous, it can be used safely and achieve therapeutic effect under the guidance of TCM theory and reasonable compatibility. However, in recent years, with the modernization of TCM and the progress of integrated Chinese and western medicine treatment, TCM therapy has been widely used in clinical practice, and the reports of adverse reactions of TCM are increasing. According to the reports, 2.185 million cases of suspected drugs were involved in adverse drug reaction/event reports in 2022, of which TCM accounted for 12.8%; 339 000 cases of suspected drugs were involved in serious adverse reactions/event reports, of which TCM accounted for 5.9%[1]. Therefore, it is urgent to improve the public awareness of toxic TCM and their toxicity, and improve the ability of TCM practitioners to use TCM safely and accurately.

There are various reasons for the toxicity of TCM, including the toxic and side effects of TCM itself (toxic components), improper cultivation and storage (agricultural residues, heavy metals and microorganisms), improper processing or preparation, and unreasonable prescription[2-4]. The toxicity of different TCM can cause damage to different human organs and physiological systems. As metabolic organs, liver and kidney are most easily damaged by toxic drugs. This paper discusses the causes of TCM toxicity and analyzes the relationship between the toxicity and safety of TCM by taking nephrotoxicity and hepatotoxicity of TCM as examples.

2 TCM kidney damage and aristolochic acid nephropathy

2.1 Common nephrotoxic drugs Studies have proved that diuretic weight loss drugs such as *Stephania tetrandra*, *Akebia quinata*, Rhizoma Alismatis, *Uncaria rhynchophylla*, *Syzygium aromaticum* and *Swertia davidi* could cause acute renal tubular necrosis; *Aristolochia debilis*, *Sophora flavescens*, *Psoralea corylifolia*, *Achyranthes aspera* and *Melia azedarach* root could induce azotemia; Fructus Xanthii, Fructus Aurantii, Fructus Aurantii Immaturus, mirabilite and *Pulsatilla chinensis* cause hematuria and hypertension; *Lysimachia christinae*, *Lemna minor*, *Prunella vulgaris* and *Achyranthes bidentata* could lead to hyperkalemia. Ingredients of traditional Chinese medicine that are irritating or toxic to the kidneys include alkaloids, glycosides, toxic proteins, volatile oils, terpenoids and heavy metals such as mercury, lead and arsenic. Some are active pharmacological ingredients and some are toxic ingredients with no pharmacological effect. For example, cantharidin in *Mylabris* spp., gelsemine in *Gelsemium* spp., arsenic sulfide in arsenic trioxide, mercuric oxide in Hydrargyri Oxydum Rubrum, emodin in *Rheum palmatum* and *Aloe vera* are both effective pharmacological components and components that cause renal toxicity. The toxic proteins contained in *Cassia occidentalis*, Fructus Xanthii, *Abrus precatorius* and *Croton tiglium* are mostly non-effective toxic ingredients, which can be removed by processing. Oral administration of external drugs such as arsenic is the common cause of renal toxicity. However, long-term administration of large doses of Rhizoma Alismatis can cause renal tubular acidosis[5-7]. At present, the mechanism of renal toxicity of TCM has not been fully clarified, and more studies have been conducted on aristolochic acids represented by *A. quinata* (Thunb.) Decne.

2.2 Aristolochic acid nephropathy

2.2.1 Aristolochic acid-containing TCM. Aristolochic acid (AA) is a nitrophenanthrene organic acid, mainly composed of aristolochic acids A, B, C, D, E and their derivatives. At present, there are more than dozens of known AA-containing TCM, mainly distributed in *Asarum*, *Akebia*, *Clematis*, *Stephania*, *Menispermum*, *etc.*[8], among which the representatives are the Chinese herbs *Aristolochia fangchi* and *Aristolochia manshuriensis*.

2.2.2 Clinical features of AA renal damage. Clinically, AA renal damage can be roughly divided into three types. The first is

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chronic AA nephropathy (patients with regular doses of TCM containing AA for a long time), with the clinical manifestations of varying degrees of progressive renal failure or chronic renal failure. The second is acute AA nephropathy (patients with short-term excessive use of TCM containing AA), with the clinical manifestations of oliguria or non-oliguria acute renal failure, often accompanied by edema, hematuria, proteinuria, renal glycosuria and increased urinary enzymes. The third type is AA nephropathy with renal tubule dysfunction (patients with intermittent use of a small amount of TCM containing AA), with clinical manifestations of proximal and distal renal tubule acidosis, and possible acidaminuria, lithuria, incomplete or complete renal glycosuria[9].

2.2.3 Pathogenesis of kidney damage caused by AA. The mechanism of AA induced nephropathy and carcinogenesis has been preliminarily identified. Studies have shown that AA I and II belong to nitrophenanthrene carboxylic acids and are genotoxic mutants. Nitrophenanthrene carboxylic acids are activated by nitroreduction *in vivo*, and the activators can cause DNA admixtures. *In vitro* cell test demonstrate that mammals have a variety of enzymes that can activate AA. The activation process forms cyclic nitrobenzene ions and changes the electron distribution, resulting in binding to the amino groups of deoxyadenylate and deoxyguanylate in the outer ring to form purine adducts. Deoxyadenylate and AA I complex can cause the transformation of nucleotide base A-T to T-A *in vivo*. This form of transformation occurs frequently at the 61st site of the proto-oncogene (H-ras). DNA binding studies have also confirmed that this process can occur on purine of human *p53* gene, and this gene mutation is not only related to the occurrence of tumors, but also plays an important role in the formation of renal interstitial fibrosis[10-12].

2.2.4 Principles of prevention and treatment of AA nephropathy. At present, there is no established treatment for AA nephropathy. Immunosuppressants are commonly used, and the steroid hormone (prednisolone) may have a definite effect, but more clinical trials are needed to confirm this. There is still no effective treatment for chronic AAN whose renal function has been seriously damaged. Kidney damage caused by *A. manshuriensis* is generally difficult to recover and often progresses to chronic kidney failure[9].

3 Liver damage of TCM and hepatotoxicity of *Tripterygium wilfordii*

3.1 Common hepatotoxic drugs So far, the commonly used TCM found to cause liver damage in clinic include: *Dioscorea bulbifera*, *Gynura segetum*, Fructus Xanthii, *Pleuropterus multiflorus*, *T. wilfordii*, *Artemisia argyi*, *Senna occidentalis*, *Atractylodes lancea*, Radix Trichosanthis, *Taxillus sutchuenensis*, *Cyrtomium fortunei*, Pollen Typhae, *Ephedra sinica*, Radix Bupleuri, Folium Sennae, *Albizzia julibrissin* cortex, *Syzygium aromaticum*, *MeLia toosendan*, *Brucea javanica*, *Ilex pubescens*, *Ricinus communis* bean, *Veratrum nigrum*, *Salvia miltiorrhiza*, *Papaver* L., *Pinellia ternate*, *Alisma plantago-aquatica*, *Rheum palmatum*, *Reynoutria japonica*, *Cyrtomium fortunei*, *Senecio scandens*, *S. tetrandra*, *Dysphania ambrosioides*, *Myristica fragrans*, *Phytolacca acinosa*, *Dichroa febrifuga*, *Hydnocarpus anthelmintica*, cinnabar, *Mylabris phalerata*, *Manis pentadactyla*, *Scutellaria baicalensis*, *Valeriana officinalis*, *Aconitum carmichaeli*, *Ginkgo biloba*, *etc.*[13-15]. The TCM compound preparations that are known to cause liver damage are: Zhuanggu Guanjie pills, Xiaochaihu decoction, Dachaihu decoction, compound Qingdai capsules (pills), Keyin pills, Xiaoyin tablets, Xiaohe tablets, Baidianfeng capsules, Baifukang granules, Baishi pills, Liushen pills, Chuangjisan, Maxingshigan decoction, Gegen decoction, Dahuang Mudanpi decoction, Fangfeng Tongsheng powder, Shiduqing tablets, Xueqing pills, Zhuifeng Tougu pills, Xiaokechuan tablets, Zhuanggu shenjin capsules, Guxian tablets, Zengshengping, Niuhuang Jiedu tablets, Tianma pills, compound Danshen injection, Diao Xinxuekang capsules, Kunming Shanhaitang tablets, *etc.*[16-17]. The TCM that can cause liver damage or induce liver cancer through animal tests include *Ilex chinensis*, *Sanguisorba officinalis*, *Gardenia jasminoides*, Chinese gall, pomegranate peel, *Terminalia chebula*, *Acorus gramineus*, fried fennel, *Zanthoxylum schinifolium*, roasted malt, cinnamon bark, anise, *Aristolochia debilis*, *A. quinata*, niter, *etc.* In addition, some external Chinese herbs can also cause liver damage to different degrees after being taken by mistake, such as *S. davidii*, *Derris trifoliata*, realgar, peppermint oil, raw cotton seed oil, tung oil, *etc.* It must be pointed out that there is still a shortage of reliable clinical data to confirm the hepatotoxicity of some of the above-mentioned TCM. However, the hepatotoxicity confirmed by animal tests, as the toxic dose exceeds the usual clinical dosage by tens or even thousands of times, not only has little significance for clinical drug guidance, but also shows that these TCM are safe in clinical routine application[18].

In recent years, the toxic substances of TCM reported to cause liver damage are related to their alkaloids, soaps, terpenoids, volatile oils, toxic proteins, tannins, heavy metals, quinones, peptides and metal components. For example, *T. wilfordii* contains wilfordine; *D. bulbifera* contains dioscin, dioscorea saponin and toxic protein; *M. azedarach*, *A. argyi*, *Senna tora* and *C. fortunei* contain terpene or lactones; and arsenic (red arsenic, white arsenic) contains arsenic trioxide[19].

3.2 Hepatotoxicity of *T. wilfordii*

3.2.1 Chemical component. The chemical components of *T. wilfordii* are complex, mainly including alkaloids, diterpenoids, triterpenoids, sesquiterpenoids and glycosides. More than 100 components have been isolated from *T. wilfordii*, among which alkaloids and diterpenoids are both active and toxic components. Most of the diterpenoids show strong immunosuppressive activity. Triptolide is one of the diterpene lactone epoxide compounds extracted and isolated from *T. wilfordii*, which has obvious biological activities such as immunosuppression, anti-inflamma-

tion, anti-fertility and anti-tumor, and is a widely used TCM monomer in clinical practice. However, it also shows obvious toxicity correlation, and liver is one of its main toxic target organs[20].

3.2.2 Clinical manifestations of liver damage. The toxicity of *T. wilfordii* is often reflected in the metabolic process, so hepatotoxicity appears more frequently. After taking decoction or preparation of *T. wilfordii*, patients are prone to abnormal liver function, with clinical manifestations similar to viral hepatitis, such as weakness, loss of appetite, nausea and vomiting, elevated aminotransferase, and a few appear jaundice. In severe cases, hepatomegaly and steatosis may occur, and even liver hemorrhage and necrosis. Long-term use can easily lead to drug-induced liver damage. There have been clinical reports of death due to liver function injury[21-22].

3.2.3 Mechanism of hepatotoxicity. Abnormal liver function, liver enlargement and increased aminotransferase, total bilirubin and direct bilirubin are often observed in patients with *T. wilfordii* poisoning, suggesting that the liver damage caused by *T. wilfordii* is mainly hepatic parenchymal cell injury. There are mainly damage to immune system, secondary β-oxidation damage caused by inhibition of mitochondrial respiratory chain, and apoptosis due to loss of chemical and physiological properties of cell membrane. The main components of *T. wilfordii* are diterpenoids, triterpenoids and sesquiterpenoids, which have damaging effects on heart, liver and kidney and can cause toxic hepatitis or chronic liver damage[21-22].

3.2.4 Attenuated study. In clinical practice, in order to utilize the efficacy of drugs and reduce the toxicity of drugs themselves, it is necessary to carry out research and transformation of drugs. Attenuating researches on *T. wilfordii* mainly include: compatibility of TCM and combined drug attenuation, processing attenuation, changing traditional dosage forms to make slow release preparations and controlled release preparations, structural modification of sexual components, combination of electroacupuncture and moxibustion with *T. wilfordii* preparations, and overall biological transformation[21-23].

4 Understanding and thinking about the toxicity and safety of TCM

4.1 Understanding of toxic and side effects of TCM In recent years, with the significant increase in the clinical application of TCM, the toxic reactions caused by TCM are gradually understood and recognized by people while exerting their own advantages. Based on the liver and kidney toxicity mentioned above, the main reasons for the toxicity of TCM are analyzed as follows.

4.1.1 Self-factor of drugs. (i) The drug itself contains toxic ingredients. Some TCM contain toxic components, improper use or overdose will lead to toxic side effects, such as *A. fangchi*, *A. manshuriensis*, *T. wilfordii* and other TCM. Such TCM need strict preparation, special decoction and limited dosage when applied in clinic. (ii) Confusable varieties. The phenomenon of homonym and synonym in TCM is common. Different sources of TCM have not only different chemical compositions and efficacies, but also different strength of toxicity. (iii) Drug pollution. With the use of a large number of pesticides containing organochlorine, organophosphorus and other components and the pollution of industrial waste, waste water and waste gas containing harmful metals to the natural environment, Chinese medicinal materials often have agricultural residues and heavy metals exceeding the standard. Once people take such medicinal materials, it will also lead to cumulative poisoning and a variety of adverse reactions. (iv) Source difference. The quality of TCM is affected by the growing environment and natural conditions. The content of active substances in medicinal materials produced in the same area may be different due to different growth years and harvesting seasons[3,6,9,24].

4.1.2 Nonstandard use of drugs. (i) Irregular processing. After processing, TCM can reduce or eliminate the toxicity of drugs and improve the efficacy. Therefore, TCM should be processed strictly and normatively before entering clinical use and feeding. Especially toxic drugs, if not prepared and processed as required, poisoning will occur. (ii) Long-term administration. Long-term administration of many types of TCM is easy to appear dependence and accumulative intoxication. (iii) Improper dosage. Each TCM has its limited dosage, which is the accumulation of experience in the long-term clinical practice of TCM. The blood concentration is too low to be therapeutic in case of too small dosage. The physiological activity is strong to inevitably produce toxic and side effects in case of too large dosage. (iv) Improper compatibility. The pharmacists of the past dynasties have known the toxic and side effects of TCM in practice, and classified the toxicity of TCM into "mild toxicity, toxicity, large toxicity, and extreme toxicity". They summarized the contraindications of "eighteen incompatibilities and nineteen counteractions" and the compatibility theories of TCM such as "mutual promotion, mutual-assistance, mutual restraint, mutual-detoxication, and opposite", to reduce toxicity and enhance efficacy. Proper compatibility can make them coordinate with each other, enhance efficacy and reduce toxicity, while improper compatibility will reduce efficacy or increase toxic side effects. (v) Improper dosage form. The overall toxicity of TCM varies with dosage forms such as soup, pill, powder, tincture, injection and so on. *Sheng Nong's Herbal Classic* pointed out: "drugs may be suitable for pills, power, boiling, macerating in wine or decocting, or there are also those who can not be prepared into soup and wine; they should follow the property of a medicine." (vi) Unreasonable decoction. The decoction of TCM should follow certain rules, such as decocted first, decocted later, decocted separately, *etc.*, which should be strictly implemented to avoid adverse reactions. In addition, improper use of drugs is also easy to cause adverse reactions. Food prohibition is also an aspect that can not be ignored while taking medicine, and adverse reac-

tions may occur if not paid attention to. (vii) Combined use of Chinese and western medicine. With the integration of Chinese and western medicine, there are more phenomena of the combination of Chinese and western medicine, but there are differences in Chinese and western medicine systems, and improper compatibility will reduce the efficacy and even produce adverse reactions[15, 19, 22, 25].

4.1.3 Individual difference. The human body's response to drugs is often different due to individual differences, such as race, gender, age, weight, genetics, physiological conditions and other differences, with different sensitivity and tolerance to TCM. For example, children, the elderly, pregnant women and nursing mothers are special groups of people, and are more prone to adverse reactions than adults[24-25].

4.2 Reflections on toxicity and safety of TCM TCM is a multi-component comprehensive system with complex components and multi-drug combination. The complexity of its components and the uncertainty of its action mechanism have predestined that TCM will have toxic and side effects in addition to curing diseases. However, as the only kind of drug system based on human "experimental objects" and practical experience, most of its toxic and side effects have long been clarified in the history of drug use for thousands of years, and the means of making drugs for some toxic and side effects are also mature. Its safety can be guaranteed as long as it is properly applied.

The toxicity and safety of TCM are not completely opposite, and as long as the "quality" and "quantity" of TCM are guaranteed, the toxicity of TCM can be controlled within the safe range. The "quality" of TCM includes the basis of TCM, source of TCM, processing standard of TCM, compatibility standard, decocting standard, taking standard, appropriate dosage form, *etc.* The "quantity" of TCM includes the limit of single flavor medicine, limit of toxic drugs, duration of taking medicine, growth and decline of compatibility, and individual dosing. Throughout the so-called "toxic TCM" or "TCM toxicity", it is just the phenomenon or performance of improper drug selection and inappropriate drug use. In clinical use, it can produce drugs and ensure the safety and effectiveness of TCM by ensuring the quality of drugs via strict processing, standard compatibility, appropriate dosage, proper dosage form, standardized decocting and taking.

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expected to provide a theoretical basis for the discovery of new pharmaceutical active compounds.

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