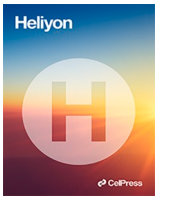
Heliyon 10 (2024) e25091

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The modern scientific mystery of traditional Chinese medicine processing——take some common traditional Chinese medicine as examples

Yiwen Tian [a,b,1], Yun Shi [a,b,1], Yujie Zhu [a,b], Huan Li [d], Jinyang Shen [a,b], Xun Gao [a,b], Baochang Cai [c], Weidong Li [c,**], Kunming Qin [a,b,*]

[a] School of Pharmacy, Jiangsu Ocean University, Lianyungang, 222005, China
[b] Co-Innovation Center of Jiangsu Marine Bio-industry Technology, Jiangsu Ocean University, Lianyungang, 222005, China
[c] College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, 210023, China
[d] School of Applied Science, Temasek Polytechnic, Singapore, 529757, Singapore

ARTICLE INFO

Keywords:
Processing of traditional Chinese medicine (TCM)
Synergism and attenuation
Chemical component
Modern analysis technique

ABSTRACT

The processing of traditional Chinese medicine (TCM) is a unique traditional pharmaceutical technology in China, which is the most important feature that distinguishes Chinese medicine from natural medicine and plant medicine. Since the record in Huangdi Neijing (Inner Canon of the Yellow Emperor), till now, the processing of TCM has experienced more than 2000 years of inheritance, innovation, and development, which is a combination of TCM theory and clinical practice, and plays an extremely important position in the field of TCM. In recent years, as a clinical prescription of TCM, Chinese herbal pieces have played a significant role in the prevention and control of the COVID-19 and exhibited their unique value, and therefore they have become the highlight of China's clinical treatment protocol and provided Chinese experience and wisdom for the international community in the prevention and control of the COVID-19 epidemic. This paper outlines the research progress in the processing of representative TCM in recent years, reviews the mechanism of the related effects of TCM materials after processing, such as changing the drug efficacy and reducing the toxicity, puts forward the integration and application of a variety of new technologies and methods, so as to reveal the modern scientific mystery of the processing technology of TCM.

1. Introduction

Chinese medicinal materials need to be processed before used as medicine and processing is the most prominent feature that distinguishes traditional Chinese medicine (TCM) from natural medicines and plant medicines. The processing of TCM is a pharmaceutical technology based on the theory of TCM, the needs of syndrome differentiation and the nature of the medicine itself, as well as the different requirements of dispensing and preparation [1]. During the prevention and control of the COVID-19, TCM has played a

* Corresponding author. School of Pharmacy and Co-Innovation Center of Jiangsu Marine Bio-industry Technology, Jiangsu Ocean University, Lianyungang, Province, China.
** Corresponding author. College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Province, China.
E-mail addresses: liweidong0801@163.com (W. Li), qinkm123@126.com (K. Qin).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e25091
Received 28 July 2023; Received in revised form 19 January 2024; Accepted 19 January 2024
Available online 20 January 2024

unique role, and the TCM represented by the "three formulas and three medicines" has played an important role. According to statistics, more than 50 % of the Chinese medicinal materials in the guidelines and prescriptions issued by the state for the prevention and control of the COVID-19 epidemic need to be processed by different methods such as frying, frying with honey, and stir-frying with wine [2,3].

According to the processing theory of TCM, the processing of TCM has the functions of enhancing effect and reducing toxicity, changing drug properties, and facilitating dispensing [4]. Recently, with the development of modern science and technology and the wide application of various new technologies and methods, the processing mechanism of some TCMs has also been explained through the combination of chemical component research and pharmacological and pharmacodynamic research, making TCM processing shine again.

Due to the diversity of TCM ingredients and the complexity of efficacy, the scientific connotation of Chinese medicine processing has not yet been fully elucidated. Therefore, we would like to conduct a study on the mechanism of TCM processing, thereby clarifying the internal law and scientific connotation of TCM processing. We reviewed the published studies of TCM processing in recent years and took some common TCM processing as examples, that summarize the current research on the processing theory of TCM. In order to clarify the changes in chemical composition and their mechanisms during the processing of TCM, better understand the mechanism of TCM processing, and guide the improvement of processing technology and the formulation of quality standards.

2. Transformation of TCM ingredients and changes in drug efficacy caused by processing

2.1. The mechanism of ginseng processing

Ginseng is the dried root of *Panax ginseng* C. A. Mey, with ginsenoside as the main active ingredient, which has been used for thousands of years in China. Traditional processing methods of ginseng are mainly sun-drying and steaming. Red ginseng is a processed product obtained by steaming fresh ginseng at high temperature and then drying, while white ginseng is made by drying fresh ginseng under the sun (moisture $\leq$12 %) [5]. Studies have found that red ginseng has better pharmacological effects than fresh ginseng, including antioxidant activity, as well as antidiabetic, antitumor, and antistress effects [6,7]. Compared with fresh ginseng, the contents of total saponins and malonyl ginsenosides in white ginseng were decreased, but the contents of ginsenosides Rb1 and Rg1 were increased [8]. The content of ginsenosides Rg2, Rg3, Rh2, and Rh1 in red ginseng was greater than that in fresh ginseng, and there are also rare ginsenosides such as Rk1, Rs3 and Rg5 [9]. It can be seen that the efficacy changes in different processed products of ginseng are mainly attributed to the structural changes of ginsenosides [10].

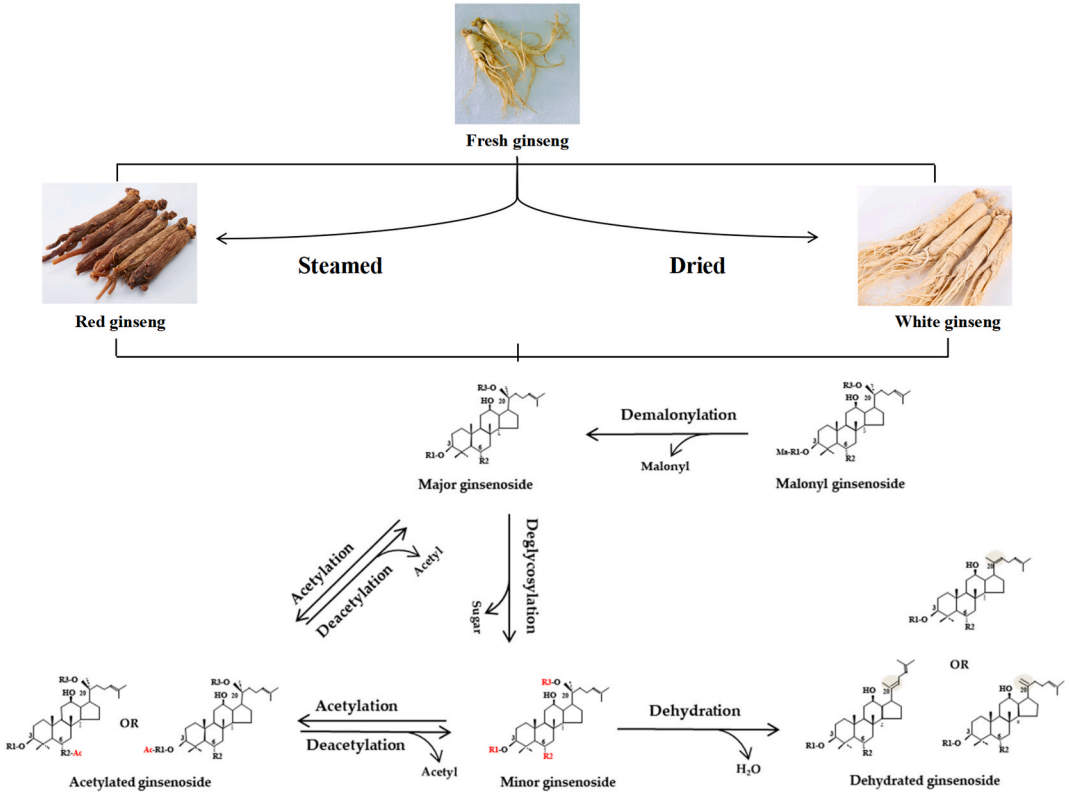


Fig. 1. The transformation pathway of ginsenosides during processing [8].

During the processing of ginseng, the change of saponin components involves a variety of transformation pathways (Fig. 1). For example, the unstable malonyl ginsenosides were transformed into the corresponding neutral ginsenosides at high-temperature degradation; Some ginsenosides will undergo acetylation reaction. Some ginsenosides lose the sugar groups at C-3, C-6 or C-20 positions to generate rare ginsenosides. For instance, ginsenosides Rb1, Rb2, and Rc can be transformed into ginsenosides Rg3 and Rh2. Some ginsenosides dehydrate at the C-20 position to form double bonds, resulting in producing different types of ginsenosides. For example, ginsenoside Rg3 can be converted into ginsenoside Rk1 and Rg5 after dehydration [11]. Meanwhile, studies have shown that when fresh ginseng is steamed, the content of ginsenosides increases at 98 °C but decreases at 120 °C, indicating that the content of ginsenosides changes along with the processing temperature [12]. Therefore, the time and temperature should be strictly controlled during the steaming process, so as to avoid the structural damage of ginsenosides.

2.2. The mechanism of Rehmanniae Radix processing

Rehmanniae Radix is a commonly used TCM in clinical practice, which is the main prescription drug of Liuwei Dihuang Pills, a well-known Chinese patent medicine. It has been reported that different processing methods can cause changes in the chemical components of *Rehmanniae Radix* [13,14]. The processed *Rehmanniae Radix* products mainly refer to *Rehmanniae Radix Praeparata*. *Rehmanniae Radix Praeparata* are obtained by braising or steaming *Rehmanniae Radix* with wine, and are commonly used for the treatment of "blood deficiency syndrome" in clinical practice [15]. Studies have shown that the polysaccharides and iridoids in *Rehmanniae Radix* constitute its main material basis. Li et al. [16] clarified the transformation mechanism of the main chemical components during *Rehmanniae Radix* processing through the research method of marker discovery and simulated processing based on chemoomics. During the processing of *Rehmanniae Radix*, the sugar (polysaccharides, oligosaccharides, and monosaccharides) and glycosides (iridoid glycosides and phenylethanol glycosides) are gradually converted into furfural (glycosylated/non-glycosylated hydroxymethyl furfural) through desugar and dehydration.

The glycosidic bond between the furfuran fructose at the end of raffinose and glucose is easy to hydrolyze to produce melibiose and fructose, which are then dehydrated and converted into monosaccharide based 5-hydroxymethylfurfural (5-HMF) and HMF respectively during the processing of *Rehmanniae Radix*. Through simulating processing, it was found that in mannotriose and melibiose,

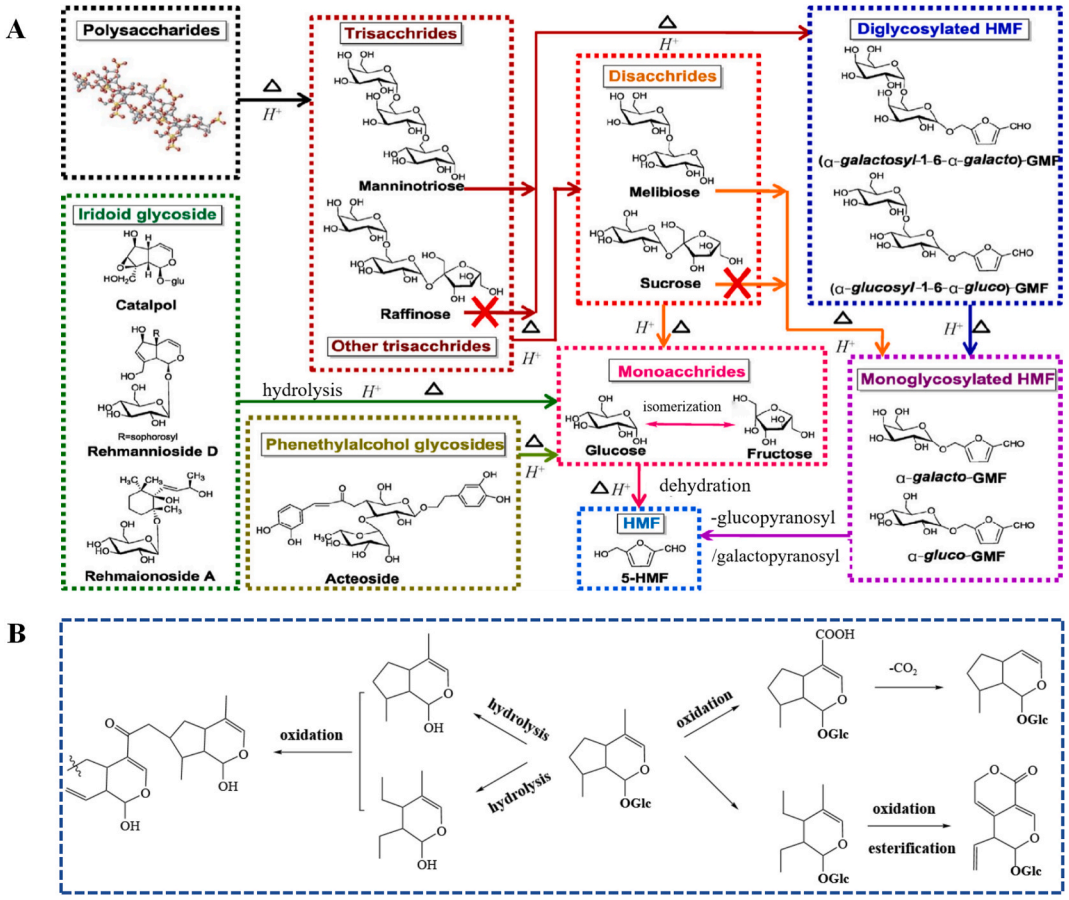


Fig. 2. The main mechanism of the changes in polysaccharide composition and iridoids during the processing of *Rehmannia glutinosa* [16].

besides the hydrolyzed furfural product, there was glycosylated HMF from its prototype, which further verified the gradual conversion process of sugar during the processing of *Rehmanniae Radix*. Chemical analysis results showed that HMF and the glycosylated analogs of HMF were the main characteristic components of *Rehmanniae Radix Praeparata*. Fig. 2 (A) revealed the main transformation mechanism of polysaccharide components during the processing of *Rehmanniae Radix*. 5-HMF can effectively bind to sickle hemoglobin to inhibit the sickling of red blood cells, which has the potential to treat sickle cell anemia [17]. Therefore, it is speculated that the 5-HMF-related components produced in the processing of *Rehmanniae Radix* are the material basis that causes the change of the drug efficacy of *Rehmanniae Radix Praeparata*, which provides a scientific basis for the effect of *Rehmanniae Radix Praeparata* on "tonifying blood and nourishing yin".

Processing can also lead to changes in the iridoid components in *Rehmanniae Radix* [18]. HPLC/Q-TOF-MS technology was used to characterize the chemical components before and after *Rehmanniae Radix* processing. The results showed that the content of iridoid glycosides decreased and the content of furfural derivatives increased after *Rehmanniae Radix* processing, which may be the material basis for the change of drug efficacy, see Fig. 2 (B). The iridoids in *Rehmanniae Radix* are mainly catalpol. Experimental results demonstrated that under heating conditions, the enene ether structure and acetal group of catalpol would be decomposed, casuing the lose of sugar groups and rearrangement, or the occurrence of nucleophilic reaction to generate black substances, which would lead to changes in the color and drug properties of the medicinal materials, and thus result in changes in the antithrombotic and hematopoietic effects of *Rehmanniae Radix* and *Rehmanniae Radix Praeparata* [19]. By establishing a mouse model of cyclophosphamide-induced myelosuppression, the pharmacological effects of casuing before and after processing were evaluated, and the results showed that the hematopoietic effect of *Rehmanniae Radix Praeparata* was more obvious [20].

2.3. The mechanism of Polygoni Multiflori Radix processing

Polygoni Multiflori Radix raw products have the functions of relaxing bowel and detoxification. After processing, it has the effects of blacking hair, nourishing liver and kidney, tonifying blood essence, strengthening muscles and bones, eliminating dampness and decreasing lipid, which belongs to the typical TCM with different uses of raw and cooked products [21]. Since the Song Dynasty, *Polygoni Multiflori Radix* has undergone various processing methods, such as steaming, and processing with black bean juice, wine, and fermentation. According to the records in "Compendium of Materia Medica" of the Ming Dynasty, *Polygoni Multiflori Radix* has a better curative effect after being processed "nine-time repeat of steaming and drying". The main chemical components of *Polygoni Multiflori Radix* include stilbene glycosides, anthraquinones, and phospholipids, etc, which will change significantly after being processed by different methods [22]. However, the research on its processing and transformation mechanism still lacks of systematic elaboration. Stilbene glucoside is a kind of component with a higher content in *Polygoni Multiflori Radix*, among which 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (TSG) has the highest content, and has various biological activities such as anti-inflammatory and anti-oxidation [23]. It has also been reported that excessive or long-term use of TSG will produce certain toxic and side effects [24]. Dong et al. [25] found that the content of stilbene glycosides in *Polygoni Multiflori Radix* presented a downward trend after nine-time repeat of steaming and drying. The reason is that stilbene glycosides can be hydrolyzed to the corresponding aglycones in the process of steaming and drying. Therefore, the speculated mechanism of the TSG degradation reaction was deduced under heating condition.

Anthraquinone derivatives in *Polygoni Multiflori Radix* are mainly divided into free anthraquinone and conjugated anthraquinone, which have important functions such as purgative, diuretic, anti-inflammatory, and hemostatic effects, etc. [26]. Studies have shown that the toxicity of *Polygoni Multiflori Radix* is reduced after processing. It is speculated that processing can decompose anthraquinone glycosides in *Polygoni Multiflori Radix* to convert into anthraquinone aglycones, and therefore the content of total anthraquinones decreases as a whole, thereby achieving the purpose of reducing toxicity and increasing efficiency [27]. Sugar is also an important component of *Polygoni Multiflori Radix*. The "Properties" of *Polygonum Multiflorum Radix Preparata* in "Chinese Pharmacopoeia" and local processing specifications are described as "brown color inside and outside after steaming". Color is used as an important index to distinguish raw *Polygoni Multiflori Radix* and *Polygonum Multiflorum Radix Preparata*. Studies have found that the main reason for the color change during the processing of *Polygoni Multiflori Radix* is the Maillard reaction, that is, the chemical reaction between the carbohydrate components and proteins or amino acids under the acidic high temperature environment leads to the change of the property. Thus, the color becomes darker and darker, from yellow to brown [28].

3. Reduction of toxicity and efficacy retention of TCM caused by processing

3.1. The mechanism of the detoxification of aconitum processing

The raw Aconitum is highly toxic and may lead to cardiotoxicity [29]. and therefore it is often used after processing of boiling. On the basis of inheriting the traditional processing experience, Aconitum can be used safely and effectively to treat various rheumatic pain diseases [30] by boiling processing and reasonable compatibility. Studies have found that alkaloids are the main pharmacodynamic components of Aconitum, and are also the main toxic components. Previous researches have explored that alkaloids are the main medicinal components of aconitum, which are also the main toxic components. During the processing of Aconitum, various alkaloid components are changed, resulting in the reduction of toxicity, while the pharmacodynamic effect is preserved [31]. Therefore, it is of great significance to study the processing method and mechanism of Aconitum, so as to provide a scientific basis for the safe clinical application of Aconitum.

Studies have shown that the detoxification of Aconitum after processing is due to the fact that diester diterpene alkaloids (aconitine and hypoconitine) are hydrolyzed into monoester diterpene and amine diterpene alkaloids. According to the differences in

substituents, aconitine alkaloids are divided into highly toxic diester diterpene alkaloids (DDA), low toxic monoester diterpene alkaloids (MDA) and non-toxic non-esterified diterpene alkaloids (NDAs). Thereinto, DDA is unstable, and the acetyl group at the C8 position and the benzoyl group at the C14 position are easily hydrolyzed or decomposed in the presence of water or heating. First of all, DDA loses one acetyl group to generate corresponding MDA with the toxicity decreased to 1/200–1/500. Secondly, the C14 position will lose benzoyl group to generate corresponding NDA, as shown in Fig. 3. Therefore, the toxicity of Aconitum can be reduced by heat treatment, mainly due to the promotion of the hydrolysis of DDA into low toxic MDA and NDA [32].

3.2. The mechanism of the detoxification of Genkwa Flos processing

Genkwa Flos is the dry bud of *Daphne genkwa* Sieb. et Zucc, which has sedative, analgesic, antiviral, anti-cancer, and anti-inflammatory effects [33]. Modern studies have shown that excessive or long-term use of *Genkwa Flos* can cause damage to the heart, liver, kidney, and gastrointestinal tract [34]. After stir-baking with vinegar, the volatile components and contents in *Genkwa Flos* are changed significantly, causing toxicity reduction and curative effect improvement [35].

Genkwakine and genkwain in *Genkwa Flos* may be one of the potential hepatotoxic substances [36]. Tao et al. [37] established a UHPLC-MS/MS method to conduct a comparative study on the pharmacokinetics of raw *Genkwa Flos* and the samples fried with vinegar, as shown in Fig. 4 (A-F). After oral administration of *Genkwa Flos* fried with vinegar, the parameters of C_{max} and $AUC_{0\text{-}t}$ of genkwain, 3′-hydroxygenkwaline, apigenin, and luteolin significantly increased ($p < 0.05$), while that of genkwakine in raw *Genkwa Flos* significantly decreased ($p < 0.05$). The results showed that *Genkwa Flos* fried with vinegar could increase the bioavailability of genkwain, 3′-hydroxygenkwain, apigenin, and luteolin, and produce synergistic and detoxifying effects.

3.3. The mechanism of the detoxification of Kansui Radix stir-baked with vinegar

Kansui Radix is the dry root tuber of *Euphorbiakan-sui* T.N. Liou ex T.P. Wang, which is first recorded in “Shen Nong’s Herbal Lection”. Due to the extreme irritation to the skin, gastrointestinal tract, and mucous membrane, the " stir-baking with vinegar method” has been used in the past dynasties to alleviate the purgative effect and reduce the toxicity of raw *Kansui Radix* in vivo and in vitro. At present, some scholars have investigated the toxicity reduction mechanism of *Kansui Radix* fried with vinegar, the changes of chemical components before and after processing, and the effects of different processing methods on reducing toxicity [38]. Diterpenoids are the main toxic components of kanziol, and the changes of these components may be the potential mechanism of the toxicity reduction of *Kansui Radix* after vinegar processing. The content of the main diterpenoid 3-O-(2′E, 4′Z-decadienoyl)-20-O-acetylingenol (3-O-EZ) in *Kansui Radix* is significantly reduced after vinegar processing, and the ester bond structure is broken and transformed into the less toxic compound of ingenol.

The conversion reaction of 3-O-EZ in *Kansui Radix* is discovered by simulating the vinegar processing of *Kansui Radix* (Fig. 5) to verify the change process and mechanism of the diterpene structure [39]. The experimental results showed that 3-O-EZ could not be converted into ingenol without vinegar treatment, which indicated that vinegar processing had a crucial effect on the changes of terpenoids [40]. Through the study of metabolomics, it was found that *Kansui Radix* stir-baked with vinegar can cause changes in metabolites in the liver and kidney of rats, adjust glycolysis and amino acid metabolism disorders, and significantly reduce toxicity [41]. Further studies have found that *Kansui Radix* stir-baked with vinegar can inhibit the intrinsic pathway of liver cell apoptosis by blocking the release of mitochondrial cytochrome C and the activation of Caspase-3 and Caspase-9, thereby reducing liver toxicity [42], which lays a foundation for further elucidating the detoxification mechanism of *Kansui Radix* stir-baked with vinegar.

4. Changes in the internal process of TCM and efficacy enhancement caused by processing

4.1. In vivo pharmacokinetic study of Rhei Radix Et Rhizoma

Rhei Radix Et Rhizoma is the dried root and rhizome of Rhubarb palmatum of the Polygonaceae plant with bitter in taste and cold nature. It is originally recorded in “the Shennong Classic of Materia Medica” and has the functions of purgation, clearing heat and fire, cooling blood and detoxifcation, removing blood stasis and restoring menstrual flow, remove-dampness and relieving jaundice [43]. In

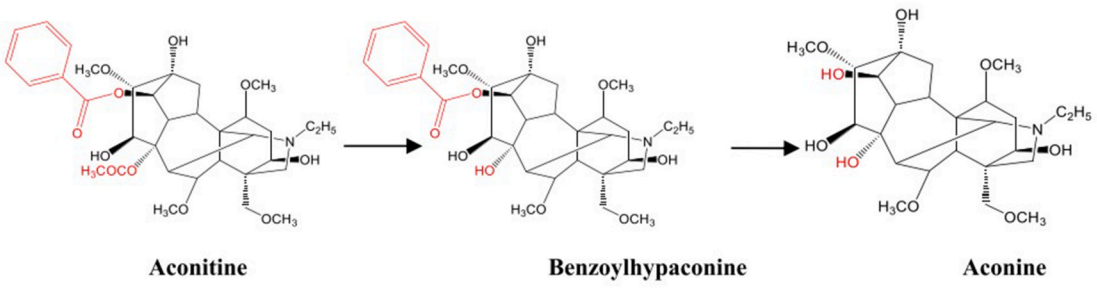


Fig. 3. Hydrolysis process of alkaloids during the processing of Aconitum.

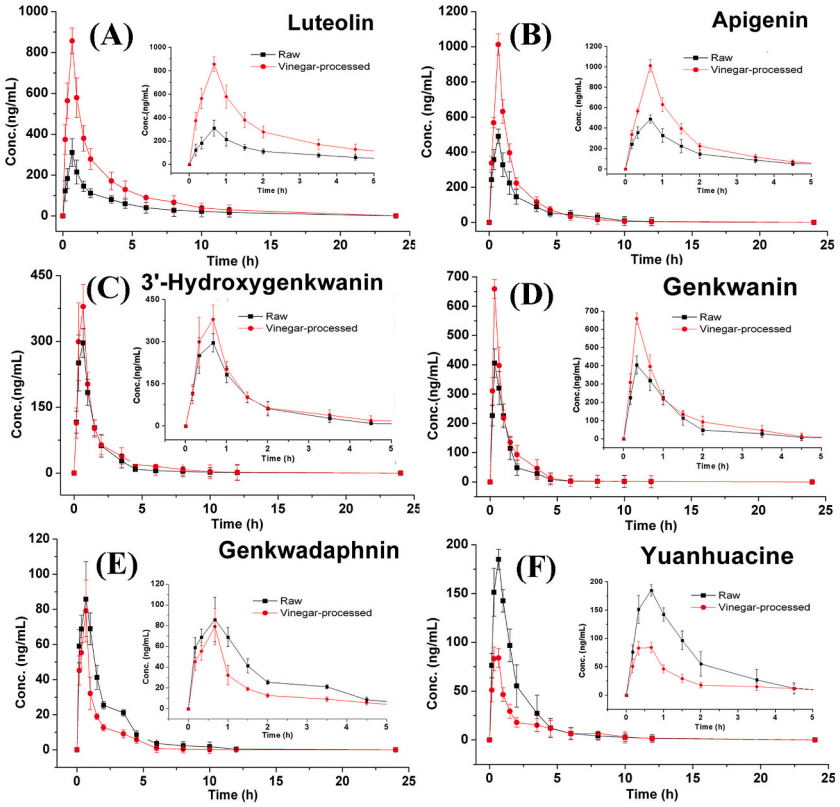


Fig. 4. Pharmacokinetic curves of six components in *Daphne genkwa* before and after stir-baking with vinegar [37].

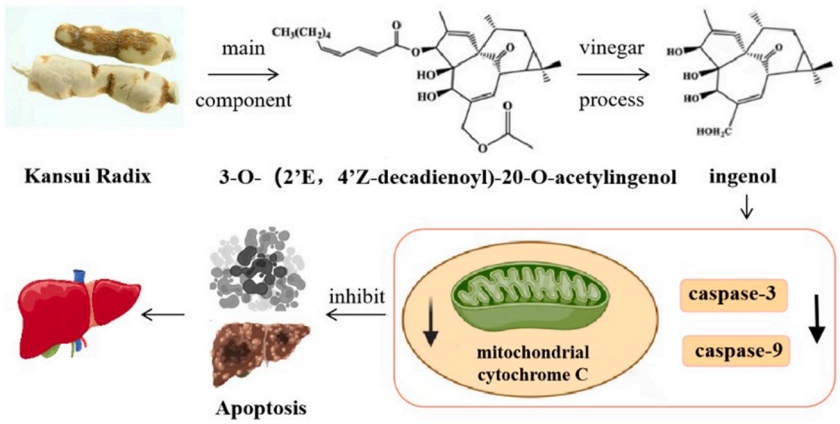


Fig. 5. The conversion reaction of diterpenoid 3-O-EZ in *Euphorbia Kansui* [39].

order to alleviate its severe laxative effect, wine-treated rhubarb is often prepared by cooking with yellow rice wine for a long time [44]. The processed rhubarb products were first recorded in the "Jin Kui Yu Han Jing" by Zhang Zhongjing in the Han Dynasty, which said: "All the black skins of processed rhubarb or raw rhubarb are removed, followed by washing with wine and soaking in wine. "The 2020 edition of "Chinese Pharmacopoeia" records that "cooked rhubarb" is prepared by steaming with wine or stewing with wine. The sennosides and anthraquinone glycosides in *Rhei Radix Et Rhizoma* are the main purgative components [45]. Some studies explored the differences between raw rhubarb and wine rhubarb from the perspective of in vivo processes.

The concentrations of 6 components in rat plasma after oral administration of raw and processed rhubarb are determined. The results showed that cooking with wine could change the pharmacokinetics of rhubarb in vivo. The pharmacokinetic parameters of the representative free anthraquinone compounds (emodin and aloe-emodin) were significantly changed, and the maximum plasma concentration (RP value) was significantly increased (Fig. 6) [46]. Studies have shown that the content of bound anthraquinones in

raw rhubarb is the highest. After processing, the content of bound anthraquinones decreases and the content of free anthraquinones increases. This is because the bound anthraquinones in rhubarb are transformed into free anthraquinones under heat treatment [47]. Therefore, it is very important to investigate the effects of processing methods on the main chemical components, metabolism and in vitro biological activity of rhubarb, so as to expand the application range of rhubarb, enhance its efficacy and improve the safety of use.

4.2. *In vivo pharmacokinetic study of Bupleuri Radix*

Bupleuri Radix is the dried root of umbelliferae *Bupleurum chinense* D C. or *Bupleurum scorzonerifolium* Willd., which has pharmacological effects such as antipyretic, analgesic and antidepressant effects. "Chinese Pharmacopoeia" contains two kinds of processed products: raw *Bupleuri Radix* and *Bupleuri Radix* fried with vinegar. Some studies have shown that the antidepressant effect of vinegar-baked *Bupleuri Radix* is stronger [48]. Saikosaponins is the main pharmacodynamic ingredient in *Bupleuri Radix* [49]. Lu et al. [50] developed a UPLC-MS/MS method to simultaneously and quantitatively analyze eight saikosaponins (SSa, SSb1, SSb2, SSb3, SSb4, SSc, SSd and SSf) in rat plasma, and study the pharmacokinetic differences of the above ingredients in the depression rat model before and after *Bupleuri Radix* was stir-baked with vinegar. The results showed that there were significant differences in AUC_{0-t} and C_{max} of each component after oral administration of the extracts of raw *Bupleuri Radix* and vinegar-baked *Bupleuri Radix*, as shown in Fig. 7, and these changes may be related to the different contents of ingredients in raw and vinegar-baked *Bupleuri Radix* [51].

During the process of *Bupleuri Radix* fried with vinegar, saikosaponins a and saikosaponins d will be transformed into secondary saikosaponins b1 and saikosaponins b2, which is an effective ingredient for anti-inflammation, enhancing immunity, inhibiting lipolysis, and stimulating PGE2 synthesis [52]. The transformation of the above components is caused by the hydrolysis of the glycosidic bond under heating or acidic conditions. Meanwhile, the vinegar processing of *Bupleuri Radix* can promote the hydrolysis of the allyl oxygen bonds at 13 and 28 positions in bupleurum saponins to their corresponding heterocyclic diene structure, which is

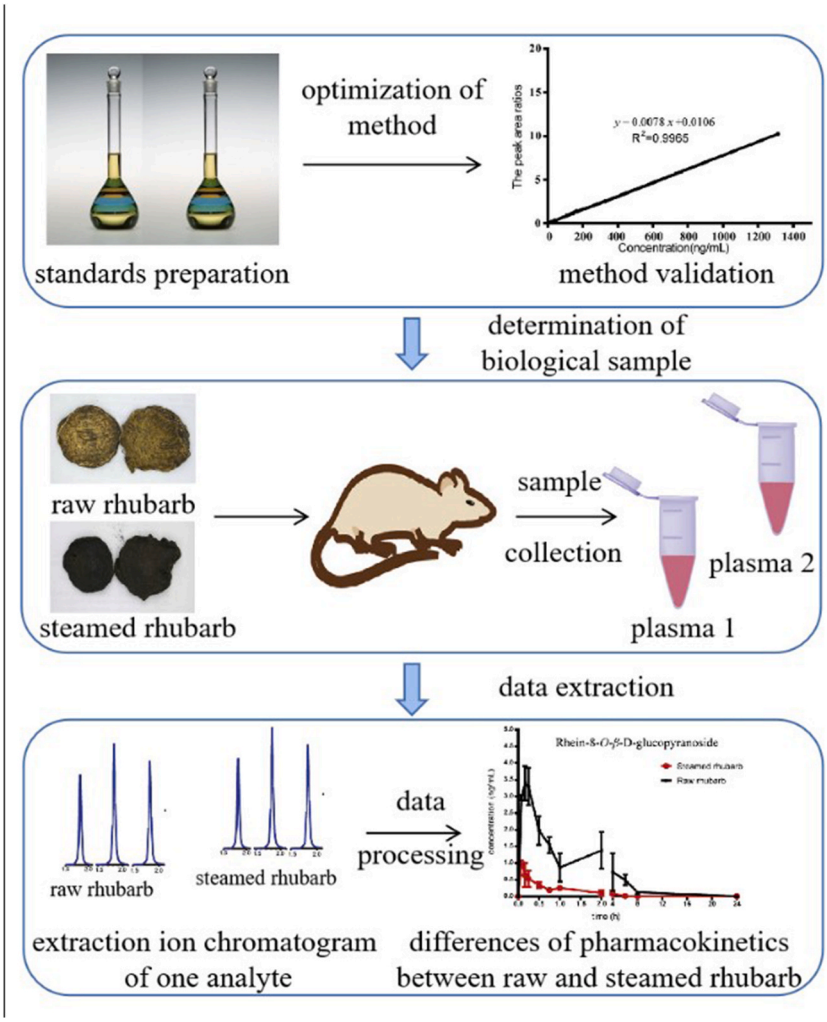


Fig. 6. Comparison of pharmacokinetics between raw rhubarb and rhubarb stir-fried with wine [46].

transformed from type I to type II [53], as shown in Fig. 7. As an important medicine for dispersing liver and relieving depression, these effects of *Bupleuri Radix* can be enhanced after stir-baking with vinegar. The above study explains the effect of stir-frying with vinegar on the composition of saikosaponins, thereby providing a scientific basis for exploring the processing.

5. Conclusions and prospect

Since the processing of TCM is closely related to the efficacy, safety, and quality of TCM, it is very important to study the changes of chemical components during the processing of TCM for the development of reliable quality control methods of TCM. The chemical component is the main material basis for the efficacy of TCM, and the change of composition is the basis for the efficacy change of TCM before and after processing. In order to clarify the effect of different processing methods on the properties of TCM, many scholars have carried out a large number of studies on impact of the processing on the changes in chemical components of TCM by modern analytical techniques [54–56].

In recent years, various new technologies and methods have emerged continuously, the main technologies and methods are listed in Table 1 below. As a new technology to study metabolites, metabolomics has been used in previous researches on the processing theory of TCM and the processing technology and quality standard of TCM decoction pieces, which is helpful to promote the standardization of processing technology and the improvement of quality standard of TCM decoction pieces [57–59]. In a recent study, Song et al. established a research strategy of integrating metabolomics and pseudo-targeted spectrum-effect relationships to elucidate potential hepatotoxic components in *Polygoni Multiflori Radix* [60]. It was found that the combination of metabolomics and chemometrics could quickly screen the difference markers before and after *Polygoni Multiflori Radix* processing, which provides a reference for elucidating the hepatotoxicity of *Polygoni Multiflori Radix*. To sum up, the processing of TCM can change the structure and content of the effective ingredients in drugs, improve the efficacy, reduce or alleviate the toxicity of drugs, etc., which is a key link in the production and use of TCM. With the deep integration of traditional processing technology and modern technology, it is helpful to display the processing mechanism more scientifically and visually. Conducting researches on the processing of TCM can effectively avoid the risk of drug use, guide clinical rational drug use and the development of TCM, which is of great significance to promote the development of the TCM industry.

Funding

National Nature Science Foundation of China (No. 82374038, 82104349, 81973484); Major Projects of Natural Science Foundation of Jiangsu Higher Education Institutions (No. 21KJA360005).

Declarations

Conflict of interest The authors declare no known conflict of interest.

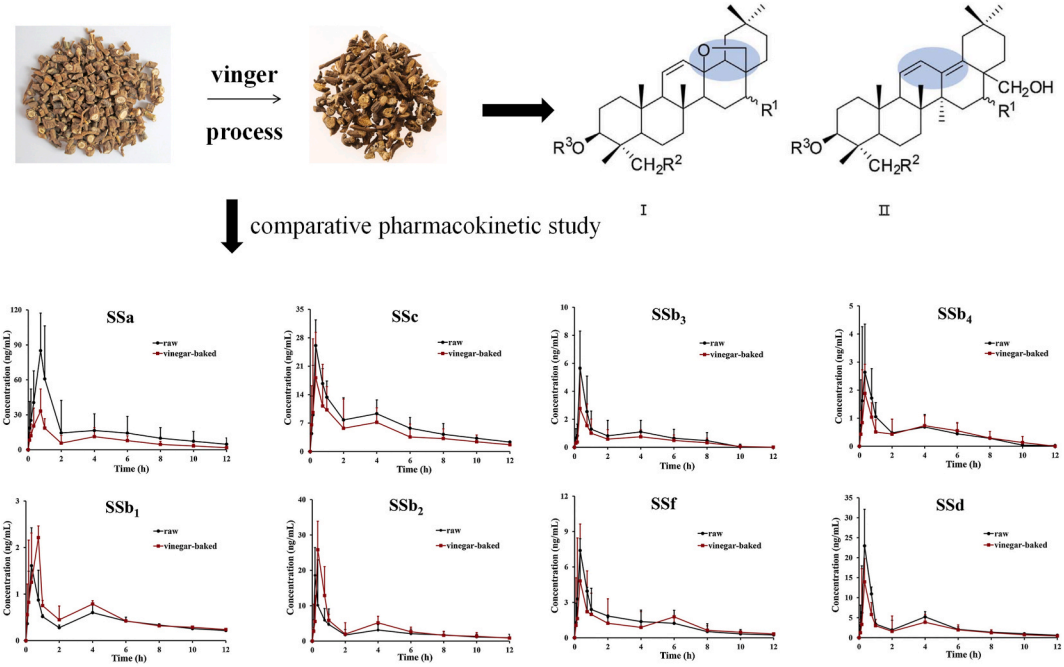
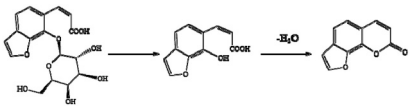
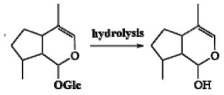
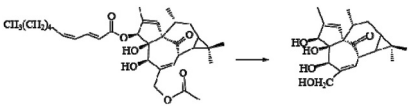
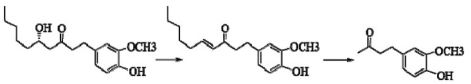
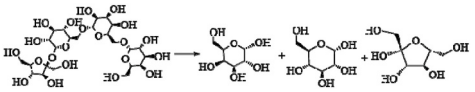


Fig. 7. Structural transformation and pharmacokinetic curves of saikosaponins in *Radix Bupleuri* before and after stir-baked with vinegar [51].

Table 1
Techniques applied in the study of the processing of TCM.

Technologies and methods	Type of reaction	Example	Reactive component	Chemical reaction	References
Pharmacokinetic and Toxicokinetic Study	dehydration reaction	*Psoraleae Fructus*	psoralen and isopsoralen		[61]
Metabolomic strategies and biochemical analysis	hydrolysis reaction	*Rehmanni-ae Radix*	iridoids		[19]
Simulation processing	hydrolysis reaction	*Kansui Radix*	diterpenoid		[39]
Non-targeted metabonomics combining with SIBDV method	decomposition reaction	*Zingiberis Rhizoma*	6-gingerol		[62]
Spectrum-effect relationship analysis	hydrolysis reaction	*Rehmanniae Radix*	polysaccharide		[1]

Data availability statement

All data generated or analysed during this study are included in this published article.

CRediT authorship contribution statement

Yiwen Tian: Writing – original draft, Visualization, Methodology, Investigation. **Yun Shi:** Writing – original draft, Resources, Investigation. **Yujie Zhu:** Investigation, Data curation. **Huan Li:** Methodology, Investigation. **Jinyang Shen:** Resources, Methodology, Investigation. **Xun Gao:** Formal analysis, Data curation. **Baochang Cai:** Resources, Investigation, Funding acquisition, Formal analysis, Data curation. **Weidong Li:** Writing – review & editing, Funding acquisition, Data curation. **Kunming Qin:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by National Nature Science Foundation of China (No. 82374038, 82104349, 81973484), Major Projects of Natural Science Foundation of Jiangsu Higher Education Institutions (No. 21KJA360005).

References

[1] P.Y. Gong, Y.J. Guo, Y.S. Tian, L.F. Gu, J. Qi, B.Y. Yu, Reverse tracing anti-thrombotic active ingredients from dried Rehmannia Radix based on multidimensional spectrum-effect relationship analysis of steaming and drying for nine cycles, J. Ethnopharmacol. 276 (2021) 114177, https://doi.org/10.1016/j.jep.2021.114177.
[2] Y.H. Shi, Y.F. Huang, W.Y. Wang, L. Yang, H. Zhou, Z. Sang, Analysis on the current quality standards of Chinese materia Medica used in COVID-19 prevention and treatment, Pharmacol. Res. 160 (2020) 105074, https://doi.org/10.1016/j.phrs.2020.105074.
[3] S. Kumar, M. Verma, Y.A. Hajam, R. Kumar, Honey infused with herbs: a boon to cure pathological diseases, Heliyon 10 (2024) e23302, https://doi.org/10.1016/j.heliyon.2023.e23302.
[4] J. Yang, M. Miao, Analysis of the influence of different drying methods on the active ingredients of fresh medicine, Chin. Med. Nat. Prod. 2 (2022) e1–e4, https://doi.org/10.1055/s-0042-1745645.
[5] C. Chen, Q. Lv, Y. Li, Y.H. Jin, The anti-tumor effect and underlying apoptotic mechanism of ginsenoside Rk1 and Rg5 in human liver cancer cells, Molecules (2021) 26, https://doi.org/10.3390/molecules26133926.

[6] J. Hou, R. Ma, S. Zhu, Y. Wang, Revealing the therapeutic targets and mechanism of ginsenoside Rg1 for liver damage related to anti-oxidative stress using proteomic analysis, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms231710045.

[7] S.W. Kim, B.C. Han, S.H. So, C.K. Han, G. In, C.K. Park, S.H. Hyun, Biodistribution and pharmacokinetic evaluation of Korean Red Ginseng components using radioisotopes in a rat model, J. Ginseng Res. 47 (2023) 74–80, https://doi.org/10.1016/j.jgr.2022.05.001.

[8] X.M. Piao, Y. Huo, J.P. Kang, R. Mathiyalagan, H. Zhang, D.U. Yang, M. Kim, D.C. Yang, S.C. Kang, Y.P. Wang, Diversity of ginsenoside profiles produced by various processing technologies, Molecules 25 (2020), https://doi.org/10.3390/molecules25194390.

[9] W. Fan, Y. Yang, L. Li, L. Fan, Z. Wang, L. Yang, Mass spectrometry-based profiling and imaging strategy, a fit-for-purpose tool for unveiling the transformations of ginsenosides in Panax notoginseng during processing, Phytomedicine : Int. J. Phytother. Phytopharmacol. 103 (2022) 154223, https://doi.org/10.1016/j.phymed.2022.154223.

[10] J.W. Lee, S.H. Ji, B.R. Choi, D.J. Choi, Y.G. Lee, H.G. Kim, G.S. Kim, K. Kim, Y.H. Lee, N.I. Baek, D.Y. Lee, UPLC-QTOF/MS-Based metabolomics applied for the quality evaluation of four processed Panax ginseng products, Molecules 23 (2018), https://doi.org/10.3390/molecules23082062.

[11] L. Zhu, X. Luan, D. Dou, L. Huang, Comparative analysis of ginsenosides and oligosaccharides in white ginseng (WG), red ginseng (RG) and black ginseng (BG), J. Chromatogr. Sci. 57 (2019) 403–410, https://doi.org/10.1093/chromsci/bmz004.

[12] M. Murugesan, R. Mathiyalagan, V. Boopathi, B.M. Kong, S.K. Choi, C.S. Lee, D.C. Yang, S.C. Kang, T. Thambi, Production of minor ginsenoside CK from major ginsenosides by biotransformation and its advances in targeted delivery to tumor tissues using nanoformulations, Nanomaterials (2022) 12, https://doi.org/10.3390/nano12193427.

[13] S. Xue, L. Wang, S. Chen, Y. Cheng, Simultaneous analysis of saccharides between fresh and processed radix Rehmanniae by HPLC and UHPLC-LTQ-orbitrap-MS with multivariate statistical analysis, Molecules (2018) 23, https://doi.org/10.3390/molecules23030541.

[14] X.M. Lu, L.Y. Zhong, S. Wang, Y.W. Deng, H. Liu, M.X. Chen, Y. Huang, H.L. Tong, [Effect of processing method on chemical constituents of Rehmanniae Radix: based on UHPLC-LTQ-Orbitrap MS], Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China J. Chin. Mater. Med. 48 (2023) 399–414, https://doi.org/10.19540/j.cnki.cjcmm.20220816.301.

[15] U.J. Youn, B.S. Gu, K.H. Kim, C. Ha, I.C. Jung, Variation of main components according to the number of steaming and drying of Rehmanniae radix preparata, J. Pharmacopuncture 21 (2018) 112–119, https://doi.org/10.3831/kpi.2018.21.014.

[16] L. Zhou, J.D. Xu, S.S. Zhou, H. Shen, Q. Mao, M. Kong, Y.T. Zou, Y.Y. Xu, J. Xu, S.L. Li, Chemomics-based marker compounds mining and mimetic processing for exploring chemical mechanisms in traditional processing of herbal medicines, a continuous study on Rehmanniae Radix, J. Chromatogr. A 1530 (2017) 232–240, https://doi.org/10.1016/j.chroma.2017.11.036.

[17] W. Zhang, N. Cui, F. Su, Y. Wang, B. Yang, Y. Sun, W. Guan, H. Kuang, Q. Wang, Comprehensive metabolomics and network pharmacology to explore the mechanism of 5-hydroxymethyl furfural in the treatment of blood deficiency syndrome, Front. Pharmacol. 12 (2021) 811331, https://doi.org/10.3389/fphar.2021.811331.

[18] S. Xue, Y. Fu, X. Sun, S. Chen, Changes in the chemical components of processed Rehmanniae radix distillate during different steaming times, evidence-based complementary and alternative medicine, eCAM 2022 (2022) 3382333, https://doi.org/10.1155/2022/3382333.

[19] P.Y. Gong, Y.S. Tian, Y.J. Guo, L.F. Gu, J.Y. Li, J. Qi, B.Y. Yu, Comparisons of antithrombosis, hematopoietic effects and chemical profiles of dried and rice wine-processed Rehmanniae Radix extracts, J. Ethnopharmacol. 231 (2019) 394–402, https://doi.org/10.1016/j.jep.2018.10.025.

[20] Y.Y. Wang, N. Zhou, Z.F. Shan, Y.Y. Ke, Z. Liu, Z.H. Liu, W.S. Feng, X.K. Zheng, Metabolomic strategies and biochemical analysis of the effect of processed Rehmanniae radix extract on a blood-deficient rat model, BMC Complement. Med. Ther. 22 (2022) 89, https://doi.org/10.1186/s12906-022-03560-x.

[21] W.S. Kong, G. Zhou, L.W. Xu, K. Wang, Y.M. Feng, L.Y. Tao, R.F. Xie, M. Yang, X. Zhou, Beware of the potential risks for Polygoni Multiflori caulis-induced liver injury, Front. Pharmacol. 13 (2022) 868327, https://doi.org/10.3389/fphar.2022.868327.

[22] L. Kang, D. Li, X. Jiang, Y. Zhang, M. Pan, Y. Hu, L. Si, Y. Zhang, J. Huang, Hepatotoxicity of the major anthraquinones derived from Polygoni Multiflori radix based on bile acid homeostasis, Front. Pharmacol. 13 (2022) 878817, https://doi.org/10.3389/fphar.2022.878817.

[23] Y. Lin, R. Xiao, B.H. Xia, Z.M. Zhang, C. Li, P. Wu, D.F. Liao, L.M. Lin, Investigation of the idiosyncratic hepatotoxicity of Polygonum multiflorum Thunb. through metabolomics using GC-MS, BMC Complement. Med. Ther. 21 (2021) 120, https://doi.org/10.1186/s12906-021-03276-4.

[24] L. Zhang, J. Chen, Biological effects of tetrahydroxystilbene glucoside: an active component of a rhizome extracted from Polygonum multiflorum, Oxid. Med. Cell. Longev. 2018 (2018) 3641960, https://doi.org/10.1155/2018/3641960.

[25] J. Qian, M. Hou, X. Wu, C. Dai, J. Sun, L. Dong, A review on the extraction, purification, detection, and pharmacological effects of 2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucoside from Polygonum multiflorum, Biomed. Pharmacother. = Biomed. Pharmacother. 124 (2020) 109923, https://doi.org/10.1016/j.biopha.2020.109923.

[26] D. Xin, H. Li, S. Zhou, H. Zhong, W. Pu, Effects of anthraquinones on immune responses and inflammatory diseases, Molecules 27 (2022), https://doi.org/10.3390/molecules27123831.

[27] X.R. Zhai, Z.S. Zou, J.B. Wang, X.H. Xiao, Herb-induced liver injury related to reynoutria multiflora (Thunb.) moldenke: risk factors, molecular and mechanistic specifics, Front. Pharmacol. 12 (2021) 738577, https://doi.org/10.3389/fphar.2021.738577.

[28] H. Li, X. Wang, Y. Liu, D. Pan, Y. Wang, N. Yang, L. Xiang, X. Cai, Y. Feng, Hepatoprotection and hepatotoxicity of Heshouwu, a Chinese medicinal herb: context of the paradoxical effect, Food Chem. Toxicol. : Int. J. Publ. Brit. Indus. Biol. Res. Assoc. 108 (2017) 407–418, https://doi.org/10.1016/j.fct.2016.07.035.

[29] J. Zhang, D. Li, D. Zhong, Q. Zhou, Y. Yin, J. Gao, C. Peng, Processed lateral root of Aconitum carmichaelii Debx.: a review of cardiotonic effects and cardiotoxicity on molecular mechanisms, Front. Pharmacol. 13 (2022) 1026219, https://doi.org/10.3389/fphar.2022.1026219.

[30] M. Wang, W.J. Hu, X. Zhou, K. Yu, Y. Wang, B.Y. Yang, H.X. Kuang, Ethnopharmacological use, pharmacology, toxicology, phytochemistry, and progress in Chinese crude drug processing of the lateral root of Aconitum carmichaelii Debeaux. (Fuzi): a review, J. Ethnopharmacol. 301 (2023) 115838, https://doi.org/10.1016/j.jep.2022.115838.

[31] M. Yang, X. Ji, Z. Zuo, Relationships between the toxicities of radix aconiti lateralis preparata (Fuzi) and the toxicokinetics of its main diester-diterpenoid alkaloids, Toxins 10 (2018), https://doi.org/10.3390/toxins10100391.

[32] S. Liu, F. Li, Y. Li, W. Li, J. Xu, H. Du, A review of traditional and current methods used to potentially reduce toxicity of Aconitum roots in Traditional Chinese Medicine, J. Ethnopharmacol. 207 (2017) 237–250, https://doi.org/10.1016/j.jep.2017.06.038.

[33] R. Guo, Q. Ren, Y.X. Tang, F. Zhao, B. Lin, X.X. Huang, S.J. Song, Sesquiterpenoids from the roots of Daphne genkwa Siebold et Zucc. With potential anti-inflammatory activity, Phytochemistry 174 (2020) 112348, https://doi.org/10.1016/j.phytochem.2020.112348.

[34] D.C. Zhou, G. Zheng, L.Y. Jia, X. He, C.F. Zhang, C.Z. Wang, C.S. Yuan, Comprehensive evaluation on anti-inflammatory and anti-angiogenic activities in vitro of fourteen flavonoids from Daphne Genkwa based on the combination of efficacy coefficient method and principal component analysis, J. Ethnopharmacol. 268 (2021) 113683, https://doi.org/10.1016/j.jep.2020.113683.

[35] Y.W. Sun, Y. Bao, H. Yu, Q.J. Chen, F. Lu, S. Zhai, C.F. Zhang, F. Li, C.Z. Wang, C.S. Yuan, Anti-rheumatoid arthritis effects of flavonoids from Daphne genkwa, Int. Immunopharm. 83 (2020) 106384, https://doi.org/10.1016/j.intimp.2020.106384.

[36] Z. Wang, Y. Chu, Y. Zhang, Y. Chen, J. Zhang, X. Chen, Investigation of potential toxic components based on the identification of Genkwa Flos chemical constituents and their metabolites by high-performance liquid chromatography coupled with a Q Exactive high-resolution benchtop quadrupole Orbitrap mass spectrometer, J. Separ. Sci. 41 (2018) 3328–3338, https://doi.org/10.1002/jssc.201800424.

[37] Y. Tao, D. Su, W. Li, B. Cai, Pharmacokinetic comparisons of six components from raw and vinegar-processed Daphne genkwa aqueous extracts following oral administration in rats by employing UHPLC-MS/MS approaches, J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 1079 (2018) 34–40, https://doi.org/10.1016/j.jchromb.2018.02.005.

[38] Q. Zhang, Z.L. Li, Y. Zhang, K. Wang, M. Zhang, P.D. Chen, W.F. Yao, Y.P. Tang, J.H. Wu, L. Zhang, Effect of the vinegar-process on chemical compositions and biological activities of Euphorbia kansui: a review, J. Ethnopharmacol. 252 (2020) 112557, https://doi.org/10.1016/j.jep.2020.112557.

[39] Q. Zhang, Y. Zhang, S.K. Zhou, K. Wang, M. Zhang, P.D. Chen, W.F. Yao, Y.P. Tang, J.H. Wu, L. Zhang, Toxicity reduction of Euphorbia kansui stir-fried with vinegar based on conversion of 3-O-(2'E,4'Z-Decadi-enoyl)-20-O-acetylingenol, Molecules 24 (2019), https://doi.org/10.3390/molecules24203806.

[40] Q. Zhang, Y.H. Ju, Y. Zhang, K. Wang, M. Zhang, P.D. Chen, W.F. Yao, Y.P. Tang, J.H. Wu, L. Zhang, The water expelling effect evaluation of 3-O-(2'E,4'Z-decadienoyl)-20-O-acetylingenol and ingenol on H22 mouse hepatoma ascites model and their content differences analysis in Euphorbia kansui before and after stir-fried with vinegar by UPLC, J. Ethnopharmacol. 267 (2021) 113507, https://doi.org/10.1016/j.jep.2020.113507.
[41] Y. Zhang, J. Gao, Q. Zhang, K. Wang, W. Yao, B. Bao, L. Zhang, Y. Tang, Interpretation of Euphorbia kansui stir-fried with vinegar treating malignant ascites by a UPLC-Q-TOF/MS based rat serum and urine metabolomics strategy coupled with network pharmacology, Molecules (2018) 23, https://doi.org/10.3390/molecules23123246.
[42] X. Yan, L. Zhang, J. Guo, Y. Cao, E. Shang, Y. Tang, A. Ding, J.A. Duan, Processing of kansui roots stir-baked with vinegar reduces kansui-induced hepatocyte cytotoxicity by decreasing the contents of toxic terpenoids and regulating the cell apoptosis pathway, Molecules 19 (2014) 7237–7254, https://doi.org/10.3390/molecules19067237.
[43] Q. Ma, C.Z. Wang, W.R. Sawadogo, Z.X. Bian, C.S. Yuan, Herbal medicines for constipation and phytochemical comparison of active components, Am. J. Chin. Med. 50 (2022) 723–732, https://doi.org/10.1142/s0192415x2250029x.
[44] T. Zhuang, X. Gu, N. Zhou, L. Ding, L. Yang, M. Zhou, Hepatoprotection and hepatotoxicity of Chinese herb rhubarb (Dahuang): how to properly control the "general (Jiang Jun)" in Chinese medical herb, Biomed. Pharmacother. = Biomed. Pharmacother. 127 (2020) 110224, https://doi.org/10.1016/j.biopha.2020.110224.
[45] Y. Cheng, H. Zhang, L. Qu, Y. He, M.N. Routledge, Y. Yun Gong, B. Qiao, Identification of rhein as the metabolite responsible for toxicity of rhubarb anthraquinones, Food Chem. 331 (2020) 127363, https://doi.org/10.1016/j.foodchem.2020.127363.
[46] J. Zhang, Y. Fu, L. Li, Y. Liu, C. Zhang, D. Yu, Y. Ma, Y. Xiao, Pharmacokinetic comparisons of major bioactive components after oral administration of raw and steamed rhubarb by UPLC-MS/MS, J. Pharmaceut. Biomed. Anal. 171 (2019) 43–51, https://doi.org/10.1016/j.jpba.2019.04.002.
[47] P. Zhou, J. Zhang, Y. Xu, P. Zhang, Y. Xiao, Y. Liu, Simultaneous quantification of anthraquinone glycosides, aglycones, and glucuronic acid metabolites in rat plasma and tissues after oral administration of raw and steamed rhubarb in blood stasis rats by UHPLC-MS/MS, J. Separ. Sci. 45 (2022) 529–541, https://doi.org/10.1002/jssc.202100623.
[48] Y. Wu, L. Liu, Y. Zhao, R. Zhao, Polysaccharides of vinegar-baked radix bupleuri promote the hepatic targeting effect of oxymatrine by regulating the protein expression of HNF4α, Mrp2, and OCT1, J. Ethnopharmacol. 267 (2021) 113471, https://doi.org/10.1016/j.jep.2020.113471.
[49] X. Li, X. Li, N. Huang, R. Liu, R. Sun, A comprehensive review and perspectives on pharmacology and toxicology of saikosaponins, Phytomedicine : Int. J. Phytother. Phytopharmacol. 50 (2018) 73–87, https://doi.org/10.1016/j.phymed.2018.09.174.
[50] T. Lei, D. Zhang, K. Guo, M. Li, C. Lv, J. Wang, L. Jia, J. Lu, Validated UPLC-MS/MS method for simultaneous quantification of eight saikosaponins in rat plasma: application to a comparative pharmacokinetic study in depression rats after oral administration of extracts of raw and vinegar-baked Bupleuri Radix, J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 1060 (2017) 231–239, https://doi.org/10.1016/j.jchromb.2017.06.007.
[51] B. Yuan, R. Yang, Y. Ma, S. Zhou, X. Zhang, Y. Liu, A systematic review of the active saikosaponins and extracts isolated from Radix Bupleuri and their applications, Pharmaceut. Biol. 55 (2017) 620–635, https://doi.org/10.1080/13880209.2016.1262433.
[52] R. Fu, J. Liu, Y. Xue, Z. Zhang, R. Song, Effects of animal strain, dose, and cotreatment with saikosaponin b(2) on the pharmacokinetics of saikosaponin a in rats, Eur. J. Drug Metabol. Pharmacokinet. 44 (2019) 827–836, https://doi.org/10.1007/s13318-019-00569-5.
[53] Y. Tao, Y. Ren, W. Li, B. Cai, L. Di, L. Shi, L. Hu, Comparative pharmacokinetic analysis of extracts of crude and wine-processed Dipsacus asper in rats by a sensitive ultra performance liquid chromatography-tandem mass spectrometry approach, J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 1036–1037 (2016) 33–41, https://doi.org/10.1016/j.jchromb.2016.09.024.
[54] G. Xue, S. Su, P. Yan, J. Shang, J. Wang, C. Yan, J. Li, Q. Wang, X. Xiong, H. Xu, Integrative analyses of widely targeted metabolomic profiling and derivatization-based LC-MS/MS reveals metabolic changes of Zingiberis Rhizoma and its processed products, Food Chem. 389 (2022) 133068, https://doi.org/10.1016/j.foodchem.2022.133068.
[55] L. Hu, Y. Xiong, Z. Zou, Y. Yang, J. He, L. Zhong, Y. Wang, M. Yang, Identifying the chemical markers in raw and wine-processed Scutellaria baicalensis by ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry coupled with multiple statistical strategies, Biomed. Chromatogr. : BMC (Biomed. Chromatogr.) 34 (2020) e4849, https://doi.org/10.1002/bmc.4849.
[56] Y. Song, B. Shan, S. Zeng, J. Zhang, C. Jin, Z. Liao, T. Wang, Q. Zeng, H. He, F. Wei, Z. Ai, D. Su, Raw and wine processed Schisandra chinensis attenuate anxiety like behavior via modulating gut microbiota and lipid metabolism pathway, J. Ethnopharmacol. 266 (2021) 113426, https://doi.org/10.1016/j.jep.2020.113426.
[57] T. Jiang, T. Wu, P. Gao, L. Wang, X. Yang, X. Chen, Y. Chen, C. Yue, K. Liang, L. Tang, Z. Wang, Research on processing-induced chemical variations in polygonatum cyrtonema rhizome by integrating metabolomics and glycomics, Molecules (2022) 27, https://doi.org/10.3390/molecules27185869.
[58] F. Xia, C. Liu, J.B. Wan, Characterization of the cold and hot natures of raw and processed Rehmanniae Radix by integrated metabolomics and network pharmacology, Phytomedicine : Int. J. Phytother. Phytopharmacol. 74 (2020) 153071, https://doi.org/10.1016/j.phymed.2019.153071.
[59] Y. Tao, E. Jiang, B. Cai, A biochemometrics strategy combining quantitative determination, bioactivity evaluation and relationship analysis for identification of analgesic alkaloids of raw and vinegar-processed Corydalis turtschaninovii, J. Separ. Sci. 43 (2020) 1183–1189, https://doi.org/10.1002/jssc.201901021.
[60] Y. Song, J. Yang, X. Hu, H. Gao, P. Wang, X. Wang, Y. Liu, X. Cheng, F. Wei, S. Ma, A stepwise strategy integrating metabolomics and pseudotargeted spectrum-effect relationship to elucidate the potential hepatotoxic components in Polygonum multiflorum, Front. Pharmacol. 13 (2022) 935336, https://doi.org/10.3389/fphar.2022.935336.
[61] L. Yang, Y.L. Yu, L.Y. Cheng, P.Y. Zhang, Y. Zhang, K. Zhou, The accumulation of psoralen contributes to its hepatotoxicity revealed by pharmacokinetic and toxicokinetic study after repeated administration, ACS Omega 5 (2020) 7307–7315, https://doi.org/10.1021/acsomega.9b04153.
[62] G. Xue, S. Su, P. Yan, J. Shang, J. Wang, C. Yan, J. Li, Q. Wang, Y. Du, L. Cao, H. Xu, Quality control of Zingiberis Rhizoma and its processed products by UHPLC-Q-TOF/MS-based non-targeted metabonomics combining with SIBDV method, Food Res. Int. 154 (2022) 111021, https://doi.org/10.1016/j.foodres.2022.111021.