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Review Article

Current application of metabolomics in the elucidation of processing mechanisms used in Chinese materia medica: A review

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Abstract

Processing, a key characteristic of traditional Chinese medicine (TCM), enhances the efficacy and safety of Chinese materia medica (CMM) in clinics. It plays an important role in TCM. Studies on processing mechanisms involved in CMM promote the development of TCM. However, most studies on the mechanisms used for processing CMM do not reflect the holistic theory of TCM because they are based only on analysis of some specific chemical components and biochemical indices which do not support the TCM characteristics of network target and multicomponent therapeutics. Fortunately, the perspective of systems biology is consistent with the holistic theory of TCM. Metabolomics, a key tool in systems biology, has been widely used to investigate the processing mechanism of CMM for many years. In this work, current applications of metabolomics in elucidating mechanisms used for processing of CMM were systematically reviewed and discussed in terms of changes in chemical components, toxicity and efficacy of CMM before and after processing. This work provides researchers a clear and concise reference on the current application of metabolomics in investigation of mechanisms used in processing of CMM. Moreover, this work provides a guide on how to investigate the mechanisms used in processing of CMM, based on metabolomics.

Keywords: *Chinese materia medica, Processing mechanism, Metabolomics, Holistic theory*

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INTRODUCTION

Unlike Western herbs, most Chinese materia medica (CMM) may be steamed, fried, charred, boiled, or treated with excipients such as vinegar or yellow rice wine before they are used in manufacturing CMM products and decoctions [1]. These specific treatments are referred to as processing (*Paozhi* in Chinese), and they are ancient Chinese pharmaceutical techniques for enhancing the clinical application of CMM [2].

The main processing methods for CMM, as outlined in the Chinese pharmacopoeia (2015 edition), are summarized in Table 1.

Table 1: Main processing methods of CMM and corresponding representative CMM in the Chinese pharmacopoeia (2015 edition)

Method	Excipient	Representative CMM
Stir-frying	-	Arecae Semen
Stir-frying with solid excipient	Sand	Strychni Semen
	Bran	Aurantii Fructus
	Rice	Mylabris
	Fine powders of terra	Dioscoreae Rhizoma
Stir-frying with liquid excipient	Vinegar	Kansui Radix
	Salt-water	Eucommiae Cortex
	Yellow rice wine	Angelicae Sinensis Radix
	Ginger juice	Tsaoko Fructus
	Refined honey	Lilii Bulbus
	Refined suet	Epimedii Folium
Steaming	Steaming only	Polygoni Multiflori Radix
	Vinegar	Schisandrae Chinensis Fructus
	Salt-water	Morindae Officinalis Radix
	Yellow rice wine	Rhei Radix et Rhizoma
	Medicinal juice	Polygoni Multiflori Radix
Boiling	-	Aconiti Radix
	Edible mother liquor of mineral salt	Aconiti Lateralis Radix Praeparata
	Zingiberis Rhizoma Recens and alumen	Pinelliae Rhizoma
	Glycyrrhizae Radix et Rhizoma and lime	Pinelliae Rhizoma
Calcining	-	Gypsum Fibrosum
Water trituration	-	Cinnabaris

The major objectives of CMM processing are attenuation of toxicity and enhancement of efficacy. Indeed, changes in chemical components of CMM during processing are responsible for the changes in toxicity and efficacy of CMM after processing [3]. Nowadays, several studies have determined the effect of processing on chemical components, toxicity and efficacy of CMM. However, the perspectives of most of these studies do not reflect the holistic theory of traditional Chinese medicine (TCM) because they involve investigations of the effect of processing on toxicity and efficacy of CMM based only on measurements of some specific chemical components and biochemical indices [4,5]. This is at variance with the characteristics of TCM i.e. network target and multicomponent therapeutics [6,7]. Therefore, these studies are not adequate for elucidating the mechanisms involved in the processing of CMM based on the holistic theory of TCM. For example, it was reported that the toxicity and efficacy of areca nut, a frequently-used CMM, were attenuated and increased, respectively, after processing, due to changes in some specific components and biochemical indices such as arecoline, cell/animal toxicity, and gastrointestinal tract functions [8,9]. Obviously, these indices do not reflect network target and multicomponent therapeutics, which are the characteristics of TCM. Thus, these studies cannot elucidate the mechanism used in processing areca nut based on the holistic theory of TCM.

The perspective of systems biology, which is consistent with the holistic theory of TCM, has been widely used to study TCM-related issues such as chemical components, toxicity and efficacy of CMM [10-12]. At present, omics techniques have become the key tools of systems biology, with metabolomics constituting an important part [13]. Metabolomics research procedures comprise three steps: sample collection and preparation, metabolome data collection, and data analysis [14,15]. Metabolomics has been widely used for investigation of mechanisms used in the processing of CMM for many years [16]. In the present study, the applications of metabolomics in elucidating mechanisms used in processing of CMM were systematically reviewed and discussed in terms of the changes in chemical

components, toxicity and efficacy of CMM before and after processing. This was with a view to enhancing the investigations on mechanisms used for processing of CMM based on metabolomics.

DECIPHERING THE EFFECT OF PROCESSING ON CHEMICAL COMPONENTS OF CMM, BASED ON METABOLOMICS

The effect of processing on chemical components of CMM can been comprehensively determined using metabolomics. Metabolomics can be used for direct demonstration of the effect of processing on chemical component profiles of CMM. The differences in chemical component profiles of CMM before and after processing consist of changes in contents of components, production of new components, and elimination of original components. The biomarkers of processing-related chemical components identified using multivariate statistical analysis of metabolomics data can be used to further elucidate precisely the effect of processing on chemical components of CMM.

It has been reported that after steaming or boiling with vinegar or yellow rice wine, the results of metabolomics analysis indicated marked changes in chemical component profile of Ligustri Lucidi Fructus, with significant increase in the content of processing-related chemical component biomarker (ligustaloside B) [17]. Following stir-frying with refined honey or licorice juice, the chemical component profile of Polygalae Radix exhibited marked changes, based on metabolomics analysis [18]. Metabolomics analysis revealed that the levels of 127 components of Rhubarb were changed after it was steamed with yellow rice wine [19]. There are many similar studies in the literature, such as the effect of processing on the chemical components of Schisandrae Chinensis Fructus, Euphorbiae Pekinensis Radix, and Asari Radix et Rhizoma [20-22].

METABOLOMICS-BASED ELUCIDATION OF THE EFFECT OF PROCESSING ON TOXICITY OF CMM

Changes in chemical components of CMM are the underlying causes of changes in toxicity of CMM after processing. Generally, the effect of processing on toxicity of CMM is investigated based on metabolomics by comparing the differences in endogenous metabolites of experimental animals treated with crude CMM and processed CMM. To better elucidate the effect of processing on toxicity of CMM, changes in chemical components of CMM before and after processing should be investigated simultaneously. However, extant literature suggests that the current application of metabolomics in elucidating the attenuating effect of processing on toxicity of CMM has focused mainly on analysis of endogenous metabolites of organism. The processing-related endogenous metabolite biomarkers and chemical component biomarkers identified using multivariate statistical analysis of metabolomics data can be used to further elucidate precisely the attenuating effect of processing on toxicity of CMM.

After being processed with sand or oil, the results of metabolomics analysis showed obvious differences in the chemical component profile of Strychni Semen: its main toxic and bioactive components strychnine and brucine were converted to less-toxic and equally-active components strychnine *N*-oxide and brucine *N*-oxide, respectively [23]. The liver and kidney toxicities of Myristicae Semen were decreased after processing with wheat bran, and the results of metabolomics analysis indicated significant reversal (to normal) of the Myristicae Semen-induced abnormality in rat endogenous metabolite profile. Moreover, 17 endogenous metabolites were identified as biomarkers related to processing-induced attenuation of Myristicae Semen toxicity [24].

A study has demonstrated that, after nine sessions of steaming and sunning, the liver toxicity of Polygoni Multiflori Radix was attenuated. Moreover, metabolomics analysis revealed that Polygoni Multiflori Radix-induced changes in rat endogenous metabolite profile were significantly reversed to normal [25]. In addition, 10 metabolites were identified as biomarkers related to processing-induced attenuation of Polygoni Multiflori Radix toxicity [25]. It has been reported that processing reduced the toxicity of Pinelliae Rhizoma, and results of metabolomics analysis suggested that processing significantly reversed Pinelliae Rhizoma-induced abnormality in rat endogenous metabolite profile [26]. Moreover, 10 metabolites were identified as biomarkers related to processing-induced reduction in the toxicity of Pinelliae Rhizoma [26].

METABOLOMICS-BASED INVESTIGATON OF THE EFFECT OF PROCESSING ON EFFICACY OF CMM

Similar to their influence on toxicity of CMM, changes in chemical components of CMM also result in changes in efficacy of CMM after processing. The major objectives of CMM

processing are to increase original efficacy, and to produce new efficacy. Simultaneous analyses of changes in chemical components of CMM before and after processing, and comparison of the differences in endogenous metabolites of experimental animals treated with crude CMM and processed CMM would enhance elucidation of the effect of processing on efficacy of CMM. However, studies on the effect of processing on efficacy of CMM have focused mainly on analyses of endogenous metabolites of organisms, with very few chemical component analyses. Similarly, processing-related endogenous metabolite biomarkers and chemical component biomarkers can be used to determine precisely the effect of processing on efficacy of CMM.

A study has shown that after stir-frying with vinegar, the liver-soothing and analgesic efficacies of *Bupleuri radix* were enhanced, and Bupleuri Radix-induced rat endogenous metabolite profile was significantly changed, based on metabolomics analysis, suggesting obvious differences in the efficacy of *Bupleuri radix* before and after processing [27]. The major processed products of *Angelicae sinensis* Radix (ASR), which have been widely used in TCM prescriptions, are charred ASR, oil-parched ASR, wine-parched ASR, and soil-parched ASR. It has been reported that charred ASR and wine-parched ASR produced better anti-inflammatory effects than ASR parched with oil or soil, and metabolomics analysis suggested that charred ASR and wine-parched ASR were better at reversing abnormality of endogenous metabolite profiles of rats with acute inflammation, than oil- or soil-parched ASR [28].

There are many similar metabolomics-based studies on the effect of different processing methods on the efficacy of ASR [29,30]. Raw Vladimiriae Radix promotes the circulation of *qi*, but the efficacy was converted to anti-diarrhea effect after simmer processing. Results of metabolomics analysis have suggested that the chemical component profile of Vladimiriae Radix was different after processing, and 7 chemical components were identified as biomarkers related to processing-induced changes in Vladimiriae Radix efficacy [31]. Based on metabolomics study, the differential influences of *Psoraleae fructus* and salt-processed *Psoraleae fructus* on 22 common biomarkers and associated metabolic pathways showed that salt-processing enhanced the effect of *Psoraleae fructus* and reduced its cardiovascular and renal toxicities in rats [32].

It has been reported that wine-processed *Scutellariae radix* (WSR) exhibited a more remarkable mitigating effect on acute lung injury than crude Scutellariae Radix (CSR). Pathway analysis of metabolomics data indicated that CSR acted on acute lung injury by regulating the metabolic pathway of abnormal sphingolipids, but WSR-mediated treatment was related mainly to reversal (to normal) of the abnormality in retinol and tryptophan metabolic pathways. These findings suggested that wine processing changed the mechanism of action of *Scutellariae radix* against acute lung injury [33]. There are many similar studies on the effect of processing on efficacy of CMM, based on metabolomics. These include effect of processing on the efficacies of Gardeniae Fructus, Zingiberis Rhizoma, Rehmanniae Radix, and Codonopsis Radix [34-37].

METABOLOMICS-BASED ELUCIDATION OF CMM PROCESSING MECHANISM FROM CHEMICAL COMPONENTS, TOXICITY AND EFFICACY

At present, the investigations on processing of CMM focus mainly on elucidating the effects of processing methods on chemical components, toxicity and efficacy of CMM [38]. Processing-induced changes in chemical components of CMM result in changes in toxicity and efficacy of CMM. The effect of processing on the chemical component profiles of CMM, and CMM-induced endogenous metabolite profiles of experimental animals can be comprehensively determined using metabolomics. Chemical component and endogenous metabolite profiles can be used to show the holistic differences in chemical components, toxicity and efficacy of CMM before and after processing. The differences can be further elucidated through chemical component biomarkers and endogenous metabolite biomarkers identified using multivariate statistical analysis of metabolomics data.

Endogenous metabolite biomarkers can be used to elucidate the pathways associated with the differences in toxicity and efficacy of CMM before and after processing, with the aid of Kyoto Encyclopedia of Genes and Genomes [39]. In brief, the mechanisms involved in attenuation of toxicity and enhancement of efficacy in CMM processing can be elucidated through analysis of the differences in the chemical components of CMM and CMM-induced endogenous metabolites of experimental animals before and after processing, with the aid of metabolomics. However, the current application of metabolomics in CMM processing shows that the relationships between chemical components and

toxicity/efficacy of CMM are not well analyzed. As a result, studies on the mechanisms used in processing of CMM are not in-depth enough: they require further enhancement.

FINAL REMARKS

This review has systematically summarized the current application of metabolomics in studies on the effect of processing on chemical components, toxicity and efficacy of CMM. The approaches to elucidating processing mechanism of CMM based on metabolomics are presented. This work provides a clear and concise reference for researchers on the mechanisms used for processing CMM and their effects on chemical components, toxicity and efficacy, based on metabolomics.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors have read and approved the publication of manuscript. Guihua Jiang and Yunbin Jiang conceived and designed the study, while Ting Huang, Yanfei Zhang and Yutian Lei collected and analyzed the literatures. Ting Huang and Yunbin Jiang wrote the manuscript. Ting Huang and Yunbin Jiang contributed equally to this work and should be considered as co-first authors.

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