JOURNAL OF FOOD AND DRUG ANALYSIS 26 (2018) S96–S114

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journal homepage: www.jfda-online.com

Review Article

Effects of processing adjuvants on traditional Chinese herbs

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ARTICLE INFO

Article history:
Received 1 October 2017
Received in revised form
27 January 2018
Accepted 1 February 2018
Available online 19 March 2018

Keywords:
Adjuvant
Processing
Synergism
Traditional Chinese medicine

ABSTRACT

Processing of Chinese medicines is a pharmaceutical technique that transforms medicinal raw materials into decoction pieces for use in different therapies. Various adjuvants, such as vinegar, wine, honey, and brine, are used in the processing to enhance the efficacy and reduce the toxicity of crude drugs. Proper processing is essential to ensure the quality and safety of traditional Chinese medicines (TCMs). Therefore, sound knowledge of processing principles is crucial to the standardized use of these processing adjuvants and to facilitate the production and clinical use of decoction pieces. Many scientific reports have indicated the synergistic effects of processing mechanisms on the chemistry, pharmacology, and pharmacokinetics of the active ingredients in TCMs. Under certain conditions, adjuvants change the content of active or toxic components in drugs by chemical or physical transformation, increase or decrease drug dissolution, exert their own pharmacological effects, or alter drug pharmacokinetics. This review summarizes various processing methods adopted in the last two decades, and highlights current approaches to identify the effects of processing parameters on TCMs.

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https://doi.org/10.1016/j.jfda.2018.02.004

1. Introduction

Chinese medicinal processing is a pharmaceutical technique that transforms medicinal raw materials into decoction pieces for use in different therapies based on traditional Chinese medicine (TCM). Processing of crude drugs into decoction pieces is a precious heritage and traditional practice in China, which plays an important role in disease prevention and treatment. The Chinese medicinal materials (CMM) originate from plants, animals, or minerals must undergo appropriate treatments before use as a decoction or other TCM preparations. The Chinese herbal property theory, one of the basic theories in TCM, provides directions for the clinical use of herbs. This theory classifies Chinese herbal properties into four natures, five flavors, ascending or descending, floating or sinking, channel tropism, and toxicity [1]. According to this theory, herbs have special affinities to certain organs and channel systems of the body, and exhibit special effects on diseases of these systems and organs [2]. The potency and toxicity of these herbs may be standardized by processing them according to their characteristics and clinical purpose. Traditional methods, such as stir-frying and steaming, are widely used in herb-processing to prevent exaggerated pharmacological actions, alleviate side effects, modify energy properties (nature, flavor, and channel tropism), mask disagreeable odors, or prolong the shelf-life of crude herbs [3]. Adjuvants are often added to enhance therapeutic effects or minimize drug toxicity, thereby broadening the spectrum of clinical application of the processed drugs. Commonly used adjuvants include vinegar, honey, wine, brine, ginger juice, bran, and rice. Drugs are processed with selected adjuvants based on their specific properties—frying with vinegar adds to the liver-soothing and analgesic effects of drugs, and honey confers Qi-nourishing and lung-moistening effects. Accordingly, the source and quality of adjuvants notably affect the efficacy of processed drugs. The Chinese Pharmacopoeia (2015 edition) lists 117 decoction pieces that are processed with various adjuvants, accounting for 55% of the total number of listed drugs [4]. Compared to simple heat treatment, addition of adjuvants allows tailored enhancement of therapeutic properties of drugs. However, it also complicates the standardization of drug processing methods. Despite being officially described in the Chinese Pharmacopoeia, standards of quality control for processing adjuvants and processed drugs are still lacking. Zhao et al. have discussed the various problems in CMM processing, and emphasized that traditional processing procedures need to be further organized, validated and implemented with scientific understanding to safeguard the quality of decoction pieces [3].

Processing makes TCMs different from other oriental and Western herbal medicines. However, classical TCM theories emphasize on the holistic understanding of diseases and drugs, instead of studying their isolated details. Though classic processing theory and methods have been proven reasonable and reliable in the long-standing clinical practice of TCM, the underlying scientific principles remain largely unknown, affecting the production and use of decoction pieces. Standardization of processing methods, quality control of adjuvants, and related clinical studies were neglected in the past until serious drug misadventures occurred due to improperly processed herbs. Approximately 2396 of 12,354 (19.4%) adverse events, associated with TCM use between 1949 and 2008 in China, are reported to be ascribable to improper processing; besides, over 7000 cases of poisoning due to unprocessed aconitum plants have been reported in the past decade [5,6]. A multi-herb formula is therapeutically more beneficial than a single herb, due to its effects on multiple targets. Synergistic pharmacological effects are often observed with herbal medicines because plant extracts contain compounds that potentiate the action of each other [7]. We speculate that adjuvants similarly act to potentiate the pharmacological effects of drugs. However, identifying their targets at a molecular level is challenging. Fortunately, advanced analytical tools such as MS, NMR, high-throughput screening and omics, offer new avenues to conduct research on TCM at the cellular and molecular level [8]. Significant progress made in this direction in the past two decades necessitates a systematic review to summarize the accumulated knowledge. This review summarizes the commonly used adjuvants and their chemical, pharmacological, and pharmacokinetic mechanisms of synergistic potentiation of drug therapy as well as recent methodological approaches to identify these mechanisms.

2. Mechanisms of interaction between herbs and various processing adjuvants

2.1. *Vinegar*

Vinegar is consumed as a food condiment worldwide, especially in Chinese cuisines, and also has medicinal uses due to its physiological effects. Different types of vinegars contain organic acids, aldehydes, esters, alcohols, phenols, flavonoids, and ligustrazine [9]. Traditionally, vinegar is widely used in the processing of herbs that soothe the liver, relieve depression, prevent blood stasis, relieve pain, and act as purgatives.

Bupleuri Radix (Chaihu in Chinese), the dried root of *Bupleurum falcatum* L., is used as a herbal medicine in East Asia to treat influenza, common cold, fever, inflammation, malaria, and menstrual disorders [10]. Vinegar-baked Chaihu has a stronger effect than unprocessed Chaihu on soothing liver and relieving depression. Volatile oils and saikosaponins are the main active ingredients of Chaihu. Baking in vinegar is reported to significantly decrease the content of volatile oils and other antipyretic and anti-inflammatory components, including

n-hexanal, n-heptanal, 2-amylfuran, and (*E*,*E*)-2,4-sebacic olefin aldehyde [11]. The combined action of heat and acetic acid in vinegar transforms the 13,28-epoxy bridge into a heteroannular diene structure, which accordingly changes saikosaponins a, c, and d to saikosaponins b1 and b2 [12]. Saikosaponins a and d possess notable anti-inflammatory activities, whereas saikosaponin b is a hepatoprotective [13]. In a CCl_4-induced liver injury rat model, processed Chaihu exhibited better hepatoprotective effects than raw Chaihu [14]. Additionally, vinegar-baked Chaihu is reported to be a stronger inducer of monoamine neurotransmitters in the depressed mouse brain than crude Chaihu [15]. These findings verify that crude Chaihu may be used for relieving exterior syndromes (cold and fever, white tongue coating, and floating pulse), whereas vinegar-baked Chaihu soothes the liver and relieves depression.

Kansui Radix (Kansui) is the dried root tuber of *Euphorbia kansui* T. N. Liou ex. T. P. Wang, well-known for treating edema, ascites, and asthma. However, side effects of Kansui, such as inflammation, skin irritation, tumorigenesis, and hepatorenal lesions, limit its clinical use [16]. Ingenol and jatrophane diterpene esters are supposed to be responsible for its toxicity, and these terpenes were found decreased in vinegar-baked Kansui [17]. Transesterification also occurred during baking, leading to the conversion of the toxic 3-acyl ester into the non-toxic 20-acyl ester [18]. Additionally, toxic diterpenes react with organic acids in vinegar to form less water-soluble acylated diterpenes, which diminishes their toxicity [19]. Vinegar-baked Kansui has better effects on relieving ascites, reducing gastrointestinal irritation, and attenuating hepatorenal toxicity than unprocessed [20]. Both Phytolacca Radix (Shanglu), the dried root of *Phytolacca acinosa* Roxb. or *Phytolacca americana* L. (Phytolaccaceae), and Genkwa Flos (Yuanhua), the dried flower bud of *Daphne genkwa* Sieb.et Zucc. (Thymelaeaceae), are diuretics and are processed by vinegar-baking to reduce their toxicities. Vinegar significantly decreases the content of the toxic saponins, EsC and EsB, in Shanglu and increases the content of the therapeutically active saponin, EsA [21–24]. Furthermore, vinegar-baking decreases the levels of the toxic benzoyl-diterpenes, yuanhuacin and genkwadaphnin, practically eliminating the toxicity of Yuanhua [25,26].

In addition to its detoxifying effects, vinegar increases the water solubility of active substances in herbs, thereby increasing their pharmacological activities. Corydalis Rhizoma (Yanhusuo), the dried tuber of *Corydalis yanhusuo* (Papaveraceae), promotes blood circulation and relieves pain. Vinegar-baking potentiates these effects as the acetic acid in vinegar solubilizes the free alkaloids of Yanhusuo [27,28].

In general, acetic acid in vinegar along with the high temperature of baking promotes complex chemical reactions, such as pyrolysis, hydrolysis, esterification, and salification. Moreover, various pharmacological effects of vinegar *per se* have been explored, and the improved therapeutic effect of vinegar-processed drugs could be due to several mechanisms of actions [29]. Further research works are needed to support the reports of the benefits of vinegar on drug processing.

2.2. Honey

Herbs are usually fried with honey to improve their Qi-nourishing and lung-moistening effects. Ephedrae Herba (Mahuang), the dried stem of *Ephedra sinica* Stapf (Ephedraceae), is notably used for diaphoresis and relieving exterior syndromes in Chinese medicine. Frying in honey reduces the volatile oil content, responsible for diaphoresis, whereas the contents of ephedrine and pseudoephedrine only decrease slightly [30,31]. Thus, the cough-relieving and anti-asthmatic effects become relatively prominent when the effect of diaphoresis is weakened [32]. Consequently, Mahuang is traditionally processed by frying in honey for its effects of relieving cough and asthma. Nevertheless, honey may also possess its own antitussive effects, which might be majorly responsible for synergistically increasing the cough-relieving properties of Mahuang, rather than its effects on volatile oil composition. This is evident in many cultures, where honey is used as an alternative remedy to treat the symptoms of upper respiratory tract infections (URIs), including cough [33]. Honey-frying is also used to process other lung-moistening and antitussive herbs, such as Peucedani Radix (Qianhu), Farfarae Flos (Kuandonghua), Eriobotryae Folium (Pipaye), and Stemoae Radix (Baibu) [34–40].

Due to its high glucose and fructose contents, honey boosts nonspecific immunity and macrophage phagocytosis *in vivo* [41]. TCM theory proposes that Qi-tonifying effects on the body are associated with improved immune function, including the activation of T and B lymphocytes and regulation of innate immunity [42]. Therefore, licorice [the root of *Glycyrrhiza glabra* L. (Fabaceae)] and other tonic herbs are fried with honey to increase their spleen-stimulating and Qi-enhancing effects. A study showed that, compared with simply fried product, honey-frying does not alter the composition of licorice; however, honey-fried licorice aids weight gain, prevents fatigue, and improves the spleen and thymus indices in mice [43].

Several foods and drugs either induce or inhibit CYP activity to alter drug pharmacokinetics and pharmacodynamics [44]. Animal studies have shown that multiple doses of honey induce CYP3A4 but inhibit CYP2C9 activity, whereas a clinical trial revealed that honey from south India only induces CYP3A4 activity in healthy volunteers [45]. Flavones and polyphenols in honey were shown to be responsible for the CYP3A4 induction; however, further studies on the therapeutic effects of honey-processed herbs are required [46]. It is worth noting that herbs are usually processed with refined honey, which differs from raw honey in its chemical and pharmacological characteristics. Because the source of honey has a great influence on its composition and herb-processing effects, mentioning the source is crucial.

2.3. Wine

Wine is popularly used in herb processing. Ancient literature reports that wine changes herbal nature by promoting the upward direction and cleaning the upper-energizer heat, thereby enhancing the efficacy of herbs for invigorating the blood [47]. Alcohol is a good organic solvent that dissolves most water-soluble or insoluble substances in herbs. Due to its good permeability, it enters plant tissues to promote displacement, diffusion, and dissolution of the phytoconstituents. Rhubarb, the root of *Rheum palmatum* L., is a potent purgative, and only a small dose for a short treatment period is recommended [48].

To moderate its potency and toxicity, rhubarb is fried (Shudahuang) or steamed (Jiudahuang) with yellow wine to prepare wine-processed rhubarb. Rhubarb, processed in these ways, exhibits lower purgative and higher anti-blood stasis effects than raw rhubarb [49–51]. Wine decreases conjugated anthraquinone content, and dramatically increases free anthraquinone content, causing mild diarrhea and toxicity [52,53]. It may be hypothesized that heat treatment decomposes the conjugated anthraquinones, and wine promotes the dissolution of active ingredients, thereby reducing the toxicity and enhancing the efficacy of rhubarb [54]. Radix Scutellariae (Huangqin), the dried root of *Scutellariae baicalensis* Georgi, is a well-known TCM used for the treatment of inflammation, ulcers, and hepatitis. Flavonoids, such as baicalin, are responsible for the pharmacological effects of this herb [55]. Pharmacokinetic parameters, such as C_{max} and AUC_{0-t}, of some flavonoids remarkably increased in the upper-energizer tissues (lung and heart) but decreased in the middle- and lower-energizer tissues (spleen, liver, and kidney) of rats administered wine-processed Huangqin compared with those in rats administered unprocessed Huangqin [56]. Tissue distribution of flavonoids agrees with the ascending and descending theory, indicating that wine has the ability to "induce medicine upward" and concentrate drug components on upper-energizer tissues [47]. Wine processing along with heat treatment increases the dissolution of flavonoids in Huangqin, by increasing the total surface area, fractal dimension, and mesopores [57]. Baicalin and wogonoside are the main active flavonoid glycosides of Huangqin that tend to be hydrolyzed by some enzymes in crude herbs. Wine-processing could deactivate the enzymes to reduce their loss, thereby improve the antibacterial and anti-inflammatory effects [58].

Moreover, alcohol, being a natural preservative, allows the storage of medicinal liquor for months or years without deterioration. Wine also masks unpleasant odors and increases palatability. Drugs of animal origin, such as those obtained from the *Zaocys* (Wushaoshe) or *Agkistrodon* (Qishe) genera of snakes, Pheretima (Dilong) and geckos (Gejie), have a foul reptilian odor due to trimethylamine. This gut microbial metabolite of choline evaporates with ethanol when such drugs are fried with wine [59].

2.4. *Brine*

Brine is a highly-concentrated solution of salt, especially sodium chloride. According to TCM theory, herbs are processed by frying or steaming after moistening with brine to conduct the drug to the kidney meridian and improve the curative effect on lower-energizer syndrome. Frying the bark of *Eucommia ulmoides* (Duzhong) with brine improves its kidney-tonifying function and alleviates osteoporosis [60]. Salt-frying promotes the absorption and bioavailability of geniposide in Duzhong, even its absolute content decreased sharply after processing [61]. Presence of sodium and chloride ions plausibly improves its intestinal absorption [62]. Psoraleae Fructus (Buguzhi) is the ripe fruit of *Psoralea corylifolia* L. (Fulse). Salt-frying increases the contents of psoralen and isopsoralen coumarins in Buguzhi, increasing their intestinal absorption in rats [63,64]. Salt-processing of Buguzhi is also reported to increase the distribution of psoralen and isopsoralen to generative organs, the heart, and the spleen. Moreover, their distribution to generative organs (lower-energizer) is significantly higher than that to the heart and spleen, thereby directing drugs to the kidney meridian [65]. Although salt-processing alters the pharmacokinetics of both these coumarins, the change in chemical composition is believed to occur by heating. Whether salt participates directly in chemical reactions is yet to be proven. Recently, salt was reported to affect the cell wall permeability of plant tissues, which makes them more susceptible to rupture during processing and help dissolve the phytoconstituents in the decoction. Moreover, by changing the ionic composition of the reaction system, brine processing influences the chemical reactions in herbs [66]. Dietary salt has been proved to affect drug disposition by modulating sympathetic activity and the intestinal expression of CYP3A4 or P-glycoprotein, resulting in a local alteration of drug-metabolizing activity and drug transport in intestine [67,68].

2.5. *Herbal juice*

The processing of crude drugs with juices of herbs is an important part of CMM processing. Ginger and licorice, two herbs frequently appear in TCM formula, are commonly served as adjuvants in drug processing. In addition to modifying the properties of other drugs by chemical or physical interactions, these adjuvants exert their own pharmacological activities via synergistic action on multiple pathways.

Rhizoma Coptis (Huanglian), the dried rhizome of *Coptis chinensis* Franch, is a classic heat-clearing and detoxifying herb that is bitter-cold in nature. After processing with ginger juice, its effect on heat-clearing and the stomach meridian is strengthened. Huanglian has a good anti-bacterial property and serves as a remedy for intestinal infections. An *in vitro* study confirmed that its antibacterial effect was enhanced in combination with ginger juice, which also exerts some anti-bacterial effect [69]. This combination inhibits ethanol-induced damage to the gastric mucosa in rats, owing to the synergistic inhibition of pro-inflammatory cytokine release [70]. Danfupian is obtained by processing desalted aconite [the lateral root of *Aconitum carmichaeli* Debx. (Ranunculaceae)] with juices of licorice and black bean (semen of *Glycine max*). This processing transforms toxic diester alkaloids in aconite into less toxic monoester alkaloids through transesterification with fatty acids of licorice. Moreover, these diester alkaloids form insoluble precipitates with glycyrrhizic acid, thereby reducing aconite toxicity [71].

2.6. *Oil*

Epimedii Folium (Yinyanghuo), the dried leaf of *Epimediium brevicornu* Maxim (Berberidaceae), is used to treat erectile dysfunction in East Asia. However, poor solubility of the active flavonoid components results in poor bioavailability and limited clinical efficacy of Yinyanghuo [72]. According to traditional processing methods, frying with suet oil strengthens its effect of warming kidney and enhancing yang, which has been proved in hydrocortisone-induced kidney-yang deficiency rat models [73]. The synergy between heating and suet oil in the processing of Yinyanghuo perfectly solves the problem of absorption. Heating initiates the deglycation of flavonoid glycosides in Yinyanghuo to produce easily absorbable bioactive flavonoids, such as icariin and baohuoside. Moreover, suet oil along with sodium deoxycholate, an endogenous bile salt, forms self-assembled nanomicelles to promote carrier-mediated absorption [74,75].

2.7. Alum/lime

Pinellia Rhizoma (Banxia), the dried tuber of *Pinellia ternata* (Thunb.) Breit. (Araceae), improves Qi, alleviates external pain and swelling, acts as an anti-emetic, and relieves stuffiness. Sharp raphides of calcium oxalate and an agglutinin present in crude Banxia cause toxicity that manifests as mucosal irritation, leading to tingling sensations on the tongue, tongue swelling, aphonia, vomiting, and diarrhea [76]. Raphides directly pierce the mucous membranes and lead to cell damage. The pro-inflammatory agglutinin stimulates the release of inflammatory mediators and causes pain. Calcium oxalate is water-insoluble at neutral pH; however, soaking in alum/lime water, solubilizes these raphides. It also degrades the toxic agglutinin and diminishes the irritation caused by crude Banxia [77]. To enhance its therapeutic effects, ginger or licorice is used as a secondary adjuvant. Although ginger does not neutralize Banxia toxicity, it acts as an immunosuppressant to reduce inflammatory response [78]. Multi-adjuvant processing also reduces the toxicity of Arisaematis Rhizoma (Tiannanxing) and Typhonii Rhizoma (Baifuzi) [79]. Use of multiple adjuvants in combination synergistically enhances the chemical, physical, and pharmacological aspects of herbs, which is a subtle application of compatibility theory of TCM in herbal processing.

2.8. Solid adjuvants

Solid materials, such as sand, bran, rice, and gecko shell powder, are commonly used to assist stir-frying. Although not chemically involved, these solid adjuvants physically interact with treatment agents. Pangolin scales (Manis Squama) become crisp and easy to decoct after scalding by hot sand [80]. Upon frying, wheat bran absorbs the volatile oils of Rhizoma Atractylodis Macrocephalae (Baizhu) and reduces its dryness [81]. Rice is added while stir-frying the Chinese blister beetle, *Mylabris phalerata* (Meloidae), to keep it at a moderate heat and prevent excessive charring. Furthermore, the added rice absorbs cantharidin, a toxic sesquiterpene secreted by the beetle [82].

2.9. Overview of CMMs processing research

Multifarious materials appeared and phased out over the long course of development of Chinese medicines. At present, over 14 types of adjuvants are recorded in the Chinese pharmacopoeia and applied to more than 100 kinds of drugs. Various commonly used processing adjuvants along with their chemical, pharmacological, toxicological and pharmacokinetic modifications of the processed drugs are listed in Table 1. A diagram of general effects of adjuvants in CMM processing is shown in Fig. 1.

3. Analytical tools for evaluating the effects of processing on herbs

3.1. Chemical characterization by chromatographic or spectroscopic methods

Herbal medicines rely on multiple components to exert pharmacological effects. Accordingly, the isolation and identification of individual components in most herbs remain a great challenge due to their structural diversity and complexity. Novel chromatographic and high-resolution tandem mass spectrometric methods facilitate the structural characterization of complex compounds in TCM with improved accuracy and sensitivity [211]. Astragali Radix (Huangqi), the dried root of *Astragalus propinquus* (Fabaceae), is widely used as a tonic in TCM. It is processed with honey to yield a product with reduced side effects and improved efficacy in tonifying Qi. To identify the pharmacological benefits of processing with honey, 35 compounds in crude and honey-processed Huangqi were detected and identified in a 23-min run using UPLC/ESI-Q-TOF-MS. Quantitative analysis revealed that honey processing reduces isoflavonoid contents and increases saponin contents. Since Astragalus saponins are known to regulate the immune functions of macrophages, an increase in their contents translates into enhanced immunity [212]. Being a quick, label-free, and nondestructive analytical technique, infrared spectroscopy allows the *in situ* monitoring of the changes in herb composition during processing. Thermal processing of Gardeniae Fructus (Zhizi), the ripe fruit of *Gardenia jasminnoides* Ellis (Rubiaceae), decreases its organic acid content, as studied by thermogravimetry-infrared spectroscopy. This was found to reduce its toxic effects on the intestines and stomach. Stir-baking to yellow (125–145 °C) remarkably reduces organic acid content, whereas most iridoids, such as geniposide, remain unaffected by baking at this temperature. Consequently, the pathogenic heat clearing activity of this fruit is retained. However, stir-baking to scorched (165–190 °C) destroys most iridoids so that tannins in the fruit exert hemostatic effects [213]. Other spectroscopic approaches, such as NMR, XRD, and Raman spectroscopy, in combination with appropriate chemometric methods, also aid in interpreting the mechanistic alteration of pharmacological effects by adjuvants and the dynamic monitoring of TCM processing [57,214,215].

3.2. Dose-effect correlation analysis

Because processing alters the chemical composition and efficacy of drugs, it is necessary to evaluate the quality of processed products by specific components in light of their pharmacological effects. Chemometric methods, such as correlation analysis and principal component analysis (PCA), facilitate the evaluation of the chemical profile in relation to the pharmacological and toxicological profile of TCMs [216]. Chronic treatment with rhubarb is reported to cause hepatorenal lesions, whereas wine processing enhances its anti-blood stasis effects and reduces its toxicity [8]. A previous bioactivity assay reported that wine-treated rhubarb has a higher potency than crude and charred rhubarb. Furthermore,

Table 1 – Interaction between herbs and processing adjuvants as reported in the literatures.

Herb processed	Adjuvant	Type of interaction		Clinical outcomes	Ref.
		Chemistry	Pharmacology/Toxicology/Pharmacokinetics		
Bupleuri Radix	vinegar	(↑) saikosaponins b1 and b2; (↓) *n*-hexanal, *n*-heptanal, 2-pentylfuran, (*E*,*E*)-2,4-decadienal, and saikosaponins a, c, d	(↑) estrogen regulation, hepatoprotection, choleretic effect, and anti-depressant and analgesic effects[1]; (↓) anti-inflammatory effects[1]; (–) induction of CYP2C9 and CYP2C19[1]; (↑) C_{max} and AUC_{0-t} of saikosaponins b1 and b2[1]; (↓) C_{max} and AUC_{0-t} of saikosaponins a, b3, and d[1]	Improves liver soothing and choleretic effects, weakens exterior syndrome relieving and antipyretic effects	[10–15,83–88]
Kansui Radix	vinegar	(↓) toxic diterpenoids (kansuinine A, B, D, kansuiphorin C, euphol, etc.) and triterpenoids (euphol, kansenone, epi-kansenone, 11-oxo-kansenonol)	(↑) diuretic effect[1]; (↓) hepatotoxicity, gastrointestinal toxicity, carcinogenesis, purgation[1]; inflammation, skin irritation[2]	Reduces toxicity, improves diuretic action	[16–20,89–93]
Schisandrae Chinensis Fructus	vinegar	(↑) lignans (schisandrin, gomisin D, schisantherin A), and protocatechuic acid; (↓) lignans (schisantherins B, C, D, 6-O-benzoylgomisin O), neokadsuranic acid, and volatile oil	(↑) antidiarrheal, sedative, hypnotic, anti-lipid peroxidation, and immunity enhancement effects[1]; (↑) CYP3A4 induction and inhibit CYP1A2 activity[1]; (↑) T_{max}, MRT_{0-t}, AUC_{0-t}, R_e, and C_e of schisantherin and deoxyschisandrin in liver, and causes biliary excretion of metabolites with acute liver injury[1]	Leads drug to the liver meridian, improves astringent action	[94–100]
	wine	(↑) lignans (Gomisin D, T, schisandrins A, B, and C); (↓) lignans (schisantherins B, C, and D), and neokadsuranic acid	(↑) increases murine splenic lymphocyte proliferation[2]; renoprotection[1];	Majors in warming kidney and strengthening yang	
Schisandrae Sphenantherae Fructus	vinegar	(↓) volatile oil	(↑) hepatoprotection[1]; (↑)T_{max}, MRT_{0-t}, AUC_{0-t}, R_e, and C_e of schisantherin and deoxyschisandrin in liver[1]	Leads drug to the liver meridian	[101,102]
Olibanum	vinegar	(↑) α-boswellic acid, 11-keto-β-boswellic acid, and 11-keto-β-acetyl- boswellic acid; (↓) β-boswellic acid and 3-acetyl-β- boswellic acid	(↑) anti-platelet adherence, anti-inflammation and anticoagulation[1] (↑) C_{max}, AUC, $T_{1/2}$, and MRT[1]	Promotes blood circulation to treat blood stasis, reduces digestive tract irritation, eases pulverization	[103–106]
Cyperi Rhizoma	vinegar	(↑) cyperotundone and luteolin; (↓) nootkatone and α-cyperone	(↑) analgesic and anti-inflammatory effects, intestinal propulsion rate[1]	Soothes the liver to relieve pain, and relieves dyspepsia	[107–109]
Corydalis Rhizoma	vinegar	(↑) tetrahydropalmatine (THP), protopine, palmatine (↓) α-allocryptopine, coptisine, palmatine, and dehydrocorydaline (DHC)	(↑) analgesic and spasmolytic effects[1]; (↑) THP level in the rat plasma and liver[1]; T_{max} of DHC in the heart, kidney, cerebrum, cerebellum, brain stem, and striatum[1]; and T_{max} of protopine in brain[1]; (↓) MRT of DHC in the spleen, lung, cerebrum, and diencephalon; MRT of protopine in the heart, spleen, and kidney[1]	Promotes Qi circulation to relieve pain	[27,28,110,111]
	wine	(↑) tetrahydrocolumbamine, THP, corydaline, tetrahydroberberine, and tetrahydrocoptisine; (↓) protopine, α-allocryptopine, coptisine, palmitine, berberine, and DHC	(↑) T_{max} of tetrahydroberberine in all the tissues[1]; (↓) T_{max} of protopine and DHC in the liver and spleen[1]; and T_{max} of protopine in the lungs[1]	Promotes blood circulation and treats blood stasis	

(*continued on next page*)

Table 1 – (*continued*)

Herb processed	Adjuvant	Type of interaction		Clinical outcomes	Ref.
		Chemistry	Pharmacology/Toxicology/Pharmacokinetics		
Curcumae Rhizoma	vinegar	(↓) curdione, germacrone, bisdemethoxycurcumin, demethoxycurcumin, and curcumin	(↑) anti-platelet aggregation, anticoagulation, hepatoprotective, anti-inflammatory, analgesic[1]; and anti-tumor effects[2]; (+) inhibition on CYP1A2 and CYP2E1, and induction of CYP3A4[1]	Leads the drug to the liver meridian, treats blood stasis, and relieves pain	[112–116]
Phytolaccae Radix	vinegar	(↑) esculentoside A; (↓) esculentosides B and C	(↑) diuretic effect[1]; (↓) conjunctival irritation, gastric mucosal irritation, intestinal edema, diarrhea, and purgation[1]	Reduces toxicity, moderates potent diuretic action, and majors in relieving edema	[21–24]
Strychni Semen	vinegar	(↓) strychnine and brucine	(↑) anti-inflammatory and analgesic effects[1]; (↓) LD_{50}[1]	Reduces toxicity	[117–119]
Genkwa Flos	vinegar	(↑) kaempherol, apigenin, 3′-hydroxy-genkwanin, genkwanin, genkwanine N, and genkwadaphnin (↓) luteolin, isodaphnoretin, yuanhuacine, genkwadaphnin, and genkwanin-5-O-*β*-D-primeveroside	(↑) diuretic effect[1]; (↓) toxicity[1]	Reduces toxicity and improves diuretic effect	[25,26]
Radix Paeoniae Alba	vinegar	(↑) albiflorin (↓) paeoniflorin	(↑) analgesic and sedative effects[1]	Leads the drug to the liver meridian, nourishes the blood, soothes the liver, and relieves depression	[120–122]
Ephedrae Herba	honey	(↓) ephedrine, pseudo-ephedrine, and volatile oil	(↑) anti-asthmatic effect[1]; (↓) diaphoresis[1]	Moderates diaphoresis, major in freeing lung and relieves asthma	[30–32,123]
Peucedani Radix	honey	(↑) praeruptorins A, B, and E	(↑) antitussive, expectorant, and anti-asthmatic effects[1]	Moistens the lung to stop cough	[34,35]
Farfarae Flos	honey	(↑) rutin, isoferulic acid, and tussilagone; (↓) chlorogenic acid, apigenin, and senkirkin	(↑) antitussive and expectorant effects[1]; (↓) toxicity[2];	Moistens the lung to stop cough	[36,124]
Stemonae Radix	honey	(↓) stenine, oxystemoninine, stemonine, N-oxytuberostemonine, and tuberostemonine H	(↑) antitussive and anti-asthmatic actions[1]; (↓) acute toxicity[1]	Moistens the lung to stop cough, moderates gastric irritation	[38,40]
Glycyrrhizae Radix et Rhizoma	honey	(↑) 5-HMF; (↓) glycyrrhizin, liquiritin, liquiritin apioside, licuraside, and isoliquiritin	(↑) immunity[1]; (↓) antitussive and expectorant effects, detoxication, CYP3A4 induction[1]	Tonifies the spleen and stomach	[43,125–128]
Astragali Radix	honey	(↑) astragalosides I, III, and IV, calycosin-7-O-β-D-glucoside, and formononetin-7-O-β-D-glucoside; (↓) calycosin, formononetin, and astragaloside IV	(↑) anti-fatigue effect and anoxia endurance[1]	Exerts center-supplementing and Qi-boosting effects	[129–131,206]
Cimicifugae Rhizoma	honey	(↑) caffeic acid, ferulic acid and isoferulic acid	(↑) analgesic and sedative effects[1]	Moderates diaphoresis, majors in elevating spleen-yang	[132,133]
Aristolochiae Fructus	honey	(↓) aristolochic acids I, II, C, and D	(↓) nephrotoxicity[1]	Moderates the bitter-cold nature, moistens the lung to stop cough, modifies the taste, and reduces vomiting	[134,135]

Polygalae Radix	honey	(↑) sibiricose A_6, glomeratose A, (↓) polygalacic acid, senegenin, onjisaponin B, tenuifoliside B sibiricose A5, and 3, 6′- disinapoyl sucrose	(↑) LD_{50}, antitussive and expectorant effects[1]; (↓) inhibition on gastrointestinal motility and digestive function[1]	Improves cough relieving effect and dissipates phlegm	[136–143]
	licorice	(↑) Tenuifolin, polygalacic acid, glomeratose A, senegenin, organic acids (sinapic acid, *p*-coumaric acid, ferulic acid, benzoic acid, cinnamic acid); (↓) sibiricose A5 and A6; tenuifoliside B, and 3, 6′-disinapoyl sucrose	(↑) anti-alcoholism effect[1]; (↓) inhibition on gastrointestinal motility and digestive function[1]	Moderates dryness, eliminates tongue numbing and throat irritation; tranquilizes the mind and promotes intelligence	
Rhei Radix et Rhizoma	wine	(↑) emodin, rhein, aloe-emodin, and gallic acid (↓) physcion, chrysophanol, and sennosides A and B	(↑) antipyretic and anticoagulant effects, permeability of blood–brain barrier, ulcer healing, and embryotoxicity[1]; (↓) purgative effect, and hepatorenal toxicity[1]; (↓) anthraquinone metabolites[1]	Moderates bitter-cold nature, majors in clearing virulent pyropathogen of upper energizer	[48–54,144–146]
Radix Scutellariae	wine	(↑) baicalin, oroxylin A-7-O-glucuronide, and wogonoside	(↑) antibacterial[2]; antiviral, analgesic, and anti-inflammatory effects[1]; (↓) antioxidant effect[2]; (↑) C_{max} and $AUC_{(0-t)}$ of major flavonoids in the lungs[1]; (↓) C_{max} and $AUC_{(0-t)}$ of major flavonoids in the kidneys[1]	Leads the drug upwards, clears the lung heat and damp heat of limbs	[55–58]
Salvia Miltiorrhiza Radix et Rhizoma	wine	(↑) dihydrotanshinone I and tanshinone I; (↓) tanshinone IIB, cryptotanshinone, salvianolic acid B, neotanshinone B, tanshinone IIA, miltirone, and protocatechuic aldehyde	(↑)anticoagulation activity[1]; α-glucosidase inhibition, antimicrobial, and antioxidant activity[2]	Moderates cold nature, activates blood circulation to treat blood stasis, regulates menstruation, and relieves pain	[50,147–149]
Achyranthis Bidentatae Radix	wine	(↑) benzyl glucoside, polypodine B, β-ecdysterone, and ginsenoside Ro; (↓) zingibroside R1, bidentatoside I, and chikusetsusaponin IV	(↑) analgesic and anti-inflammatory effects, immunity, and hemorheology[1]; (↓) EBV-EA activation[2];	Tonifies the liver and kidney, strengthens the bones and muscles, treats blood stasis, and relieves pain	[150–153]
	salt	(↑) benzyl glucoside, polypodine B, β-ecdysterone, achyranthesterone A, β-ecdysterone, and inokosterone; (↓) zingibroside R1, ginsenoside Ro, bidentatoside I, and chikusetsusaponin IV	(↑) EBV-EA activation[1]; (↓) LD_{50}[1]	Leads the drug to the liver meridian, tonifies the liver and kidney, strengthens the physique, promotes diuresis, and relieves stranguria	
Corni Fructus	wine	(↑) gallic acid, sweroside, cornin, 5-hydroxymethylfufural, 7α-O-ethylmorroniside, and 7β-O– ethylmorroniside; (↓) cornuside, morroniside, and loganin	(↑) antioxidant activity[2]; immunity enhancement, and protection against acute liver injury[1]; (↓) α-glucosidase inhibition activity[2]; hypoglycemic activity[1]; (↑) $T_{1/2}$, AUC_{0-t}, and C_{max} of morroniside and loganin[1]	Nourishes yin and tonifies the kidney	[154–157]
Polygonati Rhizoma	wine	(+) DDMP and 5-HMF; (↑) low molecular weight saccharides; (↓) diosgenin	(↑) antioxidant activity[2]; immunity enhancement[1]	Reduces irritation, nourishes yin, and tonifies the kidney	[158–161]

(*continued on next page*)

Table 1 – (*continued*)

Herb processed	Adjuvant	Type of interaction		Clinical outcomes	Ref.
		Chemistry	Pharmacology/Toxicology/Pharmacokinetics		
Coptidis Rhizoma	wine	(↑) berberubine, noroxyhydrastinine, and worenine; (↓) magnoflorine, jatrorrhizine, columbamine, epiberberine, coptisine, plamatine, and berberine	(↑) anti-bacterial and improvement in insulin resistance effects[2]; hypoglycemic activity, and sedative–hypnotic activity[1]; (↓) antioxidant activity[2]; (↑) C_{max} of coptisine and 8-oxocoptisine, AUC_{0-t} of coptisine, palmatine, and 8-oxocoptisine[1]	Improves drug ascending, moderates cold nature, and majors in clear heat of up-energizer	[69,70,162–166]
	ginger	(↓) berberine, plamatine, epiberberine and coptisine	(↑) Na/K-ATPase activity, and gastric mucosal protection[1]; antibacterial effect[2]	Moderates bitter-cold nature and arrests vomiting	
	Euodiae Fructus	(↓) berberine, epiberberine and coptisine	(↑) anti-bacteria[2]; anti-diabetes, anti-gastric ulcer[1]	Moderates bitter-cold nature, and majors in clearing stagnated heat in the liver and stomach	
Eucommiae Cortex	salt	(↑) coniferylaldehyde, pinoresinol, epipinoresinol, medioresinol, and medioresinol; (↓) genipin, geniposide, geniposidic acid, caffeic acid, chlorogenic acid, quercetin, and pinoresinol diglucoside	(↑) prevents osteoporosis[1]; (↑) C_{max} and AUC of geniposidic acid[1]	Leads the drug to the kidney meridian, and tonifies the liver and kidney	[60–62,66]
Psoraleae Fructus	salt	(↑) psoralen, isopsoralen, bavachin, corylin, isobavachalcone, and bavachalcone; (↓) bavachromanol, bakuchiol, and bavachinin A	(↑) anti-diarrheal[1]; antioxidant, anti-osteoporosis, α-glucosidase inhibitory activities[2]; (↓) toxicity[2]; (↑) K_a of psoralen and isopsoralen[2]	Increases drug disposition into kidney, promotes warming kidney, and activates yang	[63–65,167–172]
Anemarrhenae Rhizoma	salt	(↑) timosaponin BIII; (↓) timosaponins I, E1, and BII	(↑) α-glucosidase inhibition, hypoglycemic effect[2]; anti-hyperthyroidism, and laxation[1]; (↑) C_{max}, AUC, and MRT of neomangiferin[1]	Leads the drug to the kidney meridian, nourishes yin to reduce pathogenic fire	[173–178]
Morindae Officinalis Radix	salt	(↑) monotropein	(↑) anti-inflammatory and anti-hypoxic effects; renoprotection, and improves thyroid dysfunction[1]; (↑) distribution of monotropein in the kidney, liver, and spleen[1]	Reinforces the kidney-yang	[179–182]
	licorice	(↑) monotropein	(↑) distribution of monotropein in the spleen[1]; (↓) distribution of monotropein in the kidney and liver[1]	Majors in tonifying the kidney-yang	
Phellodendri Chinensis Cortex	salt	(↑) berberubine; (↓) limonin, obacunone, berberin, plamatine, and jateorizine	(↑) anti-hyperthyroidism[1]; (↓) antioxidant effect[2]; weight loss, and gastrointestinal dysfunction[1]; (↑) CYP3A4 induction[1]; (–) CYP1A2 inhibition[1]	Leads the drug to the kidney meridian; moderates bitterness and dryness; nourishes yin; and purges fire	[183–187]
	wine	(↓) berberin, plamatine, jateorizine, limonin, and obacunone	(↑) anti-oxidation[2]; bacteriostatic[1]; (↓) anti-hyperthyroidism and gastrointestinal dysfunction[1]; (+) CYP2C9 induction[1]; (↑) CYP3A4 induction[1]; (↓) CYP1A2 inhibition[1]	Weakens the bitter-cold nature, leads the drug upward, and majors in clearing heat in up-energizer	
Alismatis Rhizoma	salt	(↑) alisol A, B and alisol A 24-acetate; (↓) alisol B 23-acetate	(↑) diuretic, anti-inflammatory, immunomodulation[1]	Nourishes yin and promotes diuresis	[188–190]

Magnoliae Officinalis cortex	ginger	(↑) magnolol and honokiol	(↑) analgesic and anti-inflammatory effects, bacteriostasis and gastrointestinal motility[1]; (↓) irritation[1]	Eliminates throat irritation and promotes stomach harmonization	[191–193]
Polygoni Multiflori Radix	black bean	(↑) emodin, chrysophanol, and physcion; (↓) stilbene glycoside, catechin, 2,3,4′,5-tetrahydroxystilbene 2-O-β-D-glucoside, and emodin-8-O-β-D-glucoside	(↑) improve hematopoietic and hemorheological function[1]; (↓) hepatotoxicity, laxation effects[1]; antioxidant[2]	Improves tonifying kidney, essence, and blood; blackening hair, strengthens physique, and lowers toxicity	[194–197]
Aconiti Lateralis Radix Praeparata	salt, licorice, and black bean	(↓) diester alkaloids	(↑) analgesic and anti-inflammatory effects[1]; (↓) acute toxicity[1]	Reduces toxicity	[71,198]
Epimedii Folium	Suet oil	(↑) icariin and baohuoside	(↑) anti-prostatic hyperplastic and HPAT functions[1]; (↑) P_{app}, T_{max}, C_{max}, and AUC of icariside I[1]	Improves warming kidney and strengthening yang	[199–201]
Pinelliae Rhizoma	alum	(↓) calcium oxalate raphides, total protein, guanosine and uridine	(↑) anti-inflammatory and antitussive effects[1]; (↓) pro-inflammatory effect[1,2]	Majors in removing dampness to reduce phlegm	[76–78,202–205]
	alum/ginger		(↑) antitussive, expectorant, analgesic, antiemetic and anti-inflammatory effects[1]; (↓) emesis, embryo toxicity[1] and pro-inflammatory effect[1,2]	Improves downbear counterflow and prevents vomiting, majors in warming middle, and dissipating phlegm	
	licorice/lime		(↑) antitussive and sedative effects[1]; (↓) pro-inflammatory effect[2]	Dispels cold phlegm; harmonizes the liver and spleen	
Typhonii Rhizoma	alum/ginger	(↑) 5-HMF and bis (5-formylfurfuryl) ether; (↓) calcium oxalate raphides	(↑) sedative, anticonvulsant, analgesic, and anti-inflammatory effects[1]; (↓) irritation and toxicity[1]	Reduces toxicity, eliminates mucosal irritation, and dispels wind-phlegm	[205–209]
Atractylodis Macrocephalae Rhizoma	bran	(↑) atractylenolides I, II, and III; (↓) atractylon	(↓) peristalsis of the small intestine[1]	Moderates dryness, invigorates the spleen, and harmonizes the stomach	[81,210]
Mylabris	rice	(↓) cantharidin	(↑) anti-tumor activity[1]; (↓) LD_{50}, hepatic, renal, and gastrointestinal toxicity[1]	Reduces toxicity	[82]

Abbreviations (↑) increases; (↓) decreases; (+) new appeared; (–) disappeared; [1] *in vivo*; [2] *in vitro*.

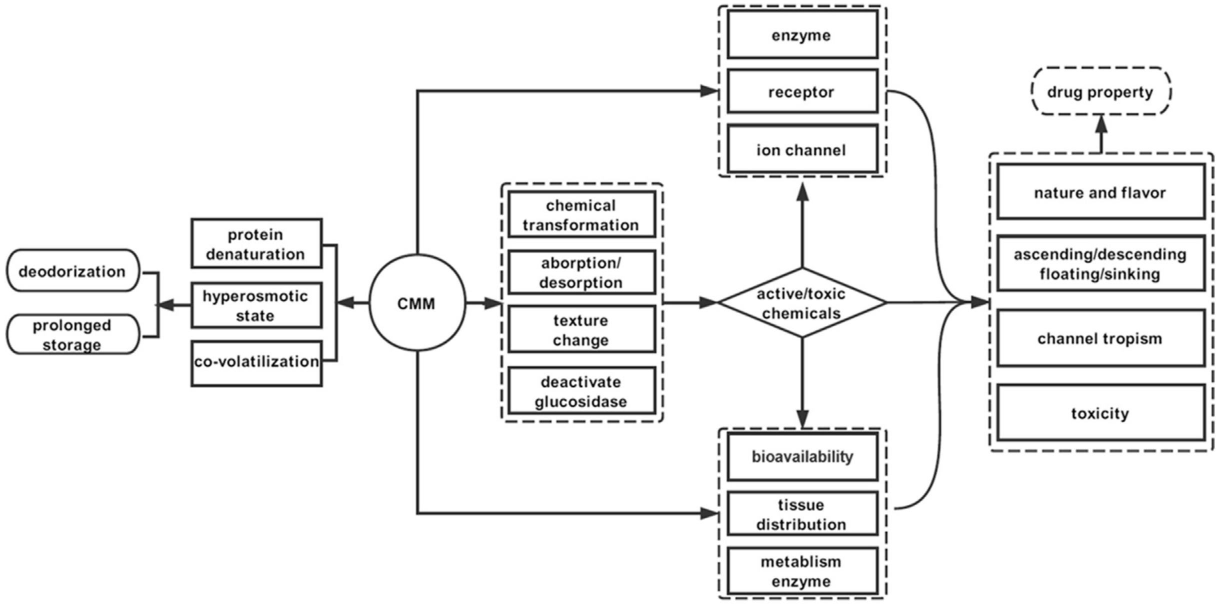

Fig. 1 – General effects of adjuvants in CMM processing.

UPLC fingerprint analysis identified that rhein-8-O-β-D-glucoside, emodin-8-O-β-D-glucoside, and rhein strongly inhibit platelet aggregation [217]. Based on canonical correlation analysis (CCA) to investigate the correlation between toxicity and chemical composition of processed rhubarb, it was reported that the reduced toxicity in processed rhubarb was due to the decrease in free and conjugated anthraquinone (aloe-emodin and physcion) and tannin concentrations [218]. Similarly, UPLC fingerprinting, microcalorimetry, and CCA were combined to explore the different effects of aconite and its processed products on energy metabolism. The results revealed that mesaconitine, benzoylaconitine, and benzoylhypacoitine affect mitochondrial energy metabolism in rats [219].

3.3. *Metabolomics*

Metabolomics involves the global profiling of endogenous metabolites and dynamic responses to both endogenous and exogenous factors to identify complex interactions among biological systems, drugs, and diseases [220]. Complex chemical compositions of TCMs demand a metabolomic approach to identify their diverse metabolic pathways in relation to their pharmacodynamic activities. Based on LC-MS analysis of endogenous biomarkers of energy metabolism in rat plasma, it is reported that processing with ginger weakens the cold nature of Huanglian, which is consistent with the traditional processing theory that the cold nature of drugs could be moderated by processing with adjuvants of hot nature (ginger juice) [221].

Cases of hepatotoxicity due to improperly processed Radix Polygoni Multiflori (Heshouwu), the root tuber of *Polygonum multiflorum* Thunb. (Polygonaceae), are reported frequently [222]. Using a urinary metabolomic approach along with conventional biochemical and histopathological analysis to identify the mechanisms of hepatotoxicity, 16 potential biomarkers have been identified to be differentially expressed in rats treated with crude Heshouwu compared with those treated with processed Heshouwu. Altered vitamin B6 and tryptophan metabolism as well as a disturbed citrate cycle are found to be responsible for the hepatotoxicity of this herb. Restoring balance in these pathways is hypothesized to prevent hepatotoxicity induced by Heshouwu [223].

Using an NMR-based metabolomic approach combined with multivariate analysis by PCA, partialleast square discriminant analysis (PLS-DA) and orthogonal partial least squares discriminant analysis (OPLS-DA), it is revealed that the hepatoprotective effect of Chaihu is related to its effect on energy metabolism and synthesis of lipids, ketone bodies, glutathione, amino acids, and nucleotides [224]. The study identified 14 metabolites in the liver that were significantly altered after administration of Chaihu prepared by Shanxi vinegar to CCl_4-treated mice in comparison with control mice. The ability of metabolomics to detect such subtle pharmacological differences sets it apart from conventional bioassays that fail to do so.

3.4. *Others*

Apart from color, taste and odor are also regulated as a sensory features to assess the processing quality. Intelligent sensor, a bionic technology comprises biochemical sensors and pattern recognition, has been developed to replace artificial judging which is subjective and inefficient. A taste-sensing system, named electronic tongue, was adopted to objectively evaluate the taste of processed aconite. Four types of processed aconite were unambiguously distinguished from each other using this system and each type was found to possess its own characteristic taste pattern [225]. Electrophoretic and DNA molecular marker techniques are employed to investigate the protein and DNA changes that occur during CMM processing. A two-dimensional SDS-PAGE was used to analyze the protein expression profiles of Hirudo, the dried body of *Whitmania pigra* Whitman (Hirudinidae), before and after stir-frying with wine. The contents of proteins in Hirudo before and after processing showed marked differences and 19 differential protein points were found [226]. DNA molecular markers are ideal genetic markers for TCM authentication. DNA fingerprinting of crude and processed Atractylodis Rhizoma (Cangzhu) was developed by randomly amplified polymorphic DNA (RAPD). The results showed DNA degradation during the processing, and the degree of degradation differed in processed products, indicating that processing conditions, such as temperature and time, greatly influence the DNA molecular identification [227].

4. Summary and future prospects

Ancient Chinese medicinal processing technology has evolved to incorporate modern processing methods and types of adjuvants to replace outdated technology, non-standard protocols, and substandard adjuvants that had become a serious impediment for the standardization and globalization of TCM. Unlike conventional processing conditions, such as heating temperature and duration, which can be controlled by automation, the sources of adjuvants used in processing demand careful selection and quality control. Therefore, research to identify the effects of adjuvant processing on the pharmacological actions of herbs holds great value. Adjuvants participate in chemical or physical transformation, directly exert pharmacological effects, or alter the pharmacokinetic behavior, to provide an enhanced therapeutic effect or counteract drug toxicity. The findings summarized in this review provide a scientific basis for the application of adjuvants and processing methods to enhance drug properties in TCM, which could bridge the gap between TCM and Western medicine.

Current research focuses on the chemical and pharmacological alterations induced by TCM processing using novel analytical methods that allow us to obtain qualitative and quantitative information of multi-component herbal products and their disposition *in vivo*. Synergism between drugs and adjuvants allows targeting multiple endogenous effectors, including enzymes, receptors, ion channels, transport proteins, and nucleic acids. Modern research tools, such as spectral–efficacy correlation analysis, combine analytical techniques, bioassays and stoichiometry to assign bioactivities to specific phytochemicals in herbs. TCM encompasses numerous disease symptoms that are not accurately represented by the concepts of Western medicine. Akin to the integrated concept of TCM, the introduction of systems biology allows the study of living organisms from a holistic perspective and offers an opportunity to reinvestigate TCM. With the new findings and in-depth study in this field, more and more factors have been found to influence the clinical efficacy of TCM. It is suggested that the following aspects should be taken into consideration in future studies on CMM processing.

4.1. *Alteration of underlying active components in CMM processing*

Current research on TCM mainly focuses on small molecules, however, macromolecules, such as polysaccharides and proteins, also exert therapeutic effects [228]. In addition, primary metabolites and inorganic ions have been overlooked, despite being vital for drug efficacy. Effects of processing methods on these active components will extend the horizons of TCM research.

4.2. *Impact of processing on intestinal flora*

TCMs are reported to modulate multiple pathways affecting the human gut microbial system, which contributes largely to the effectiveness of TCMs. Gut microflorae regulate the metabolism of TCMs, and also facilitate targeted physiological modulation by TCM [229]. Therefore, future studies must attempt to highlight the significance of gut microflora in drug processing.

4.3. *Pharmacological and toxicological studies under pathological conditions*

According to the symptom-based prescription theory, drugs that are toxic under normal physiological conditions show therapeutic effect under pathological states [230]. Pharmacological and toxicological studies have focused on drug efficacy and toxicity on healthy organisms, ignoring possible changes in drug properties induced by different pathological states. This problem is also evident in studies conducted on CMM processing. Therefore, there is a need to reappraise the therapeutic doses of drugs and redefine treatment indications after evaluating the effects of various processing methods to improve therapeutic effectiveness and avoid toxicity.

Conflicts of interest

The authors declare no conflict of interests.

Acknowledgments

This work was supported by a grant from China Medical University (CMU106-N-24) and a grant of Chang Gung Medical Research Program (CMRPF1D0123) from Chang Gung Memorial Hospital. This study was supported by China Medical University under the Higher Education Sprout Project, Ministry of Education, Taiwan.

REFERENCES

[1] Shen ML. The contribution of traditional Chinese medicine to modern pharmacology. Trends Pharmacol Sci 1983;4:496–500.
[2] Xu SN. Investigating modern research on meridian-reaching actions of traditional Chinese medicinal herbs. Chin Pharmacol Bull 2004;20:598–600.

[3] Zhao ZZ, Liang ZT, Chan K, Lu GH, Lee ELM, Chen HB, et al. A unique issue in the standardization of Chinese materia medica: processing. Planta Med 2010;76:1975–86.
[4] Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China (vol. 1). Beijing: China Medical Science and Technology Press; 2015.
[5] Li RR, Zhang ZJ, Wang ZJ, Wang F, Yuan ST. Literature analysis on toxicity, side effect and adverse reaction of traditional Chinese medicine. Chin J Exp Tradit Med Form 2010;15:068.
[6] Chan TYK. Incidence and causes of Aconitum alkaloid poisoning in Hong Kong from 1989 to 2010. Phytother Res 2015;29:1107–11.
[7] Yang Y, Zhang Z, Li S, Ye X, Li X, He K. Synergy effects of herb extracts: pharmacokinetics and pharmacodynamic basis. Fitoterapia 2014;92:133–47.
[8] Wang SF, Wang HQ, Liu YN, Wang Y, Fan XH, Cheng YY. Rapid discovery and identification of anti-inflammatory constituents from traditional Chinese medicine formula by activity index, LC-MS, and NMR. Sci Rep 2016;6:31000.
[9] Xu QP, Tao WY, Ao ZH. Antioxidant activity of vinegar melanoidins. Food Chem 2007;102:841–9.
[10] Yuan BC, Yang R, Ma YS, Zhou S, Zhang XD, Liu Y. A systematic review of the active saikosaponins and extracts isolated from Radix Bupleuri and their applications. Pharm Biol 2017;55:620–35.
[11] Xing J, Sun HM, Li ZY, Qin XM. Comparison of volatile components between raw and vinegar baked radix bupleuri by GC-MS based metabolic fingerprinting approach. Evid Based Compl Alt Med 2015;2015:653791.
[12] Xu L, Tian JX, Song R, Liu Q, Tian Y, Zhang ZJ. LC-MS/MS determination and comparison of saikosaponin a, b_2, c, d in crude and processed radix bupleuri by vinegar. J China Pharm Univ 2012;43:334–40.
[13] Lei TL, Chen SF, Wang K, Zhang DD, Dong L, Lv CN, et al. Characterization and discrimination of raw and vinegar-baked Bupleuri Radix based on UHPLC-Q-TOF-MS coupled with multivariate statistical analysis. Biomed Chromatogr 2017:e4044.
[14] Zhen YL, Sun HM, Xing J, Qin XM, Du GH. Chemical and biological comparison of raw and vinegar-baked Radix Bupleuri. J Ethnopharmacol 2015;165:20–8.
[15] Wang LN, Wang W, Jia TZ. Before and after *Bupleurum* processed with vinegar influence on the content of DA and NE in the mouse brain suffering from depression. Asia Pac Tradit Med 2014;10:4–6.
[16] Yan XJ, Zhang L, Guo JM, Cao YD, Shang EX, Tang YP, et al. 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 2014;19:7237–54.
[17] Li ZJ, Li Y, Gao L, Ding AW, Zhang L. Change of diterpenoids in different processed products of Euphorbia kansui. ChinTradit Pat Med 2011;12:2122–5.
[18] Bicchi C, Appendino G, Cordero C, Rubiolo P, Ortelli D, Veuthey JL. HPLC-UV and HPLC-positive-ESI-MS analysis of the diterpenoid fraction from caper spurge (Euphorbia lathyris) seed oil. Phytochem Anal 2001;12:255–62.
[19] Liu Y, Liu ZQ, Song FR, Liu SY. Optimization of preparing process condition of kansui roots by electrospray ionization mass spectrometry. J Chin Mass Spectrom Soc 2010;31:72–8.
[20] Zhang Q, Cao LL, Lou JW, Zhang L, Ding AW. Effect of processing with vinegar on toxicity of *Kansui Radix* in normal and cancerous ascites model rats. Chin J Exp Tradit Med Form 2016;22:1–6.
[21] Yu HL, Zhang CC, Wu H, Wang KL, Wang W, Shan XL. Effect of vinegar processing on esculentosides in n-BuOH fraction and main toxic components in Phytolaccae Radix. Chin J Chin Mater Med 2017;42:125–9.
[22] Yu HL, Gong L, Wang XZ, Wu H, Zhao TF, Wang KL, et al. Rabbit conjunctivae edema and release of NO, TNF-α, and IL-1β from macrophages induced by fractions and esculentosides isolated from *Phytolacca americana*. Pharm Biol 2016;54:98–104.
[23] Chen L, Wu H. Comparison of chemical composition and efficacy before and after processed Phytolaccae Radix with vinegar. Chin J Exp Tradit Med Form 2013;19:5–9.
[24] Zhang CC, Yu HL, Wu H, Pan YZ, Chen YQ, Wang KL, et al. Intestinal toxicity of n-BuOH fraction from Phytolacca Radix before and after being processed with vinegar. Chin J Chin Mater Med 2016;41:216–9.
[25] Dai GX. Experimental study on toxicity and efficacy of *Genkwa Flos* stir-baked with vinegar. Chin Arch Tradit Chin Med 2012;30:2766–7.
[26] Zhang YY, Zhang RW, Yuan Y, Geng LL, Zhao X, Meng X, et al. Simultaneous determination of eight active components in chloroform extracts from raw and vinegar-processed Genkwa flos using HPLC-MS and identification of the hepatotoxic ingredients with an HL-7702 cell. Anal Meth 2014;6:7022–9.
[27] Wu HW, Waldbauer K, Tang LY, Xie LW, McKinnon R, Zehl M, et al. Influence of vinegar and wine processing on the alkaloid content and composition of the traditional Chinese medicine Corydalis Rhizoma (Yanhusuo). Molecules 2014;19:11487–504.
[28] Chen DD, Mao KJ, LI X, Chen JW. Comparative study on the contents of seven alkaloids in crude and processed Corydalis Rhizoma by HPLC. Chin J Pharm Anal 2015;35:1591–5.
[29] Samad A, Azlan A, Ismail A. Therapeutic effects of vinegar: a review. Curr Opin Food Sci 2016;8:56–61.
[30] Yang JY, Lin CZ, Zhu CC, Chen K. Changes of ephedrine and pseudo-ephedrine content in Herba Ephedrae before and after honey-baking. West China J Pharm Sci 2007;22:559.
[31] Chen K, Lin W, Lin L. Change of alkaloid and volatile oil of Herba Ephedrae before and after mix-fring with honey. Chin Tradit Pat Med 2005;27:173–6.
[32] Zhong LY, Zhu J, Gong QF, Zhang DF. The study on the influence of processing on the effects of diaphoresis and relieving ashtma of Ephedra herb. Pharmacol Clin Chin Mater Med 2008;24:53–6.
[33] Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediat Adol Med 2007;161:1140–6.
[34] Zhang C, Xiao YQ, Li L, Li W, Yin XJ. Simultaneous analysis of three coumarins in processed pieces from Peucedanum praeruptorum by HPLC. Chin Pharm J 2010;45:14–6.
[35] Zhang C, Yin X, Li L, Li W, Xiao YQ, Yu DR, et al. Comparative studies on pharmacological effects for processed pieces from Peucedanum Praeruptorum. Chin J Exp Tradit Med Form 2010;15:146–8.
[36] Ling S, Yi BX, Gong QF, Xiao YQ. Antitussive and expectorant activity of different extracts from the crude and honey-stir-baked *Tussilago farfara* Flower. Chin J Exp Tradit Med Form 2013;19:187–90.
[37] Ye GY, Li SY, Chen YF, Han XQ, Liang ZF, Xu JX, et al. Comparative study of different extracts of loquat leaf in antitussive and expectorant and antiasthmatic effects. Pharmacol Clin Chin Mater Med 2013;29:100–3.
[38] Dong W, Hao XJ, Wang CZ, Guo LN, Pan H, Lin Y, et al. Variations of chemical constituents in Stemona tuberosa

before and after stir-frying with honey by UPLC/Q-TOF/MS. J Chin Tradit Pat Med 2016;38:1792–6.
[39] Chen XX, Zhang XD, Li HY, Jia TZ, Yang JX. Difference in effect between asthma-based mouse model and Stemona tuberosa extracts. Chin J Chin Mater Med 2013;38:4084–7.
[40] Chen XX, Ju CG, Xia LB, Wei XT, Jia TZ. The Difference in antitussive and expectorant activity between the different polar franctions of crude and processed Stemona tuberose. Chin J Exp Tradit Med Form 2012;18:146–9.
[41] Attia WY, Gabry MS, El-Shaikh KA, Othman GA. The anti-tumor effect of bee honey in Ehrlich ascite tumor model of mice is coincided with stimulation of the immune cells. Egypt J Immunol 2008;15:169–83.
[42] Wang MY, Zhang M, Tang QY, Li XB. Influence of honey-roasting on the main pharmacological activities and the water-soluble active glycosides of licorice. Afr J Tradit Compl Altern Med 2012;9:189–96.
[43] Zhang YL, Wang MY, Yang JY, Li XB. Research progress of chemical constituents and pharmacological effects of baked licorice. Acta Univ Tradit Med Sin Pharmacol Shanghai 2015;29:99–102.
[44] Harris RZ, Jang GR, Tsunoda S. Dietary effects on drug metabolism and transport. Clin Pharmacokinet 2003;42:1071–88.
[45] Tushar T, Vinod T, Rajan S, Shashindran C, Adithan C. Effect of honey on CYP3A4, CYP2D6 and CYP2C19 enzyme activity in healthy human volunteers. Basic Clin Pharmacol Toxicol 2007;100:269–72.
[46] Moon YJ, Wang X, Morris ME. Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. Toxicol Vitro 2006;20:187–210.
[47] Li CC, Wang Y, Xiang SM, Han L. Function and history of development of wine. Chin J Exp Tradit Med Form 2013;19:365–9.
[48] Wang M, Fu JF, Lv MY, Tian Y, Xu FG, Song R, et al. Effect of wine processing and acute blood stasis on the serum pharmacochemistry of rhubarb: a possible explanation for processing mechanism. J Sep Sci 2014;37:2499–503.
[49] Li HF, Wang JB, Qu Y, Xiao XH. Analysis on changes of purgative biopotency in different processed products of rhubarb. Chin J Chin Mater Med 2012;37:302–4.
[50] Huang ZD, Jiang ML, Yi YK, Zeng R, Huang Y, Wu P. Effects of processed Radix Salviae miltiorrhizae and Radix et Rhizoma Rhei with wine on functions of blood platelet and anticoagulation of rat. Chin Tradit Pat Med 2001;23:341–2.
[51] Sui F, Yan MJ, Li Y, Li N, Xiao YQ, Li L. Comparision of the actions on blood stasis of rhubarb with different prepared methods. Pharmacol Clin Chin Mater Med 2012;28:90–3.
[52] Zhang C, Li L, Xiao YQ, Li N, Liu CF, Li GL, et al. Anthraquinone contents in five processed products from *Rheum Palamatum*. Chin J Chin Mater Med 2009;34:1914–6.
[53] Zhu TT, Liu X, Wang XL, Cao G, Qin KM, Pei K, et al. Profiling and analysis of multiple compounds in rhubarb decoction after processing by wine steaming using UHPLC-Q-TOF-MS coupled with multiple statistical strategies. J Sep Sci 2016;39:3081–90.
[54] Wang Y, Rui TQ, Yang JH, Li JS, Zhou LL, Cai BC. Effects of wine-processing on Rhei Radix et Rhizoma on upper-energizer disease and effects on activities of energy metabolism enzymes in liver. J Chin Med Mater 2015;38:53–7.
[55] Yang XW, Wu DK, Li JS, Cai BC. Comparison of Scutellariae Radix and processed products on six flavonoids' contents. J Guangdong Pharm Univ 2012;28:282–6.
[56] Huang P, Tan SZ, Zhang YX, Li JS, Chai C, Li JJ, et al. The effects of wine-processing on ascending and descending: the distribution of flavonoids in rat tissues after oral administration of crude and wine-processed Radix scutellariae. J Ethnopharmacol 2014;155:649–64.
[57] Zhang WJ, Dong CL, Wang JY, He X, Yang XL, Fu YF, et al. Thermal effects on the dissolution enhancement of Radix scutellariae by wine-processing. Appl Therm Eng 2016;103:522–7.
[58] Huang Q, Zhang C, Wu DL, Yu DR, Gu XZ, Yao L, et al. Investigation of past and present processing of Radix Scutellaria fried with wine. Chin J Exp Tradit Med Form 2013;10:103.
[59] Ma L, Wang SB, Wang X, Yue L. Review on scientific connotation of leech processed under high temperature. Chin J Chin Mater Med 2015;40:3894–8.
[60] Weng ZB, Yan CP, Wu Y, Cai BC, Chen ZP, Li WD. Study of the effect of salt-roast processing product of *Eucommia ulmoides* Oliv. on osteoporosis in ovariectomized rats. Chin J Osteoporos 2014;20:1457–63.
[61] Gao QQ, Weng ZB, Zhao GH, Yan CP, Chen ZP, Cai BC, et al. Evaluation of salt processing on pharmacokinetics of geniposidic acid in *Eucommia ulmoides* Oliver. J Nanjing Univ Tradit Chin Med 2015;31:453–6.
[62] Tao Y, Sheng C, Li WD, Cai BC, Lu TL. Investigation on chemical constituents of processed products of eucommiae cortex. Chin J Chin Mater Med 2014;39:4352–5.
[63] Wang ZH, Fu J, Wu LB, Jiang X, Huang LF, Chen SL. Changes of chemical constituents in *Psoraleae Fructus* before and after salted based on UPLC/Q-TOF-MS technology. Chin J Exp Tradit Med Form 2014;20:51–5.
[64] Feng L, Hu CJ. Effect of processing on the absorptive proflie of *Psoralea corylifolia* L. Chin Pharm J 2009;44:766–70.
[65] Zhao GH, Yan CP, Xu ZS, Gao QQ, Chen ZP, Li WD. The effect of salt-processed *Psoralea corylifolia* on generative organ targeting. J Anal Meth Chem 2016:7484202.
[66] Deng C, Han L, Zhang YQ, Jiang Y. Changes of chemical constituents in Eucommiae cortex before and after processed with salt. Chin Tradit Pat Med 2015;37:2464–8.
[67] Fromm MF, Darbar D, Dell'Orto S, Roden DM. Modulation of effect of dietary salt on prehepatic first-pass metabolism: effects of β-blockade and intravenous salt loading. J Pharmacol Exp Therapeut 1999;290:253–8.
[68] Darbar D, Fromm MF, Dell'Orto S, Kim RB, Kroemer HK, Eichelbaum M, et al. Modulation by dietary salt of verapamil disposition in humans. Circulation 1998;98:2702–8.
[69] Deng YF, Zhong LY. The development of the study of ginger coptidis rhizoma. J Jiangxi Univ Tradit Chin Med 2014;3:93–6.
[70] Wang TT, Zhong LY. Analysis of mechanism of Coptidis Rhizoma processed with different ginger juice in inhibiting gastric mucosal injury. Chin J Exp Tradit Med Form 2017;23:18–22.
[71] Cai BC, Qin KM, Wu H, Cai H, Lu TL, Zhang XD. Chemical mechanism during Chinese medicine processing. Prog Chem 2012;24:637–49.
[72] Li J, Sun E, Tan XB, Jia XB. Promotion of suet oil to absorption and transportation of total flavonoids from Epimedii Folium. Chin Tradit Herb Drugs 2015;46:2439–44.
[73] Hou J, Li J, Sun E, Jia XB. Synergistic effect of Epimedii Folium fried with suet oil for warming kidney and enhancing yang in dosage form of self-assembled micelles. Chin J Chin Mater Med 2016;41:2633–7.
[74] Cui L, Sun E, Zhang ZH, Tan XB, Wei YJ, Jin X, et al. Enhancement of epimedium fried with suet oil based on in vivo formation of self-assembled flavonoid compound nanomicelles. Molecules 2012;17:12984–96.
[75] Sun E, Wei YJ, Zhang ZH, Cui L, Xu FJ, Jia XB. Processing mechanism of Epimedium fried with suet oil based on absorption and metabolism of flavonoids. Chin J Chin Mater Med 2014;39:383–90.

[76] Wu H, Zhong LY, Li W, Ye DJ. Study on processing mechanism of *Pinellia ternate*. Chin J Chin Mater Med 2007;32:1402–6.
[77] Yu HL, Zhang Q, Wu H, Shao C, Zhao TF, Li Z. Comparative study on pro-inflammatory toxicity of *Pinellia pedatiecta* before and after being processed with alum. Chin J Chin Mater Med 2013;38:3893–7.
[78] Yuan HJ, Jia XB, Yin WJ, Wang H, Wang HJ, Li W. Effects of processing on toxic components of *Pinellia Rhizoma* and its detoxification mechanism. Chin J Chin Mater Med 2016;41:4462–8.
[79] Tang LY, Wu HW, Wang ZJ, He Y, Fu MH. Investigation of attenuating toxicity mechanism of processing for Arisaema erubescens (I). Chin J Exp Tradit Med Form 2012;18:28–31.
[80] Wang Y, Zhang GM, Ha W. The research progress of application and preparation for endangered TCM Pangolins. Mod Chin Med 2015;17:280–4.
[81] Zhao WL, Wu H, Shan GS, Jia TZ. Verification of processing theory of "reducing ketone and dryness, and increasing ester and effect" for bran-fried atractylodes. Chin J Chin Mater Med 2013;38:3493–7.
[82] Zhang ZL, Wang ZY, Sun SP, Li J, Zhang GQ, Miao ML. Studies on the pharmacological action of varlous processed *Mylabris phalerata* Pallas. Chin J Chin Mater Med 1990;15:22–5.
[83] Jiang H, Li J, Shi RB, Yin WP. Influence of processing on four saikosaponins in Radix Bupleuri. Chin Pharm J 2009;44:1618–21.
[84] Zhao Y, Wang YJ, Zhao RZ, Xiang FJ. Vinegar amount in the process affected the components of vinegar-baked Radix Bupleuri and its hepatoprotective effect. BMC Compl Altern Med 2016;16:346.
[85] Zhao JL, Gao HM. Preliminary study on soothing liver and choleretic effects of *Bupleurum chinense* and its processed products. Chin J Exp Tradit Med From 2013;19:235–8.
[86] Wang LN, Wang W, Jia TZ. Regulative effect of *Bupleurum* and vinegar-processed *Bupleurum* on the estrogen levels of rats. Acta Chin Med Pharmacol 2014;42:56–8.
[87] Lei TL, Zhang DD, Guo K, Li MX, Lv CN, Wang J, et al. 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 2017;1060:231–9.
[88] Cheng Y, Huang Y, Tian Y, Xu L, Liu GQ, Zhang ZJ. Assessment of the effects of Radix Bupleuri and vinegar-baked Radix Bupleuri on cytochrome 450 activity by a six-drug cocktail approach. Chin J Nat Med 2013;11:302–8.
[89] Shu X, Jiang XW, Cheng BCY, Ma SC, Chen GY, Yu ZL. Ultra-performance liquid chromatography quadrupole/time-of-flight mass spectrometry analysis of the impact of processing on toxic components of Kansui Radix. BMC Compl Altern Med 2016;16:73.
[90] Yan XJ, Li L, Li Z, Li Y, Cao L, Cao YD, et al. The comparison of dose-effect relationships of crude and vinegar processed *Euphorbia kansui* with splenic lymphocyte activity and peritoneal macrophage NO release. Chin Pharmacol Bull 2011;27:629–32.
[91] Wang WX, Yang YJ, Cao LL, Zhang L, Ding AW. Triterpenes change of processing *Kansui Radix* with vinegar and their toxicity to intestinal epithelial cells. Chin Tradit Pat Med 2015;37:1045–9.
[92] Wang WX, Gao L, Zhang L, Ding AW. Attenuation by stir baking with vinegar on effect of ethyl acetate fraction from *Kansui Radix* on mice gastrointestinal permeability. Chin Tradit Herbal Drugs 2014;45:3289–94.
[93] Cao LL, Wang WX, Zhang L, Ding AW, Dou ZH, Wang YH. Comparative effects of different extracts of *Kansui Radix* stir-baked with vinegar on function of expelling water retention with drastic purgative in cancerous ascites model rats. Chin Tradit Herb Drugs 2015;46:2593–8.
[94] Su LL, Cheng X, Ji D, Wang LJ, Ding XY, Lu TL. Analysis of lignans and their metabolites derived from *Schisandra chinensis* and vinegar *Schisandra chinensis* in rats'plasma, bile, urine and faeces based on UHPLC-QTOF/MS. Acta Pharm Sin 2016;51:1600–8.
[95] Li W, Song YG, Liu KY, Yang LJ, Liu YL, Su D, et al. Rapid identification of the different constituents in Fructus Schisandrae Chinensis before and after processing by UHPLC-QTOF/MSE combining with metabonomics. Acta Pharm Sin 2016;51:1445–50.
[96] Zhou JD, Lu TL, Mao CQ, Hu JY. Determination of six lignans in different processed products of *Schisandra chinensis* (Turcz.) Baill. by HPLC. Chin Pharm J 2015;46:1353–6.
[97] Ge HQ, Jia TZ. Research on the phamacological effect of the crude and parched *Schisanara Chinensis Baill*. Liaoning J Tradit Chin Med 2007;34:636–7.
[98] Xu Y, Ge HQ, Gao H, Zhao MJ, Jia TZ. Effect of *Schisandrae Chinensis Fructus* prepared with different processing methods on splenic lymphocyte proliferation in mice. Chin J Exp Tradit Med Form 2015;21:116–9.
[99] Yao Q, Lu TL, Hu F, Mao CQ, Yin FY, Hu JY. Induction effects of the different processed Fructus *schisandrae Chinensis* on the hepatic microsomal cytochrome P450 in rats. West China J Pharm Sci 2011;26:249–51.
[100] Su T, Mao CQ, Yin FZ, Yu ZL, Lin Y, Song Y, et al. Effects of unprocessed versus vinegar-processed Schisandra chinensis on the activity and mRNA expression of CYP1A2, CYP2E1 and CYP3A4 enzymes in rats. J Ethnopharmacol 2013;146:734–43.
[101] Zheng J, Zhang M, Deng C, Song XM, Han L. Mechanism of 'Cuzhi Rugan' of *Schisandra sphenanthera* based on anti-oxidation. Chin J Exp Tradit Med Form 2012;18:189–92.
[102] Deng C, Zheng J, Jiang Y, Song XM. The steaming *Kadsura Japonica* with vinegar on distribution of lignans in liver of rat. Chin Tradit Pat Med 2015;37:145–9.
[103] Xia L, Song ZQ, Li Q, Zeng LY, Wei Z, Cao YN, et al. Influence of various processing technologies on five kinds of boswellic acids in *Olibanum*. Chin Tradit Herbal Drugs 2012;43:1087–91.
[104] Shen YL. Frankincense processed products from different processing methods and hygiene products comparison of analgesic effect. Guid J Tradit Chin Med Pharmacol 2010;16:118–9.
[105] Guan HZ, Peng ZC, Zhang SW. Comparison between effect of the un-processed *Ruxiang* on rabbit's platelet adherence and that of the vinegar-processed one. Chin Hosp Pharm J 2000;20:524–5.
[106] Pan YN, Liang XX, Niu LY, Wang YN, Tong X, Hua HM, et al. Comparative studies of pharmacokinetics and anticoagulatory effect in rats after oral administration of Frankincense and its processed products. J Ethnopharmacol 2015;172:118–23.
[107] Li NP, Lu JR, Li WB, Sheng FY, Wang SY. Influences of different vinegar processing methods on contents of index components in *Cyperi Rhizoma*. Chin J Exp Tradit Med Form 2015;21:5–7.
[108] Li YX, Lu YH, Feng W, Xing LQ. Determination of luteolin in *Cyperi rhizoma* and *Cyperi rhizoma* fried with vinegar by high-performance liquid chromatography. Chin J Exp Tradit Med Form 2011;17:56–8.
[109] Guo HL, Wang JC, Hu LJ, Zhao XJ, Gao WJ, Jiang L. The comparison of the anti-inflammatory and analgesic effects

of different processed products of *Cyperus*. J Jiangxi Univ Tradit Chin Med 2017;29:74–83.
[110] Li R, Cai QQ, Niu YB, Yang SC, Dou ZY. Comparative study between crude *Corydalis Rhizoma* and vinegar *Corydalis Rhizoma* in pharmacological action. Chin J Exp Tradit Med Form 2014;20:133–7.
[111] Dou ZY, Li KF, Wang P, Cao Liu. Effect of wine and vinegar processing of rhizoma corydalis on the tissue distribution of tetrahydropalmatine, protopine and dehydrocorydaline in rats. Molecules 2012;17:951–70.
[112] Liu HZ, Lu TL, Mao CQ, Ji D, Li L, Wang RH. Comparison on contents of sesquiterpenes and curcuminoids in different processed *Curcuma Rhizoma*. Chin Tradit Pat Med 2014;36:804–8.
[113] Qin B, Xie JX, Yang HL, Deng H, Shi QY. Effect of content of curcumin and anti-inflammation,analgesic effects on different processed products of *Curuma kwangsiensis*. Chin J Exp Tradit Med Form 2011;17:35–8.
[114] Mao CQ, Xie H, Lu TL. Studies on antiplatelet aggregation and analgestic action of *Curcuma phaeocaulis*. J Chin Med Mater 2000;23:212–3.
[115] Li JC, Lu TL, Mao CQ, Ji D, Li L, Xiao YQ. Comparison on effect of *Curcuma Rhizoma* before and after processed with vinegar on hepatic fibrosis in rats induced by CCl_4 composited factors. Chin Tradit Herbal Drugs 2013;44:2710–6.
[116] Wang J, Lu TL, Mao CQ, Xiao YQ, Gu JJ. Application of probe drugs for detecting influences of *Rhizoma Curcumae* and processed *Rhizoma Curcumae* on cytochrome P450 isoforms. Chin Pharmacol Bull 2012;28:1562–5.
[117] Zhou DG, Zhang DF, Gong QF, Chen Q. RP-HPLC determination of strychnine and brucinein from Semen Strychni and its processed products. Lishizhen Med Materia Med Res 2007;18:33–4.
[118] Yang HM, Liu RX, Li LM, Wu F, Li CQ, Guo JW. Study on anti-inflammatory and analgesic effects of different processing products of Strychnos nux-vomica Seeds. J Chin Med Mater 2016;39:1276–8.
[119] Wang N, Xu H, Sun TW, Liu XJ. Acute toxicity test of crude, sand-warmed or vinegar-boiled Maqianzi. Clin J Chin Med 2013;5:25–6.
[120] Li ZY, Fan ML, Qin XM. Comparison of chemical composition between raw and vinegar-baked *Paeoniae Radix* Alba using NMR based metabolomic approach. Acta Pharm Sin 2015;50:211–7.
[121] Li Y, Wei XZ. Comparison of the effect of different processing technique on analgesic,sedative,anti-inflammatory in *Radix Paeoniae* Alba. J Liaoning Univ Tradit Chin Med 2016;18:39–41.
[122] Nie SQ, Yang Q, Li LF, Huang LQ. Pharmacodynamics comparison of *Bupleurum* Root and red *Peony* root, vinegar-baked *Bupleurum* root and whie *Peony* root between compatibility and single application. Chin J Exp Tradit Med Form 2002;8:11–4.
[123] Cheng YZ, Zhang Y, Xing H, Qian K, Zhao LS, Chen XH. Comparative pharmacokinetics and bioavailability of three ephedrines in rat after oral administration of unprocessed and honey-fried Ephedra extract by response surface experimental design. Evid Based Compl Alternat Med 2017;2017:2802193.
[124] Li J, Zhang S, Qin XM, Li ZY. Comparison on chemical constituents in raw and honey baked Farfarae Flos by NMR-based metabolomic approach. Chin Tradit Herb Drugs 2015;46:3009–16.
[125] Zhang M, Wang MY, Liu YQ, Shi HM, LI XB. Quality analysis of raw and honey-processed licorice of Glycyrrhiza uralensis Fisch, and G. glabra L. by simultaneous determination of five bioactive components using RP-HPLC/DAD method. J Food Drug Anal 2011;19:131.
[126] Zhang M, Wang MY, Liu YQ, LI XB. Changes of contents and decocted contents of main glycosides in Glycyrrhizae Radix et Rhizoma under different processing conditions. Chin Tradit Herb Drugs 2011;42:1305–8.
[127] Liu XY, Wu N, Zhang J, Wu Y, Luo P, Wang WN, et al. Effects of Glycyrrhizae Radix et Rhizoma and honey-fried Glycyrrhizae Radix et Rhizoma on mouse liver CYP3As and detoxification of triptolide. Chin Tradit Pat Med 2014;36:2451–7.
[128] Ching H, Hou YC, Hsiu SL, Tsai SY, Lee Chao PD. Influence of honey on the gastrointestinal metabolism and disposition of glycyrrhizin and glycyrrhetic acid in rabbits. Biol Pharm Bull 2002;25:87–91.
[129] Cai JF, Dai YT, Xiao YQ, Zhao R, Zhang LW. Systemic evaluation of effect of honey-processing on therapeutical basis of Astragalus radix. Chin J Exp Tradit Med From 2016;22:47–52.
[130] Song XW, Li Q, Ye J, Zhang YT, Chen XH, Bi KS. Comparison of flavonoid components in *Astragali Radix* and its processed products. Chin J Exp Tradit Med From 2013;19:85–8.
[131] Shen XJ, Zhou Q, Sun LL, Sun FJ, Yan XS. Comparative study of Astragalus fried with honey and its compound on anti-fatigue and hypoxia tolerance in mice. Shandong J Tradit Chin Med 2014;33:475–80.
[132] Yu X, Dai YM. Impact of honey-fired processing on organic acid components in Cimicifugae Rhizoma. Shandong Sci 2015;28:25–9.
[133] Cao L, Sun H, Li Z, Pan RL. Comparison of activities of various species of Rhizoma Cimicifugae and their honey processed products. J Chin Med Mater 2007;30:1561.
[134] Yang B, Li ZH, Yang WL, Chen HF, Yuan JB. The effect of various drug processing technologies on the contents of aristolochic acid analogues in Axistolchiae Fructus. Lishizhen Med Materia Med Res 2012;23:2553–5.
[135] Li ZH, Yang BX, Yang WL, Chen HF, Yang M, Yuan HB, et al. Effect of honey-toasting on the constituents and contents of aristolochic acid analogues in Aristolochiae Fructus. J Chin Med Mater 2013;36:538–41.
[136] Meng Y, Wu P, Zhang XL, Jiang HQ, Li HF, Zhang QQ, et al. Rapid identification of chemical components in raw and processed products of polygalae radix by HPLC-TOF/MS. Chin J Exp Tradit Med From 2015;20:17–20.
[137] Meng Y, Zhang XL, Tang YQ, Li HF. Variation of five oligosaccharide esters in polygalae radix before and after processing. Chin J Exp Tradit Med From 2015;21:10–3.
[138] Song MH, Wu P, Zhang XL, Li HF, Liu JT, Meng Y, et al. Comparison of eight organic acids in three processed products of Polygalae Radix. Chin Traditi Pat Med 2016;38:1565–9.
[139] Lin JK, Yan XP, Guan SJ, Li L. The study on the content of the saponins in the different processed products of Radix Polygalae. Chin J Exp Tradit Med From 2011;11:89–91.
[140] Wang XJ, Li ZY, Xue SY, Zhang FS, Xing J, Qin XM. Quality control over different processed products of Polygalae Radix based on plant metabolomics. Chin Tradit Herb Drugs 2012;43:1727–37.
[141] Ge F, Zheng Z, Xiao W, Wang ZZ, Huang WZ, Yang ZL. Study on the anti-alcoholism effect of Polygala tenuifolia Willd. and its processed products. Asia Pac Tradit Med 2015;11:12–5.
[142] Guan SJ, Yan XP, Lin JK, Li L. Study on acute toxicity test of different processed products of Radix polygalae. Chin J Integr Tradit West Med 2012;32:398–401.

[143] Zhao HP, Wang J, Wu HH, Bao HZ, Tian H. Effects of crude radix polygalae, saponins and honey-stir-baked radix polygalae on PGE, NO and Ca^{2+}-ATPase in gaster-tissue of rat. Lishizhen Med Mater Med Res 2007;18:260–2.
[144] Sui F, Yan MJ, Li N, Xiao YQ, Li L. Comparative study on antipyretic effects and its mechanisms by four processed Rhei Radix et Rhizoma products. Chin J Exp Tradit Med Form 2012;18:167–70.
[145] Zhu SZ, Li YB, Chen ZG, Li GQ, Yan R, Yao MC. Effect of processed rhubarb on Zebrafish embryos. Lishizhen Med Materia Med Res 2014;25:796–8.
[146] Gao JW, Shi Z, Zhu SZ, Li GQ, Yan R, Yao MC. Influences of processed rhubarbs on the activities of four CYP isozymes and the metabolism of saxagliptin in rats based on probe cocktail and pharmacokinetics approaches. J Ethnopharmacol 2013;145:566–72.
[147] Li CQ, Zhao L, Yang YT, Kang WY. Antimicrobial activity of Salvia miltiorrhiza and different processed products. Chin Tradit Pat Med 2011;33:1948–51.
[148] Wu P, Li HF, Zhang XL, Cui WL, Jiang HL, Meng Y, et al. Changes of Chemical Components in Raw and Processed Products of Salviae Miltiorrhizae Radix et Rhizoma by HPLC-TOF/MS. Chin J Exp Tradit Med Form 2016;22:6–9.
[149] Wang PQ, Kong XM, Kang WY. Antioxidant activity of *Salvia miltiorrhiza* bunge and different processed products. Nat Prod Res Dev 2014;26:1132–5.
[150] Tao Y, Du YS, Huang SR, Li WD, Cai BC. Analysis of chemical constituents in different processed products of *Achyranthis Bidentatae* Radix by UPLC-Q-TOF/MS. Chin J Exp Tradit Med Form 2017;23:1–5.
[151] Zhang ZL, Hu TT, Tian SS, Wu JT. Effect of different salting methods on content of effective components in *Achyranthis Bidentatae* radix. Chin J Exp Tradit Med From 2017;23:10–3.
[152] Wu GX, Gao XL, Zhang ZL. An comparative study on enhancing the immune function before and after Achyranthis bidentatae Radix sunburned with wine. Chin J Tradit Chin Med Pharm 2012;27:114–7.
[153] Wu GX, Zhang ZL, Zhao LN. Effect of *Radix Acanthopanacis* Bidentatae (stir-baking with wine) on blood rheology of model rats with acute blood stasis. Chin J Tradit Chin Med Pharm 2011;26:498–500.
[154] Cai H, Cao G, Cai B. Rapid simultaneous identification and determination of the multiple compounds in crude Fructus Corni and its processed products by HPLC–MS/MS with multiple reaction monitoring mode. Pharm Biol 2013;51:273–8.
[155] He LH. Comparative study for α-glucosidase inhibitory effects of total iridoid glycosides in the crude products and the wine-processed products from Cornus officinalis. Yakugaku Zasshi 2011;131:1801–5.
[156] Du WF, Wang MY, Cai BC. Effect of polysaccharides in crude and processed Cornus officinalis on the immunologic function of mice with immunosuppression induced. J Chin Med Mater 2008;31:715–7.
[157] LI JS, YU ZL, WANG MY, Cai BC. Protecting effect of Fructus Corni Officinalis before and after preparation on mice acute liver damage. J Nanjing TCM Univ 2008;24:236–8.
[158] Zeng LY, Wei Z, Cao YN, Zhang LL, Song ZQ, Liu CS, et al. Content Variations of low molecular weight waccharide from Rhizoma Polygonation during processing. Chin J Exp Tradit Med From 2012;18:69–72.
[159] Zhong LY, Zhou Y, Gong QF. Influence of process on diosgenin in rhizoma polygonati. Chin Arch Tradit Chin Med 2009;27:538–40.
[160] Zeng LY, Song ZQ, Zheng W, Cao YN, Zhang LL, Du ZY, et al. Isolation of chemical constituents produced in processing of Polygonati Rhizoma and their content changes. Chin Tradit Herb Drugs 2013;44:1584–8.
[161] Zhang Y, Zhong LY. Study on Chemical constituents and pharmacological effects in pre- and post-processed of Polygonatum. J Jiangxi Univ Tradit Chin Med 2010;22:77–9.
[162] Huang P, Qian XC, Li JS, Cui XB, Chen LH, Cai BC, et al. Simultaneous determination of 11 alkaloids in crude and wine-processed rhizoma coptidis by HPLC-PAD. J Chromatogr Sci 2014;53:73–8.
[163] Yang C, Qiu X, Kong LD. Effects of different processing products of Rhizoma Coptidis on scavenging oxygen free radical and antilipid peroxidation. J Naijing Univ 2001;37:659–63.
[164] Li JC, Meng XL, Cui R, Lai XR, Fan XJ, Zeng Y. Comparison in pharmacodynamic effects of different types of processed Rhizoma Coptis on mouse diabetes. Chin Tradit Pat Med 2010;32:1922–5.
[165] Qian XC, Zhang L, Tao Y, Huang P, Li JS, Chai C, et al. Simultaneous determination of ten alkaloids of crude and wine-processed Rhizoma Coptidis aqueous extracts in rat plasma by UHPLC–ESI–MS/MS and its application to a comparative pharmacokinetic study. J Pharmaceut Biomed Anal 2015;105:64–73.
[166] Xiu YF, Xu DS, Feng Y, Lin X. Comparison of components in Coptis chinensis processed with various quantity of *Euodia rutaecarpa*. Chin Tradit Herb Drugs 2003;34:320–1.
[167] Tao Y, Jiang YH, Li WD, Cai BC. Effect of processing on contents of twelve constituents in Psoraleae Fructus. Chin J Exp Tradit Med Form 2016;22:6–9.
[168] Zhang W, Yin ZH, Peng T, Kang WY. Inhibitory activity investigation of raw and processed products of *Psoralea corylifolia* for α-Glucosidase. Chin J Exp Tradit Med Form 2013;19:24–8.
[169] Yu LY, Hu CJ, Chen J, Lian XX, Li JL. The Effect of Fructus Psoraleae processing with salt in treating diarrhea. J Sichuan Tradit Chin Med 2009;27:43–4.
[170] Zhang W, Yin ZH, Peng T, Kang WY. Antioxidant activity of *Psoralea corylifolia* and different processed products. Chin J Exp Tradit Med Form 2013;19:250–4.
[171] Gao QQ, Yan CP, Weng ZB, Zhao GH, Chen ZP, Cai BC, et al. Effect of serum containing raw and salt-processed Buguzhi on human osteoblasts. Chin Tradit Pat Med 2015;37:1402–6.
[172] Xia YN, Yu LY, Wang DJ, Cui YY, Xiong R, Zhang M. Study on the effects of different processed products of Fructus Psoraleae on kidney Yang deficiency, spleen deficiency rats. Asia Pacific Tradit Med 2016;12:5–7.
[173] Ji D, Su XN, Hang ZY, Zhang XR, Lu TL. Determination of eight constituents in Anemarrhenae Rhizoma before and after salt processing by HPLC-MS. Chin Tradit Herb Drugs 2017;48:1784–9.
[174] Zhao LL, Liu FF, Peng Y, Kan TG. Effects of different processing methods on five main chemical constituents of Anemarrhena asphodeloides Bge. studied by high performance liquid chromatography. Chin J Chromatogr 2012;30:1271–5.
[175] Wu Y, Song ZB, Xu Y, Gao H, Jia TZ. Comparison of nourishing yin effect of anemarrhenae rhizoma before and after processing. Chin J Exp Tradit Med Form 2013;19:211–4.
[176] Ying Wu, Song ZB, Gao H, Liu TF. Study on hypoglycemic effects of Rhizoma Anemarrhenae before and after processed with saltwater and its mechanism. Chin J Hosp Pharm 2014;34:1977–80.
[177] Lei X, Zhang J, Li Y, Wang QH, Xue J, Su XL, et al. Exploring effective components of laxative effect of Anemarrhenae Rhizoma based on Chinese herbal processing theory. Chin J Chin Mater Med 2015;40:1283–6.
[178] Wu Y, Zhang S, Gao H. Evaluation of salt processing on pharmacokinetics of neomangiferin in Anemarrhena Rhizoma. Liaoning J Tradit Chin Med 2016;43:1442–4.

[179] Jing HY, Shi J, Cui N, Jia TZ. Effects of different processing methods on concents of oligosaccharides and monotropein in Morindae Officinalis Radix. Chin J Exp Tradit Med Form 2014;20:20–3.
[180] Shi J, Cui N, Jia TZ. Effect of different processed products and extracts of Morinda officinalis root on adjuvant-induced arthritis in rats. J Chin Med Mater 2015;38:1626–9.
[181] Cui N, Shi J, Jia TZ. Comparative study on kidney tonifying and Yang supporting effects of different processed products of Morinda officinalis. Chin J Chin Mater Med 2013;38:3898–901.
[182] Shi J, Jing HY, Huang YQ, Fan YN, Jia TZ. Effects of monotropein in different processing products of Morindae Officinalis Radix on plasma concentration and tissue distribution in rats. Chin J Inf Tradit Chin Med 2017;24:76–81.
[183] Zhou H, Song FR, Liu ZQ, Zheng YN, Liu SY. Studies on the components of unprocessed and processed Radix et Rhizoma Rhei Cortex Phellodendri and Radix Paeoniae Rubra by HPLC-UV and ESI-MS. Chin J Pharm Anal 2009;29:883–8.
[184] Lin H, Gong YM, Deng GH. Bacteriostatic effects of Phellodendron chinense and its processed products water extract in vitro and in vivo. Chin Pharm 2012;23:2900–2.
[185] Lian L, Jia TZ. Effects on mice and rats' gastrointestinal function of *Phellodendron amurense* and its different processed products. Chin Arch Tradit Chin Med 2008;26:499–501.
[186] Zhang F, Xu F, Liu PP, Jia TZ. Effects of different processed products of Phellodendron chinense on thyroid gland and adrenocortical function of kidney-yin deficiency model rats with hyperthyroidism. Chin Pharm 2017;28:27–30.
[187] Liu PP, Jia TZ, Xu S, Zhang F. Application of cocktail probe drugs for detecting influences of raw and processed Phellodendri cortex on cytochrome P450 Isoforms. J Chin Med Mater 2015;38:2065–9.
[188] Cao L, Li QM, Fang QM, Wang XY, Zhou XJ, Yang YX. Effects of three processing methods on four triterpenoids in Alismatis Rhizoma. Chin Tradit Pat Med 2016;38:1994–8.
[189] Zheng YF, Zhu YL, Peng GP. Transformation of alisol B 23-acetate in processing of Alisma orientalis. Chin Tradit Herb Drugs 2006;37:1479–82.
[190] Zeng CH, Yang K, Liu HY, Feng X, Zhong ZG. Studies on different chemical compositions and diuretic effect in Alisma orientalis from different habitats before and after salt processing. Chin J Exp Tradit Med Form 2012;18:148–52.
[191] Guo J, Yan RY, Yang B, Wang X. Impact of processing on chemical composition in cortex magnoliae officinalis. Chin J Exp Tradit Med Form 2012;18:117–20.
[192] Zhou XB, Ouyang R. Study of Cortex Magnoliae Officinalis with differ ent frying and roasting on bacteriostasis. J TCM Univ Hunan 2008;28:38–40.
[193] Zhang Y, Wu H. Experimental studies of Houpu and Houpu processed by Gingerjuice on gastrointestinal motor function. Lishizhen Med Mater Med Res 2007;11:014.
[194] Chen QT, Zhuo LH, Xu W, Huang ZH, Qiu XH. Content changes of 5 components in Polygohum muhiflorum during processing. Chin J Exp Tradit Med Form 2012;18:66–71.
[195] Han LF, Wu B, Pan GX, Wang YF, Song XB, Gao XM. UPLC-PDA analysis for simultaneous quantification of four active compounds in crude and processed rhizome of *Polygonum multiflorum* Thunb. Chromatographia 2009;70:657–9.
[196] Yu J, Xie J, Mao XJ, Wei H, Zhao SL, Ma YG, et al. Comparison of laxative and antioxidant activities of raw, processed and fermented Polygoni Multiflori radix. Chin J Nat Med 2012;10:63–7.
[197] Wu XQ, Chen XZ, Huang QC, Fang DM, Li GY, Zhang GL. Toxicity of raw and processed roots of *Polygonum multiflorum*. Fitoterapia 2012;83:469–75.
[198] Guo W, Tan P, Wu YJ, Qin YX, Zhao LL, Li F. Effect of adjuvants on trait and the ester alkaloid from salt-Fuzi. Chin Tradit Pat Med 2015;37:1290–3.
[199] Jin XY, Jia XB, Sun E, Wang JJ, Chen Y, Cai BC. Research on variation regularity of five main flavonoids contents in Epimedium and processed Epimedium. Chin J Chin Mater Med 2009;34:2738–42.
[200] Li YC, He YX, Sun M, Huang LL, Chen HF, Gu Y, et al. Study on warming kidney yang effect of Epimedii Folium processed by different quality of oils from Capra hircus or Ovis aries. Chin J Exp Tradit Med Form 2013;19:197–202.
[201] Qian Q, Sun E, Fan HW, Cui L, Tan XB, Wei YJ, et al. Effect of suet oil on in vivo pharmacokinetic characteristics of icariside I in extract from processed Epimedii Herba in rats. J Chin Med Mater 2012;43:1981–5.
[202] Zhou X, Zhang XR, Zhang QY, Cui HM. Effect of different compositions of raw *Pinellia ternate* and processed *P. ternates* on secretion of inflammation cytokines of mice aorta endothelial cells. Chin J Exp Tradit Med Form 2013;19:261–5.
[203] Yang BY, Li M, Wu FM, Xia Q, Zhou HY, Peng L. Methodological study on quality evaluation of crude and processed *Pinelliae Rhizoma* based on antitussive bioassay. Chin Tradit Herb Drugs 2015;46:2586–92.
[204] Zhao YJ, Ji ZQ, Zhang XN, Zhang YY, Wu JF, Fang X, et al. Effect of rhizoma pinelliae on vomiting in minks. Chin J Chin Mater Med 2005;30:277–9.
[205] Nie RZ, Chen WZ, Lin JN, Peng CJ, Huang YM, Wu ZJ, et al. Comparative study on effects of Araceae toxic Chinese herbs and its processed products. Pharmacol Clin Chin Mater Med 2016;32:53–6.
[206] Zhang HW, Zhang ZL, Liu B. Isolation and identification of the newly added chemical constituent from processed Rhizoma Typhonii. Lishizhen Med Mater Med Res 2010;21:1197–8.
[207] Huang JY, Dai Z, MA SC. Research progress on Typhonii rhizoma. Chin Tradit Herb Drugs 2015;46:2816–21.
[208] Zhang ZL, Zhao LN, Zhang HW, Liu B. Comparative study on antitumor activity in vivo of Rhizoma Typhonii before and after processing. Chin J Tradit Chin Med Pharm 2010;25:1009–11.
[209] Xiong CC, Cai WP, Li JN, Chen WZ, Nie RZ, Li SY, et al. Pharmacological effects of different prepared Typhonii Rhizoma. J Chin Med Mater 2016;39:1763–6.
[210] Li W, Wen HM, Cui XB, Zhang KW. Process mechanism of Atractylodes macrocephala and conversion of sesquiterpenes. Chin J Chin Mater Med 2006;31:1600–3.
[211] Jing J, Parekh HS, Wei M, Ren WC, Chen SB. Advances in analytical technologies to evaluate the quality of traditional Chinese medicines. Trac Trends Anal Chem 2013;44:39–45.
[212] Xiao MS, Chen HY, Shi ZF, Feng YF, Rui W. Rapid and reliable method for analysis of raw and honey-processed astragalus by UPLC/ESI-Q-TOF-MS using HSS T3 columns. Anal Meth 2014;6:8045–54.
[213] Chen J, Zhou Q, Sun S. Exploring the chemical mechanism of thermal processing of herbal materials by temperature-resolved infrared spectroscopy and two-dimensional correlation analysis. Anal Meth 2016;8:2243–50.
[214] Cao S, Xia J, Yang XH, Wang XM, Wang K, Ji S. Comparative study on crude and processed realgar by X-ray diffraction. Chin Tradit Pat Med 2012;34:1136–9.
[215] Lei M, Chen L, Huang BS, Yuan MY, Chen KL. Differentiation of six kinds of traditional Chinese medicine containing sulfate and their processed products by Raman spectrometry. Tradit Chin Med Pharm 2016;31:2811–4.

[216] Gad HA, El-Ahmady SH, Abou-Shoer MI, Al-Azizi MM. Application of chemometrics in authentication of herbal medicines: a review. Phytochem Anal 2013;24:1–24.
[217] Zhang HZ, Tan P, Liu ZJ, Wang J, Wang JB, Xiao XH. Activating blood biological potency assay and chemical fingerprint chromatogram applied to quality evaluation of rhubarb. Acta Pharm Sin 2017;52:436–42.
[218] Wang JB, Ma YG, Zhang P, Jin C, Sun YQ, Xiao XH, et al. Effect of processing on the chemical contents and hepatic and renal toxicity of rhubarb studied by canonical correlation analysis. Acta Pharm Sin 2009;44:885–90.
[219] Zheng QF, Zhao YL, Wang JB, Liu TT, Zhang B, Gong M, et al. Spectrum-effect relationships between UPLC fingerprints and bioactivities of crude secondary roots of Aconitum carmichaelii Debeaux (Fuzi) and its three processed products on mitochondrial growth coupled with canonical correlation analysis. J Ethnopharmacol 2014;153:615–23.
[220] Wang X, Sun H, Zhang A, Sun W, Wang P, Wang Z. Potential role of metabolomics approaches in the area of traditional Chinese medicine: as pillars of the bridge between Chinese and Western medicine. J Pharmaceut Biomed Anal 2011;55:859–68.
[221] Zhong LY, Liao ZH, Gong QF, Xi HH. Effect of *Coptidis Rhizoma* processed with ginger juice on its property based on metabonomics. Chin Tradit Herb Drugs 2013;44:3177–81.
[222] Yu J, Xie J, Zhao RH, Cai SQ, Chen Z. Advances in studies on liver adverse reaction of Polygonum multiflorum. Chin Tradit Herb Drugs 2010;41:1206–10.
[223] Zhang CE, Niu M, Li Q, Zhao YL, Mao ZJ, Xiong Y, et al. Urine metabolomics study on the liver injury in rats induced by raw and processed Polygonum multiflorum integrated with pattern recognition and pathways analysis. J Ethnopharmacol 2016;194:299–306.
[224] Xing J, Sun HM, Jia JP, Qin XM, Li ZY. Integrative hepatoprotective efficacy comparison of raw and vinegar-baked Radix Bupleuri using nuclear magnetic resonance-based metabolomics. J Pharmaceut Biomed Anal 2017;138:215–22.
[225] Liu RX, Chen PJ, Li XL, Wu ZD, Gao XJ, Chen XF, et al. Artificial intelligence sense technology: new technology in pharmaceutical sciences. Chin J Pharm Anal 2017;37:559–67.
[226] Ma L, Ma L, Ouyang LD, Wang X, Xiao XH. Analysis of differential protein expressions in Hirudo before and after stir-frying with wine by two-dimensional electrophoresis. Chin Tradit Pat Med 2017;39:360–5.
[227] Xu LY, Xia XF, Mao WL. DNA fingerprinting of crude and processed Atractylodes lancea. Chin Tradit Pat Med 2006;28:674–6.
[228] Jiang MH, Zhu L, Jiang JG. Immunoregulatory actions of polysaccharides from Chinese herbal medicine. Expert Opin Ther Tar 2010;14:1367–402.
[229] Li HK, Zhou MM, Zhao AH, Jia W. Traditional Chinese medicine: balancing the gut ecosystem. Phytother Res 2009;23:1332–5.
[230] Cao LL, Wang WY, Zhang L, Ding AW, Dou ZH, Wang YH. Study on toxicity of vinegar-processed Kansui Radix on basis of symptom-based prescription theory. Chin J Chin Mater Med 2015;40:3249–55.