Review

Research progress on hepatotoxicity and toxicity reduction of Toosendan Fructus

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Abstract

This study reviews the hepatotoxic chemicals, mechanisms of toxicity, and detoxification methods of Toosendan Fructus (TF). Limonin-type triterpenoids, as primary hepatotoxic components, mediate toxicity though inflammation, oxidative stress, mitochondrial dysfunction, ferroptosis, and apoptosis. Hepatotoxicity can be mitigated by controlling dosage, using processed forms of the herbs, and through rational herbal compatibility. The review provides insights for enhancing the safety and clinical application of TF.

Keywords: Toosendan Fructus (TF); hepatotoxicity; hepatotoxic chemicals; hepatotoxic mechanisms; toxicity reduction

1 Introduction

Toosendan Fructus (TF), first documented in the Shennong Classic of Materia Medica, has been used over 2000 years as one of traditional Chinese medicinal herbs.

The Pharmacopoeia of the People's Republic of China 2025 Edition (hereinafter referred to as the Pharmacopoeia) stipulates that TF is derived from the dried and ripe fruits of *Melia toosendan* Sieb. et Zucc, also known as Jin Ling Zi.

TF is rich in medicinal resources and is commonly used for the treatment of liver depression and qi stagnation syndrome. Among the traditional Chinese medicine (TCM) compound preparations recorded in the Pharmacopoeia, more than ten formulas contain TF, such as Yinxuweitong Granules, Shugan Pills, Jianwei Tablets, and Ruzengning Granules. However, it has been documented in all previous editions of the Pharmacopoeia and TCM literature that TF possesses mild toxicity. This review comprehensively summarizes the research progress on the hepatotoxic chemicals and mechanisms of hepatotoxicity, with special emphasis on toxicity reduction. The review provides a scientific foundation for the further development and clinical application of TF.

2 Literature records on toxicity of Toosendan Fructus (TF)

The historical records of TF's toxicity date

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back to the Shennong Classic of Materia Medica, where TF was first documented as a traditional Chinese medicinal herb used for regulating qi. TF, originally named Lian Shi, was classified as a lower-grade herb that can treat diseases but also possess toxicity. The Shennong Classic of Materia Medica categorized 365 medicinal substances into three groups: superior-grade, middle-grade, and inferior-grade herbs according to their effects, such as tonifying deficiency, dispelling pathogenic factors, and their toxicity levels. This classification, known as the "Three-Grade Classification", highlighted that herbs of the inferior grade were mostly toxic and unsuitable for long-term use. This indicates that ancient practitioners were aware of TF's toxicity. During the Wei and Jin dynasties, the toxicity of TF was first recorded in the Ming Yi Bie Lu (Records of Famous Physicians), which stated that it was slightly toxic. Later, the Xin Xiu Ben Cao (Newly Revised Materia Medica) documented that the substance had male and female varieties. The male plant, with red roots and no seeds, are toxic, capable of causing continuous vomitting and even death. The female one, with white roots and seeds, is considered less toxic and recommended for medicinal use [1]. This Tang Dynasty pharmacopoeia not only highlighted the toxicity of TF but also suggested that the toxicity was related to the difference between the male and female varieties.

Subsequently, in Ben Cao Qiu Zhen (Seeking Truth from Materia Medica), it is mentioned that TF, which specifically acts the pericardium, small intestine, and bladder, is identical to Ku Lian Zi. Meanwhile, Ben Cao Jing Shu (Commentary on the Materia Medica) states, "TF has a bitter taste and a cold nature. Being extremely bitter and cold, it possesses mild toxicity". Ancient scholars believed that the bitter taste of TF was the reason for its toxicity [2]. The understanding of the toxicity of TF by ancient people evolved through a long historical process. However, limited by the historical conditions and the level of medical knowledge in ancient time, their understanding of medicinal substances remained incomplete, and their insight into the toxicity of TF was also limited.

3 Modern study on hepatotoxicity of Toosendan Fructus (TF)

Although the toxicity of TF has been recognized in ancient times, little is known about the target organ of its toxicity, toxic components and the molecular mechanisms that generate the toxicity. Since the Chinese herbal medicines were included in the Pharmacopoeia of the People's Republic of China in the 1963 edition, TF has been consistently recorded in the subsequent editions, with its medicinal properties and flavors described as "bitter in taste, cold in nature, and slightly toxic". The toxic components of TF tend to accumulate in the body after ingestion with higher concentrations in the liver compared to other tissues. Concurrently, the pathological changes in the liver are more pronounced than those in other tissues, indicating that the liver serves as the primary target organ for TF-induced toxicity. Therefore, this review primarily summarizes recent research advances in the hepatotoxic constituents, the underlying hepatotoxicity mechanisms and the strategies for reducing its toxicity.

3.1 Reports on toxic components

TF contains a wide variety of chemical constituents, including limonoid-type triterpenoids, lignans, flavonoids, steroids, and organic acids. Among them, triterpenoids are the most extensively reported, with limonoid-type triterpenoids being the predominant group. Limonoids are a class of highly oxidized compounds featuring a 4,4,8-trimethyl-

17-furan steroidal skeleton. The primary limonoids in TF include toosendanin, nimbinal, azadirone, salannin, isotoosendanin, and several others [3]. The hepatotoxicity induced by toosendanin (TSN) in mice exhibited a marked dose- and time-dependent relationship. Administration of TSN at 80 mg/kg for 9 d resulted in the most severe liver injury. However, after 21 d of continuous exposure, an adaptive liver injury occurred [4]. TSN is considered not only the primary active compound responsible for the therapeutic effects of TF, but also the main toxic component. Metabolic activation of the furan ring in TSN by CYP450 enzymes generates a reactive intermediate that can form an adduct with glutathione (GSH), thereby triggering hepatotoxicity (Fig. 1) [5]. Additionally, microRNA (miRNA) microarray study revealed that the expression of 81 serum miRNAs significantly changed after 12 h of TSN treatment. Notably, miR-367-3p was identified as a potential liver injury-specific biomarker for TF-induced hepatotoxicty [6].

In addition to toosendanin, other components in TF also present potential risks. Isotoosendanin, another limonoid-type triterpenoid in TF, was shown to be significantly more toxic than TSN in an oral acute toxicity study on mice, with a median lethal dose (LD_{50}) 20% of that of TSN [7]. In addition, a HepG2 cell model with fluorescent probe-labeled FDA and an automated analysis method of cellular fluorescence microscopic images were used to identify three additional triterpenoid components as the main potential hepatotoxic constituents, namely meliasenin B, trichilinin D, and 1-O-tigloyl-1-O-debenzoylohchinal. These three components exhibited a concentration-toxicity relationship in HepG2 cells [8]. The chemical structures of these hepatotoxic components are shown in Fig. 2. Except for meliasenin B, the rest are all limonoid-type triterpenoids. Collectively, these findings suggest that limonoid-type triterpenoids are the primary chemical constituents responsible for the hepatotoxicity of TF.

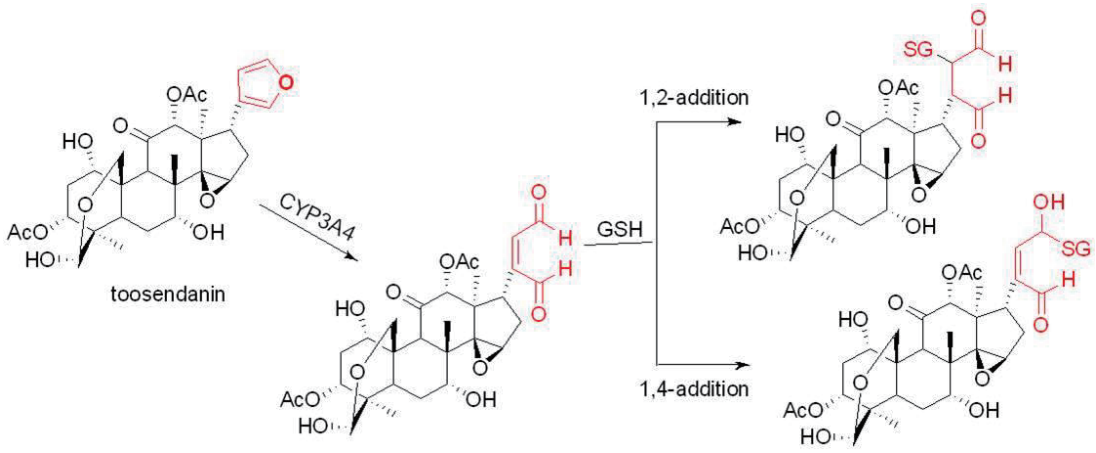

Fig. 1 The possible mechanism of toosendanin bioactivation

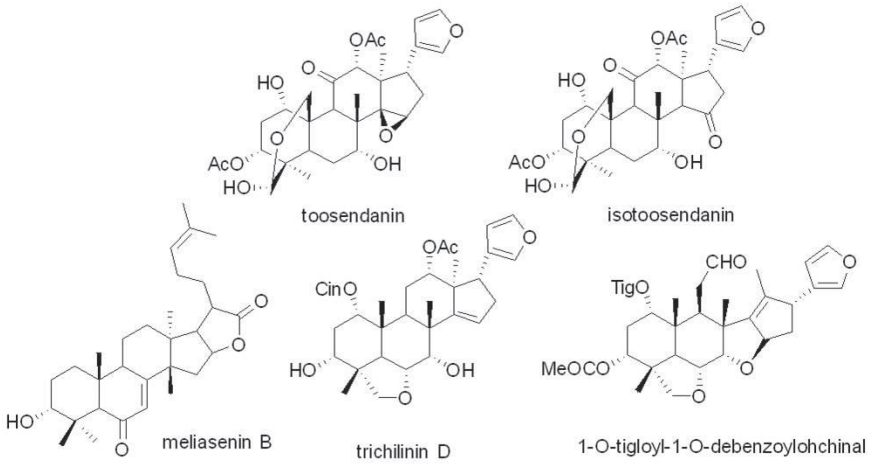

Fig. 2 The structures of hepatotoxic components in Toosendan Fructus

3.2 Hepatotoxicity mechanism

Single-dose oral administration of TF induces acute hepatotoxicity in mice, demonstrating time-effect and dose-effect relationships. Increasing evidence suggests that the mechanisms underlying liver injury caused by traditional Chinese herbal medicines are primarily associated with fatty acid denaturation, hepatocyte injury, lipid peroxidation, inflammatory responses, and mitochondrial energy supply disordor [9]. As a result, the mechanisms of drug-induced hepatotoxicity often involve the complex interplay of multiple mechanisms and contributing factors. The potential hepatotoxic mechanisms of TF reported in the literature are summarized as follows, and a visual summary of Toosendan Fructus hepatotoxicity studies is presented in Fig. 3.

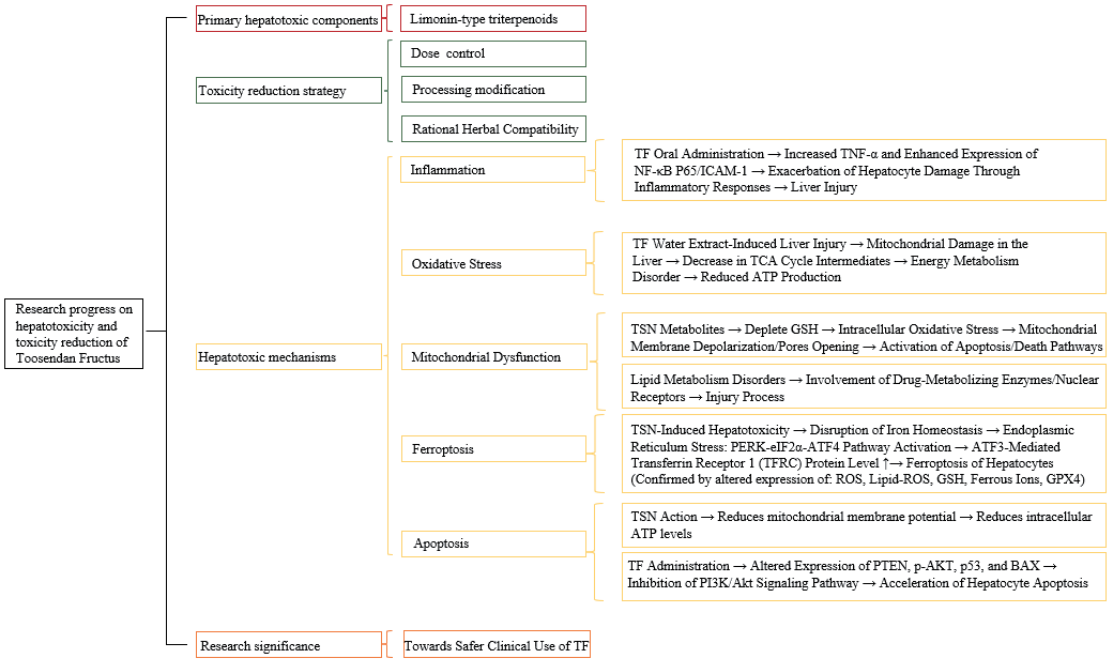

Fig. 3 Visual summary of Toosendan Fructus hepatotoxicity studies

3.2.1 Inflammatory response

Following oral administration of TF to rats for 45 d at a dose of 120 g/kg, several changes were observed. The levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in liver tissue decreased significantly. Meanwhile, the level of malondialdehyde (MDA) increased noticeably. The ratio of SOD to MDA also decreased significantly. These results suggest that TF may cause hepatocyte damage through an oxidative stress reaction. Additionally, the level of the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) increased, and the expression of nuclear factor-kappa B P65 (NF-κB P65) and intercellular adhesion molecule-1 (ICAM-1) in liver tissue was significantly enhanced. These findings suggest that TF exacerbates hepatocyte damage through inflammatory responses, ultimately leading to liver injury [10].

3.2.2 Mitochondrial energy metabolism disorder

In rats with liver injury induced by TF water extract, the levels of metabolites such as citric acid, 2-ketoglutaric acid, and succinic acid decreased. These endogenous small molecule metabolites, the intermediates of the tricarboxylic acid (TCA) cycle, are primarily produced in liver mitochondria. The reduction in these metabolites indicates mitochondrial damage in the liver, which disrupts energy metabolism and ultimately reduces ATP production. Consequently, the experimental animals exhibit behavioral manifestations such as lethargy and fatigue [11].

3.2.3 Oxidative stress and lipid metabolism disorder

By integration of the microRNA–mRNA regulatory network, it was observed that the active metabolites of TSN depleted glutathione (GSH), inducing intracellular oxidative stress. This, in turn, triggered mitochondrial membrane depolarization or the opening of mitochondrial permeability transition pores, activating the related pathways that lead to hepatocyte apoptosis or death. Meanwhile, lipid metabolism disorders, along with numerous drug-metabolizing enzymes and nuclear receptors, are involved in the injury process [4].

3.2.4 Ferroptosis mechanism

Detection of ferroptosis-related factors such as reactive oxygen species (ROS), lipid-ROS, GSH, ferrous ions, and GPX4, confirmed the involvement of ferroptosis in TSN-induced hepatotoxicity. It induces ferroptosis of hepatocytes by triggering the endoplasmic reticulum stress signal PERK-eIF2α-ATF4 pathway, thus causing an increase in the protein level of transferrin receptor 1 (TFRC) mediated by activating transcription factor 3 (ATF3). Therefore, the mechanism of the hepatotoxicity induced by TSN is mainly related to the disruption of iron homeostasis and the ferroptosis caused by the activation of endoplasmic reticulum stress [12].

3.2.5 Induction of hepatocyte death

TSN reduces mitochondrial membrane potential and intracellular ATP levels while increasing ROS levels in hepatocytes. The release of cytochrome C into the cytoplasm activates caspase-8, -9, and -3, ultimately leading to cell death [13].

3.2.6 Induction of hepatocyte apoptosis

A comprehensive analysis of serum exosomes and hepatocyte microRNA profiles in mice revealed that liver injury induced by TF involved the regulation of apoptosis-related pathways, such as the p53 signaling pathway, PI3K/Akt signaling pathway, and PTEN signaling pathway. Following the oral administering of a high dose of TF to mice, the

significant alternations were observed in the hepatic expression levels of several key proteins including PTEN, *p*-AKT, p53, and BAX. The above findings suggest that the PI3K/Akt signaling pathway in the liver is inhibited, which further accelerates hepatocyte apoptosis induced by TF [14].

3.3 Research progress on attenuation of Toosendan Fructus (TF)

Improper or prolonged use of TF may lead to cumulative toxicity and adverse effects. In practice, its toxicity can be mitigated through controlled dosage and the use of processed varieties. Additionally, TF is often prescribed in compound formulations, where its combination with other medicinal herbs can reduce toxicity through mutual compatibility (herbal synergy or "pei-wu" principle), ensuring clinical safety.

3.3.1 Strictly control the dosage and medication administration cycle of Toosendan Fructus (TF)

Excessive use of TF can lead to acute toxicity, and prolonged use may result in accumulative poisoning [15]. Given that the therapeutic effect and toxicity of TF are both primarily attributed to TSN, strict dosage control is essential for its safe application. Historically, only the pulp was used after removing the pericarp and core. The commonly used dosage in ancient times ranged from 1 to 3 qian, which is equivalent to 3 to 9 grams today. The Pharmacopoeia specifies that the medicinal part of TF is the whole fruit, with a recommended dosage of 5 to 10 grams. Of the total TSN content in TF, 76.6% is found in the pulp, 22.5% in the peel, and 0.88% in the core. Although the dosage remains similar to ancient practices, the actual content of active components has been reduced [16], making clinical use safer.

Although stir-frying reduces the toxicity of raw TF, clinical data indicates that stir-fried TF is often used at excessively high dose, sometimes up to 205 times the recommended amount, with an overdose frequency reaching 33.4% [17]. Therefore, strict control of the dosage is essential for the administration of TF in clinical settings. Moreover, the duration of treatment with any compound formula containing TF should be limited to 1 to 2 weeks to ensure patient safety [15].

3.3.2 Study on toxocity reduction through processing

The *Chinese Pharmacopoeia* currently has recorded two forms of TF, raw TF and stir-fried TF. Traditional belief holds that stir-frying (scorch-fry) reduces the bitter and cold properties, decreases toxicity, alleviates symptoms such as diarrhea caused by accelerated intestinal transit (Hua Chang syndrome in TCM), and enhances its therapeutic effects. This aligns with the processing theory that "Raw products are toxic, and the toxicity decreases after being processed". The results of pathological sections of rat livers showed that stir-fried TF caused less severe liver damage compared with raw TF at the same dosage. In the low-dose group (12.5 times the recommended pharmacopoeia dose of TF), the stir-fried TF group exhibited no significant liver cell degeneration or necrosis, while the raw TF group showed pathological changes like hepatocyte turbidity at the same dosage [18]. This indicates that stir-frying reduces liver damage. Thus, from a toxicological perspective, stir-frying leads to a decrease in the content of TSN [16]. Additionally, stir-frying significantly lowers the intestinal absorption rate and permeability of TSN, suggesting a mechanism for the reduced toxicity of TF after this processing method [19].

Additionally, the processed varieties of TF also include wine-processed, charred, salt-processed, vinegar-processed, and sand-fried TF. The degree of liver injury caused by these different forms

varies, suggesting that these processing methods can reduce liver toxicity to varying extents. *In vitro* cell experiments show that different processed varieties of TF have varying effects on the activity of human normal liver cells (LO2). The results indicate that the toxicity of these different processed forms follows this order: wine-processed TF > raw TF > charred TF > salt-processed TF > vinegar-processed TF. Among these processed forms, vinegar- and salt-processed TF exhibited the greatest reduction in toxicity, and the mechanism of toxicity reduction might be related to the alleviation of mitochondrial dysfunction [20]. In addition, the prediction of the hepatotoxicity of TF was explored based on bioinformatics and the principle of detoxification during processing was experimentally investigated, which suggested that the detoxification mechanism might involve altering the effects of TF on liver toxicity targets such as tumor protein p53 (TP53), interleukin-6 (IL-6), and caspase-3 (CASP3), reducing inflammation, and inhibiting lipid peroxidation of cell membranes, thereby decreasing liver toxicity [21]. The detoxification effects and mechanisms of various processing methods were investigated. Specifically, the content of the main toxic component, TSN, in different processed TF samples was determined using HPLC. The results showed that the TSN content in the vinegar-processed TF significantly decreased compared to the raw product, while there was no significant difference in the salt-processed TF [22]. Previous studies have proposed that this different effect may be attributed to the hemiacetal structure of TSN, and the moistening process accelerates the decomposition of the compound [23]. In summary, different processing methods of TF can reduce the hepatotoxicity through various mechanisms. Among them, vinegar-processing and salt-processing have relatively prominent detoxification effects, which may be related to factors such as reducing the content of toxic components and affecting the functions of relevant targets.

3.3.3 Toxicity mitigation through herb-herb compatibility (Pei Wu Jian Du)

Herb compatibility for toxicity reduction is an effective measure to ensure the safety of TCM and one of the characteristics of TCM application. The Shennong Ben Cao Jing was the first to systematically summarize the rules of compatibility and application of TCM, stating, “Herb combinations follow seven relationships: single application (Dan Xing), mutual accentuation (Xiang Xu), potentiation (Xiang Shi), counteraction (Xiang Wei), rebellion (Xiang Wu), clashing (Xiang Fan), and suppression (Xiang Sha). These seven relationships should be considered when formulating prescriptions [24]”. Building upon clinical experience and insights from physicians, theories such as “seven emotions harmonious (Qi Qing He He)”, “compatibility of natures and flavors (Xing Wei Pei Wu)”, “mutual complementarity (Xiang Fu Xiang Cheng)” and “Opposition-Complementarity (Xiang Fan Xiang Cheng)”, were further developed. These theories integrate concepts like “using specific medicinal bias to counteract pathological deviation (Yi Pian Jiu Pian)”, “cyclical domination-resolution of Six Excesses (Liu Yin Sheng Fu)” and “Five Tastes’ Inclination (Disinclination) for Tonifying and Reducing (Ku Yu Bu Xie)”, all of which have been regarded by later physicians as the main theoretical foundation for reducing toxicity and enhancing efficacy through herbal compatibility in TCM [25]. With the application of modern information technology and deep integration of TCM clinical data with big data, along with the prescriptions of proprietary Chinese medicines in the 2025 edition of the Pharmacopoeia of the People’s Republic of China as a reference, the potential compatibility rules of TF have been explored in depth. It was found that the compatibility of Toosendan Fructus (TF) with Liquorice Radix (Gan cao) has the highest degree of support, followed by the combination with

Paeoniae Radix Alba (Bai shao), and combination with Corydalis Rhizoma (Yan hu suo). These combinations have been shown to reduce toxicity and enhance efficacy [26]. The herbal compatibility for toxicity reduction is one of the important methods to mitigate the toxicity of TF. By applying various compatibility strategies, the toxicity of TF can be reduced, and the clinical efficacy can be improved.

*3.3.3.1 Classic herbal pair with Tonification-*Purgation *compatibility: Toosendan Fructus (TF) - Liquorice Radix (Gancao)*

Liquorice Radix is pungent in nature and sweet in taste. When combined with TF, Liquorice Radix can moderate the dissipating properties of TF. Additionally, Liquorice Radix has the action of clearing heat and detoxifying, as well as harmonizing various medicinal herbs. Li Shizhen, in the Compendium of Materia Medica, stated: "Among all medicinal herbs, Liquorice Radix is regarded as the sovereign herb. It can counteract the toxicity of seventy-two kinds of mineral drugs, relieve the toxicity of one thousand two hundred varieties of plants, and play a significant role in harmonizing various herbs." The combination of TF and Liquorice Radix has been shown to effectively relieve pathological changes in liver tissues, inhibited the increase in serum levels of AST, ALT, and ALP in mice, and reduced the levels of MDA, TNF-α, and IL-6 in liver tissue homogenates. It also counteracts the decrease in GSH levels in liver homogenates and at the same time relieves the pathological changes in liver tissues, suggesting that the combination of these two herbs can effectively alleviate the hepatotoxicity of TF [27]. The optimal compatibility ratio of TF to Liquorice Radix is 1:1.5. When TF is combined with Liquorice Radix, the content of TSN decreases, while the contents of liquiritin, isoliquiritigenin, and ammonium glycyrrhizinate, the key components mediating the detoxifying effects of Glycyrrhizae Radix, increase. This study provides preliminary insight into the material basis for Liquorice Radix to reduce the hepatotoxicity of TF [28].

3.3.3.2 Classic herbal pair for astringent compatibility: Toosendan Fructus (TF)-Paeoniae Radix Alba (Baishao)

Paeoniae Radix Alba has a sour taste and a convergent property, while TF is bitter and has a dispersing nature. When TF is combined with Paeoniae Radix Alba, they create a balance between convergence and dispersion. This herb pair works synergistically to regulate stagnant Liver Qi, nourish the liver Yin, and harmonize liver function, thereby enhancing the therapeutic effects of TF in dispersing stagnant Liver Qi, clearing heat, and relieving pain. Consequently, the 'Paeoniae Radix Alba-TF' pairing has been included in the Chinese Traditional Medicine Herb Pair Database as a typical clinical medical combination [29]. The herb pair has been shown to counteract increases in the liver enzyme levels (ALT, AST, or ALP) caused by TF, suggesting that Paeoniae Radix Alba plays a role in reducing toxicity and improving liver function [30]. Additionally, Paeoniae Radix Alba helps to reduce levels of TNF-α and IL-6 in liver tissues and down-regulate protein expressions of NF-κB and ICAM-1. Furthermore, Paeoniae Radix Alba helps to down-regulate the gene expressions of caspase-3 and bcl-2 in liver tissues, demonstrating its potential in mitigating liver injury. Therefore, the ability of Paeoniae Radix Alba to counteract liver injury caused by TF may be related to alleviation of the inflammatory response in liver tissues and regulation of the expression of genes related to hepatocyte necrosis [31]. The detoxification mechanism of this herb pair is associated with the functions of total glucosides of Paeoniae Radix Alba in scavenging oxygen free radicals, enhancing the ability to

scavenge oxygen free radicals, and regulating the immune system [29].

3.3.3.3 Classic herbal pair for concurrent regulation of Qi and Blood: Toosendan Fructus (TF) and Corydalis Rhizoma (Yanhusuo)

The herb pair of TF and Corydalis Rhizoma (Yanhusuo) is used widely for regulating Qi to soothe the liver and activating blood circulation to relieve pain. In this combination, TF clears heat from the Qi phase, while Corydalis Rhizoma addresses stagnation in the blood phase. The synergy between these two herbs enables them to treat both Qi-Blood disorders, restoring liver Qi harmony and eliminating blood cstasis-induced pain [32]. In terms of the fatty acid metabolism in serum, the metabolic profile of serum fatty acids in the mice of the TF group has changed significantly, deviating obviously from the normal level, while the metabolic profile of fatty acids in the mice of the compatibility group is closer to the normal level. Compared with the TF group, the combination group showed significantly increased levels of C22:6n3 and C20:4n6, indicating that Corydalis Rhizoma can up-regulate the level of C22:6n3 and inhibit the inflammatory metabolic pathway of the C20:4n6 cascade to protect the liver, which may be one of the molecular mechanisms of Corydalis Rhizoma in reducing the hepatotoxicity of TF [33].

3.3.3.4 Classic herbal pair for cold-warm compatibility: Toosendan Fructus (TF) and Foeniculi Fructus (Xiaohuixiang)

TF is characterized by its bitter-cold nature and excessive coldness can impair yang qi. When the liver yang declines, the body loses the warming function, resulting in endogenous yin coldness and the disruption of Qi movement. In contrast, Foeniculi Fructus possesses a pungent and warm nature and exerts liver-protective effects. The warm nature of Foeniculi Fructus can counteract the cold nature of TF to prevent excessive coldness [34]. The herb pair of TF-Foeniculi Fructus is another typical combination that can reduce toxicity. After compatibility, Foeniculi Fructus can increase the content of SOD in liver tissues, significantly decrease the levels of ALT and AST, as well as the activity of GSH-Px enzyme, thereby counteracting the hepatotoxicity caused by TF [34,35]. Its mechanism of action may be related to scavenging free radicals and inhibiting lipid peroxidation. In addition, in the compatibility group, Foeniculi Fructus can reduce the absorption and bioavailability of TSN, and accelerate its elimination to reduce the risk of cumulative toxicity. Trans-anethole is a component in Foeniculi Fructus with antioxidant and liver-protective activities. After compatibility, TF can significantly increase the absorption and bioavailability of trans-anethole, slow down the elimination rate of anethole [36], and alleviate the damage to the liver.

3.3.3.5 Compatibility of herbal pair: Toosendan Fructus (TF) and Chebulae Fructus (Hezi)

Chebulae Fructus is widely used in folk medicine in China. Mongolian medicine believes that Chebulae Fructus has the effects of detoxifying and toxicity-reducing [37], making it widely applied in Mongolian medicine. Chebulae Fructus can significantly inhibit the increase in the contents of ALT and AST in the serum of rats caused by TF and reduce the levels of differential metabolites related to hepatotoxicity, such as lysophosphatidylcholine, valine, and pyrrole-2-carboxylic acid. This suggests that the compatibility herb pair can counteract the toxic reactions caused by long-term medication and has a certain detoxifying effect on liver injury induced by oxidative stress [38].

3.3.3.6 Compatibility of Herbal Pair: Toosendan Fructus (TF) and Fiveleaf Gynostemma Herb (Jiaogulan)

Fiveleaf Gynostemma Herb (Jiaogulan), a herb characterized by its cool nature and a sweet-bitter flavor, has the effects of replenishing qi to invigorate the spleen, resolving phlegm and relieving cough, clearing heat and resolving toxin. Combined with TF, Fiveleaf Gynostemma Herb can significantly reduce the contents of AST in the serum and MDA in liver tissues of mice, indicating that Fiveleaf Gynostemma Herb has the ability to reduce lipid peroxidation products and counteract TF-induced liver injury [39].

4 Conclusion

Toosendan Fructus (TF) is a common traditional Chinese medicine used to regulate qi. However, prolonged use may induce hepatotoxicity. The primary hepatotoxic components in TF are limonoid-type triterpenoids and the underlying mechanisms are primarily associated with inflammatory responses, oxidative stress, disruptions in fatty acid metabolism, mitochondrial energy metabolism disorders, ferroptosis, and the induction of hepatocyte death or apoptosis. To ensure clinical safety, some strategies are recommended to mitigate its hepatotoxicity. These include strict control of dosage and treatment duration. the use of processed forms of TF, and combination in compound prescriptions with other herbs, such as Paeoniae Radix Alba (Bai Shao), Glycyrrhizae Radix et Rhizoma (Gan Cao), Corydalis Rhizoma (Yan Hu Suo), Foeniculi Fructus (Xiao Hui Xiang), and Fiveleaf Gynostemma Herb (Jiao Gulan), to mitigate its hepatotoxic effects (Fig. 4).

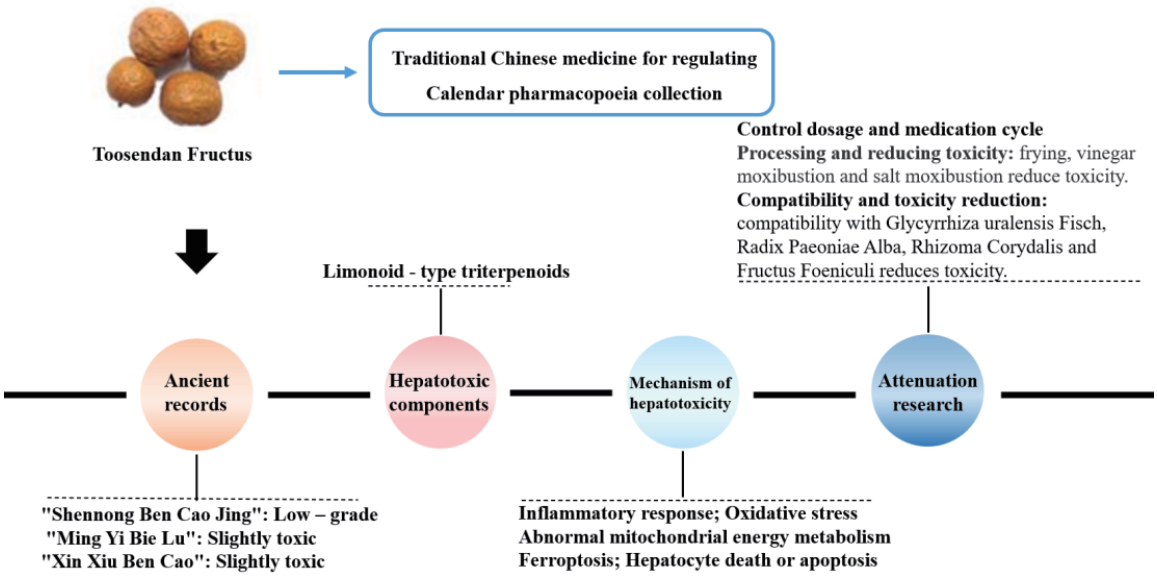

Fig. 4 The mind map of this review

References

[1] Li J, Wang JN, Zhang CB. Supplementary textual research on the herbal literature of Fructus Toosendan. J Yunnan Univ Tradit Chin Med, 2013, 36: 24-26.

[2] Chen XP, Wang JH, Du GH. Historical understanding and modern research on the toxicity of Fructus Toosendan. Pharmacol Clin Chin Mater Med, 2018, 34: 189-191.

[3] Li HB, Ma SJ, Shi DF, et al. Research progress on chemical constituents, pharmacological effects, and toxicity of Fructus Toosendan. Chin Tradit Herb Drugs,

2020, 51: 4059-4074.

[4] Lu XY, Zheng J, Ji C, et al. Study on hepatotoxicity of Fructus Toosendan based on toxicogenomics. Proc 6th Natl Annu Conf Drug Toxicol, 2016: 76-77.

[5] Yu J, Deng P, Zhong D, et al. Identification of amino acid and glutathione N-conjugates of toosendanin: bioactivation of the furan ring mediated by CYP3A4. Chem Res Toxicol, 2014, 27: 1598-1609.

[6] Yang F, Li L, Yang R, et al. Identification of serum microRNAs as potential toxicological biomarkers for toosendanin-induced liver injury in mice. Phytomed, 2019, 58: 152867.

[7] Xie JX, Yuan AX. Chemical structure and activity of isotoosendanin. Chin Pharm J, 1984: 49.

[8] Zhao XP, Ge ZW, Zhang YF, et al. Rapid screening of hepatotoxic components in Fructus Toosendan. Chin J Chin Mater Med, 2013, 38: 1820-1822.

[9] Li ZQ, Fan QQ, Chen ML, et al. Research progress on material basis and mechanisms of hepatotoxicity in traditional Chinese medicine. Chin Trad Herb Drugs, 2021, 52: 4082-4095.

[10] Qi SY, Jin RM, Liu HJ, et al. Study on the mechanism of hepatotoxicity induced by Fructus Toosendan in rats. China J Chin Mater Med, 2008: 2045-2047.

[11] Wang XJ. Study on the toxicity of Fructus Toosendan and toxicity-reducing compatibility through metabolomics. Anhui Med Univ, 2011.

[12] Liang Y, Chen S, Han S, et al. Toosendanin induced hepatotoxicity via triggering PERK-eIF2α-ATF4 mediated ferroptosis. Toxicol Lett, 2023, 377: 51-61.

[13] Zhang Y, Qi X, Gong L, et al. Roles of reactive oxygen species and MAP kinases in the primary rat hepatocytes death induced by toosendanin. Toxicol, 2008, 249: 62-68.

[14] Yu LQ, Zheng J, Li JY, et al. Integrating serum exosomal microRNA and liver microRNA profiles disclose the function role of autophagy and mechanisms of Fructus Meliae Toosendan-induced hepatotoxicity in mice. Biomed Pharmacother, 2020, 123: 109709.

[15] Wang KY, Nie AZ. Discussion on pharmacology and toxicology of Fructus Toosendan and rational medication considerations. Chin Arch Tradit Chin Med, 2022, 40: 54-58.

[16] Huang LH, Zhang ZG, Yang L. Study on ancient and modern processing methods and clinical dosage of Fructus Toosendan based on toosendanin content in different parts. Chin Pharm, 2016, 25: 40-42.

[17] Cao JL, Mao LY, Fan XR, et al. Discussion on dosage regulations of toxic Chinese medicinal decoction pieces in 2010 edition of Chinese Pharmacopoeia. Chin Pharm, 2012, 23: 1055-1056.

[18] Li WH, Wang YZ, Luo SX, et al. Effect of the fried Fructus Toosendan on liver and kidney toxicity in rats with long-term administration. J Liaoning Univ Tradit Chin Med, 2018, 20: 48-51.

[19] Zhang JZ, Wang YZ, Li WH, et al. Effects of Fructus Toosendan before and after stir-frying on intestinal absorption characteristics in rats. Acta Chin Med Pharmacol, 2018, 46: 24-27.

[20] Chen HP, Tan LP, Huang YM, et al. *In vitro* study on hepatotoxicity of different processed products of Fructus Toosendan on human normal liver cells LO2. Chin Med Mater, 2018, 41: 1869-1873.

[21] Zeng CH, Xing LR, Chen HP, et al. Prediction of hepatotoxicity of Fructus Toosendan based on bioinformatics and experimental exploration of detoxification principle of processing. Chin J Tradit Chin Med, 2025, 43: 1-6+259-261.

[22] Chen HP. Study on the detoxification effect and mechanism of processing Fructus Toosendan on liver toxicity. GXUCM, 2018.

[23] Chen B, Wemg JY, Jin LS, et al. Investigation on the effects of three processing methods on the changes of six components in Fructus Toosendan. Chin Pharm, 2020, 23: 2061-2064.

[24] Wang XH, Zhang LX, Gao YG, et al. Research progress on toxicity reduction of aristolochic acid-containing Chinese medicines. Chin Tradit Herb Drugs, 2013, 44: 3241-3244.

[25] Gao Y, Li C, Liang AH, et al. Research progress and strategies on toxicity-reducing compatibility of commonly used “toxic” Chinese medicines. Chin J Chin Mater Med, 2022, 47: 1989-1994.

[26] Wei XP, Bai L, Miao MS. Analysis of clinical compatibility patterns of Fructus Toosendan based on data mining. Acta Chin Med, 2020, 35: 1346-1349.

[27] Zhuo S, Hua BC, He KL, et al. Experimental study on Glycyrrhiza reducing hepatotoxicity of Fructus Toosendan. J Clin Rational Drug Use, 2018, 11: 93-95.

[28] Wang SY, Cui RX, Zhang JZ, et al. Exploring the effects of different compatibility ratios of Fructus Toosendan and Glycyrrhiza on chemical component dissolution and hepatocyte toxicity using entropy weight method. Cent South Pharm, 2020, 18: 38-43.

[29] Huang SX, Zhang Y, Yang LL. Research progress on commonly used hepatotoxic Chinese medicines and their toxicity-reducing compatibility. West J Tradit Chin Med, 2019, 32: 154-157.

[30] Qi SY, Jin RM, Mei CX, et al. Study on toxicity-reducing effect of Paeoniae Radix Alba on Fructus Toosendan. Pharmacol Clin Chin Mater Med, 2010, 26: 84-86.

[31] Qi SY, Jin RM, Mei CX, et al. Study on the mechanism of toxicity-reducing effect of Paeoniae Radix Alba on Fructus Toosendan. Chin Trad Pat Med, 2011, 33: 404-406.

[32] Zhao WL, Qin LP, Zhang L. Exploring formulation rules of prescriptions containing Corydalis-Fructus Toosendan herb pairs based on Traditional Chinese Medicine Inheritance Support Platform. Chin Trad Herb Drugs, 2020, 51: 4704-4711.

[33] Xiong YH, Liu XJ, Wang XT, et al. Study on hepatotoxicity of Fructus Toosendan based on fatty acid metabolic profiling analysis. Chin Tradit Herb Drugs, 2017, 48: 3104-3109.

[34] Qi SY, Jin RM, Mei CX, et al. Preliminary study on toxicity-reducing compatibility rules of Fructus Toosendan. Sichuan J Tradit Chin Med, 2009, 27: 9-11.

[35] Huang YW, Mei CX, Jin RM, et al. Experimental study on Foeniculi Fructus and Aucklandiae Radix against acute hepatotoxicity induced by Fructus Toosendan. Shanghai J Tradit Chin Med, 2012, 46: 98-100.

[36] Yu JY, Zhang RT, Zhang T, et al. Determination of toosendanin and trans-anethole in Fructus Meliae Toosendan and Fructus Foeniculi by HPLC–MS/MS and GC–MS/MS in rat plasma and their potential herb–herb interactions. Biomed Pharmacother, 2020, 34: e4747.

[37] Li H, Zhang GP, Chen TF, et al. Research progress on toxicity-reducing and efficacy-enhancing mechanisms of Mongolian medicine Terminaliae Fructus compatibility with Aconiti Kusnezoffii Radix. World Chin Med, 2021, 16: 3701-3707.

[38] Wu RH, Chen YH, Xiao TM, et al. Preliminary study on the mechanism of Terminaliae Fructus in reducing hepatotoxicity induced by Fructus Toosendan. Info Tradit Chin Med, 2022, 39: 11-18.

[39] Peng XY, Ni KW, Ding YY, et al. Experimental study on Gynostemma Pentaphyllum water extract-alcohol precipitation solution against chronic liver injury induced by Fructus Toosendan in mice. Zhejiang J Integr Tradit Chin West Med, 2018, 28: 818-820+825.