A Unique Issue in the Standardization of Chinese Materia Medica: Processing

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Abstract

Processing of Chinese Materia Medica (CMM) is a pharmaceutical technique to fulfill the different requirements of therapy, dispensing and making preparations according to traditional Chinese medicine theory. The aims of processing are to enhance the efficacy and/or reduce the toxicity of crude drugs. Those processed products are named as decoction pieces, which are used in clinics. Therefore, there is a close relationship between processing, safety, and efficacy of Chinese medicines. Some toxicity or side effects are caused by improper processing methods and some are due to improper combination of herbal mixtures. Standardization of processing methods for Chinese herbs is as important as authentication to maintain their quality and ensure their safe use. The objective of this paper is to review the literature covering the current situation and problems of CMM processing as well as recent progress in research in this area. A summary of the most urgent work needed is proposed.

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Introduction

Unlike Western herbs, many Chinese herbs are subjected to specific treatments before they are used as materia medica. Whereas Western herbs are generally used simply fresh or dried, Chinese herbs may be boiled, steamed, treated with salt or vinegar, fried, or charred, to name a few of these processes, before they are used in decoctions or in manufacturing of herbal products. In the following discussion, the word “processing” refers to any treatment which transforms raw herbs into materia medica; it does not refer to the manufacture or preparation of herbal products.

Under the guidance of the traditional Chinese medicine (TCM) theory, Chinese Materia Medica (CMM) is mostly of botanical origin. Standardization of processing methods for Chinese herbs is as important as authentication to maintain their quality and ensure their safe use [1]. Processing was clearly listed as a specific item in the Chinese pharmacopoeia (2010 edition) [2]. In contrast, only raw herbs and/or their chemical components are listed in the Japanese, North American, British, and European pharmacopoeias [3–6].

It is well known that there is a close relationship between processing and safety of CMM. Some toxicity or side effects are caused by improper processing methods. For example, improperly processed Radix Aconiti Lateralis has caused poisoning involving five thousand people in the past twenty years [7]. Similar poisoning incidents were reported in Hong Kong due to the intake of incompletely processed Radix Aconiti Preparata or Radix Aconiti Kusnezoffii Preparata [8].

In recent years, considerable confusion has developed with some of the processed products in both local Asian and overseas markets. Therefore we would like to describe the current situation and problems of CMM processing as well as recent progress in research. The development of processing methods and possible ways of solving those problems will also be explored.

History of processing

The first processing record can be found in “52 Bing Fang” (Prescriptions for fifty-two Diseases), which was written in 200 BC. It recorded some contents of processing methods, such as burning, calcining, stewing, and soaking with wine and vinegar [9]. The classic Lei Gong Pao Zhi Lun [10]
Gong Processing Handbook, 大公炮炙論) written about 500 AD summed up previous records and experiences of processing for the first time as the first monograph [10]. The Pao Zhi Da Fa (Processing Methodology, 炮製大法) published in 1662 recorded the processing methods of 439 Chinese medicines [11]. In Qing dynasty, Xiu Shi Zhi Nan (Xiu Shi Guidelines for Processing, 修事指南), written by Zhang Zhongyan, is the third monograph about processing, which cited data related to processing from many classic texts about CMM, especially Compendium of Materia Medica (Ben Cao Gang Mu) and Materia Medica Arranged According to Pattern (Zheng Lei Ben Cao) [12]. Additionally, there are plenty of classic texts about CMM or Chinese medicine which also recorded abundant figures of processing. Those records condensed the clinical experiences of ancient Chinese medicine doctors, which should be developed and studied. Nowadays, CMM processing has been developed as an academic subject which studies the theory, technology, standards, history, and development of processing.

Definition and methods of processing

Processing of CMM is a pharmaceutical technique to fulfill the different requirements of therapy, dispensing and making preparations according to the traditional Chinese medicine theory. CMM includes crude drugs, decoction pieces, and proprietary Chinese medicines. Crude drugs are fresh or dried, usually cut, sliced, or chopped parts of plants, animals, or minerals. Decoction pieces are crude drugs that have been processed. Thus, “processing” refers to any physical and/or chemical treatment by which crude natural drugs are transformed into materia medica. These processing methods are recorded in the Chinese pharmacopoeia, and have been handed down through history.

The main aims of processing are to enhance the efficacy and/or reduce the toxicity of crude drugs. Additionally, processing can moderate drastic action, diminish side effects, modify the energetic properties (flavor, nature, action), dissipate disagreeable odors and flavors, and so on. The processing methods of CMM are mainly divided into cleaning, cutting, and processing practices which include stir-frying, charing, steaming, boiling, calcining, etc. Fifteen processing methods are recorded in the Chinese pharmacopoeia; the main ones are listed in Table 1 [2]. Several commonly used methods are described below:

- Chao (炒, Stir-frying): Cleaned and cut crude drugs are put in a pot, with or without additive, heated with constantly tossing or stirring until the individual herbs reach a certain state. Usually assessed by color or scent, there are three degrees of frying in this process: stir-frying till yellow, stir-frying till scorched, and stir-frying till carbonized. For example, dried Rhizoma Zingiberis (Ganjiang) is called Rhizoma Zingiberis Preparatum (Paojiang) when it is roasted with sand until it becomes puffy and brown externally. When it is stir-fried until the surface becomes black and the interior brown, it is called Charred Rhizoma Zingiberis (Jiangtian). Ordinary Rhizoma Zingiberis (without processing) has the actions of dispelling cold from the spleen and the stomach, promoting recovery from collapse, and eliminating dampness and phlegm. Rhizoma Zingiberis Preparatum warms the middle-enerizer, dispels cold, and arrests bleeding by warming the meridians. Charred Rhizoma Zingiberis has particularly strong efficacy in arresting bleeding.

- Zhi (炙, Stir-frying with liquid adjuvants): Liquid is added to the cleaned and cut crude drugs, and then the herbs are stir-fried to make the additives gradually infuse into the interior of the crude drugs. Based on the different additives used, this method could be divided into stir-frying with wine, stir-frying with vinegar, stir-frying with salt water, stir-frying with refined honey, stir-frying with ginger juice, stir-frying with refined suet, etc. For example, in preparing Radix Glycyrrhizae Preparata, refined honey is diluted with a quantity of boiling water, added to slices of Radix Glycyrrhizae and mixed well in a closed vessel until they are infused thoroughly. The slices are then roasted in a pot with gentle heat until they become yellow to deep yellow to remove their stickiness; they are then removed and cooled. The raw Radix Glycyrrhizae is good at removing “heat” and counteracting toxicity, as well as dispelling phlegm and relieving cough. Processed Radix Glycyrrhizae invigorates the function of spleen and stomach and restores the normal cardiac rhythm.

In summary, processing CMM is a very important part of traditional Chinese medicine, and it is a key factor in achieving the expected therapeutic effects. The transformation of crude natural drugs into materia medica by processing is a process that involves physical and chemical changes, and it is also a process that involves the transformation of medicinal properties. This process is not only aimed at improving the efficacy and reducing toxicity, but also at moderating the safety and ensuring the quality of medicinal materials. Therefore, the study of processing CMM is of great significance for the development of modern Chinese medicine.
Table 1  Main methods of processing CMM as listed in the Chinese pharmacopoeia (2005).

<table>
<thead>
<tr>
<th>Processing method</th>
<th>Additives</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stir-frying without additional adjuvants (炒)</td>
<td>Fine powders of terra (土)</td>
<td>Rhizoma Atractylodis Macrophalae (processed with terra)</td>
</tr>
<tr>
<td></td>
<td>Bran (麩)</td>
<td>Rhizoma Atractylodis (processed with bran)</td>
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<tr>
<td></td>
<td>Rice (米)</td>
<td>Radix Codonopsis (processed with rice)</td>
</tr>
<tr>
<td></td>
<td>Sand (砂)</td>
<td>Radix Zingiberis (processed with sand)</td>
</tr>
<tr>
<td>Stir-frying with solid adjuvants (炒)</td>
<td>Yellow rice wine (酒)</td>
<td>Radix Angelicae Sinensis (processed with wine)</td>
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<tr>
<td></td>
<td>Vinegar (醋)</td>
<td>Radix Bupleuri (processed with vinegar)</td>
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<tr>
<td></td>
<td>Salt-water (鹽水)</td>
<td>Cortex Eucimmiae (processed with salt)</td>
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<tr>
<td></td>
<td>Refined honey (蜜)</td>
<td>Radix et Rhizoma Glycyrrhizae (processed with refined honey)</td>
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<tr>
<td></td>
<td>Ginger juice (薑汁)</td>
<td>Rhizoma Coptidis (processed with ginger)</td>
</tr>
<tr>
<td></td>
<td>Refined suet (羊脂油)</td>
<td>Herba Epimedi (processed with refined suet)</td>
</tr>
<tr>
<td>Steaming (炙)</td>
<td>Only steaming (清蒸)</td>
<td>Radix et Rhizoma Ginseng Rurba (人參)</td>
</tr>
<tr>
<td></td>
<td>Salt-water (鹽水)</td>
<td>Radix Morindae officialis (processed with salt)</td>
</tr>
<tr>
<td></td>
<td>Medicinal juice (藥汁)</td>
<td>Radix Polygonii Multiflori Praeparata (processed with black bean juice)</td>
</tr>
<tr>
<td></td>
<td>Vinegar (醋)</td>
<td>Fructus Schisandrae Chinensis (processed with vinegar)</td>
</tr>
<tr>
<td></td>
<td>Yellow rice wine (酒)</td>
<td>Rhizoma Polygonati (processed with wine)</td>
</tr>
<tr>
<td>Calcining (炮)</td>
<td>Gypsum Fibrosom Preparatum</td>
<td>血石膏</td>
</tr>
<tr>
<td>Boiling (煮)</td>
<td>Edible mother liquor of mineral salt preparation (食用鹽巴)</td>
<td>Radix Aconiti (processed)</td>
</tr>
<tr>
<td></td>
<td>Rhizoma Zingiberis Recens and alumen (薑汁、明薑)</td>
<td>Radix Aconiti Lateralis Praeparata</td>
</tr>
<tr>
<td></td>
<td>Rhizoma Zingiberis Recens and alumen (薑汁、明薑)</td>
<td>Radix et Rhizoma Ginseng Rurba (人參)</td>
</tr>
<tr>
<td></td>
<td>Rhizoma Zingiberis Recens and alumen (薑汁、明薑)</td>
<td>Radix Zingiberis (charred)</td>
</tr>
</tbody>
</table>

Current Issues

The TCM education circles there is a common view to CMM processing drugs: "obeying ancient processing methods". Today, the processing methods of many crude drugs have already changed greatly to advance with time during the development of processing. Therefore, the view of "obeying ancient processing methods" just embodies principles, and opinions differ on which processing method should be used.

Inconsistency of ancient and current processing methods

In some cases, the present processing methods are inconsistent with the ancient ones. In other cases, over time, the names of processing products have become confused. For example, in ancient times, the processing methods of Radix Polygonii Multiflori included cleaning, cutting, and processing with or without additives. The Bencaogangmu (A.D. 1593) records the processing of Radix Polygonii Multiflori (Heshouwu) as follows: "peel off the raw bark using a bamboo knife, soak overnight in washing water of rice and then cut; after soaking in water, put one layer of black bean and one layer of Radix Polygonii Multiflori in the pot, repeat the layers, and then steam. When the black beans become cooked, take out the black bean and dry Radix Polygonii Multiflori, then steam again with the black bean; repeat nine times. This is called 'processing together with washing water of rice and black bean'". The above method emphasizes "steam nine times and dry nine times" [13]. Nowadays, the main processing methods of Radix Polygonii Multiflori include steaming with black bean juice, stewing with black bean juice, steaming alone, steaming with black bean juice and yellow rice wine, and steaming under high pressure. The processing time varies from three to forty hours; there is no alternative steaming and drying. Clearly, the present processing methods of Radix Polygonii Multiflori are different from those in ancient times. As mentioned above, those
processing contents recorded by ancient documents came from the clinical experience of ancient Chinese medicine doctors. Before comparative studies are carried out, discarding the ancient experience would be inappropriate.

Inconsistency of processing practice
in different provinces of China

Until now, there are no harmonized processing practices for all regions of China. Apart from the national standard, various local standards are still in practice in different provinces and districts. Although processing procedures of 462 decoction pieces have been recorded in the Chinese pharmacopoeia (2010 edition) among a total of 822 decoction pieces, there are still many processing procedures of decoction pieces without record. For example, for Rhizoma Gastrodiae (Tianma), the processing method “clean, moisten or steam soft, cut in thin slices, dry” is recorded in Chinese pharmacopoeia while processing with ginger or wine is recorded in “The Practices of Processing Chinese Crude Drugs in Fujian Province” [14]. The processing method of Rhizoma Arisaematis (Tiannanxing) recorded in “The Practices of Processing Chinese Crude Drugs in Hunan Province” is different from that recorded in the Fujian Province. In the former, the crude drug is mixed with ginger juice as an additive and preserved and soaked with Alumen, then boiled until chewing a small piece gives only a slight numbness to the tongue. In the latter, the crude drug is mixed with fresh ginger slices as an additive and boiled with Alumen until the whole pieces are thoroughly boiled [14].
Besides the differences in processing methods, the additive used may also differ. For example, in processing Radix et Rhizoma Rhei (Dahuang, stir-fried with wine), white rice wine is used in "The Practices of Processing Chinese Crude Drugs in Hunan Province", but yellow rice wine is recorded in the Fujian, Anhui, and Guangxi Practices [14–17]. The commonly used additives in CMM processing as wine, vinegar, and refined honey, are often used in different specifications or different quantities according to different local standards. However, there are no explanations on the labels of Chinese proprietary medicines or in prescriptions given by practitioners.

The above phenomenon of "one crude drug with several processing methods and differences in different places" should be harmonized, and consistent practices based on scientific studies need to be established.

Differences in processing methods between Hong Kong and Mainland China

As an international trading center for CMM, Hong Kong plays an important role in the CMM market. The decoction pieces and herbal products are exported to all over the world from Hong Kong. Therefore, the situation of processing in Hong Kong has attracted more attention. According to our previous investigations in the Hong Kong market, 66% of the 365 species of commonly used CMM are processed locally [18]. The processing methods in Hong Kong and Mainland China are different (Table 3, Figs. 1–6).

Differences in processing methods between other countries and China

Although the pharmacopoeias of European countries and North America have records of certain CMMs, description of processing methods has been neglected so far. In the pharmacopoeias of some other Asian countries, processing methods of some species have been recorded, such as in the Japanese [3], Korean [19], and Vietnamese pharmacopoeias [20]. In the Korean pharmacopoeia, which has recorded 383 species, only nine species are listed along with their processing method: Agkistrodon (Qishe, the dried body of Agkistrodon actus Gunther), Alumen (Baifan, a processed mineral of sulfates of alumstone, containing mainly potassium aluminum sulfate), Astragali Semen (Shayuanzi, the dried ripe seed of Astragalus complanatus R. Br.), Hominis Placenta (Ziheche, the dried fresh human placenta), Natural Magnetite (Cishi, a mineral of oxides of the spinel group, containing mainly ferroferric oxide), Meretricis Concha (Geqiao, the shell of Meretrix meretrix L. or Cyclina sinensis gmelin), Piscis Colla (Yubiao, the air bladder, of which the blood vessels and the mucous membrane are removed and flattened by ironing, of Gadus macrocephalus Tlesius and Acipenser sinensis Gray), Pyritum (Zirantong, a mineral of sulfides of the pyrite group, containing mainly iron sulfide), and Sterculiae Scaphigerae Semen (Pangdahai, the dried ripe seed of Sterculia lychnophora Hance). Among them, the processing practice of Natural Magnetite is calcining, whereas cal-

<table>
<thead>
<tr>
<th>Decoction Pieces</th>
<th>Mainland China</th>
<th>Hong Kong</th>
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</thead>
<tbody>
<tr>
<td>Radix Angelicae Sinensis (Danggui, 当歸)</td>
<td>Upper part: cut into pieces; Axial root: cut lengthwise into slices; branch roots: tie into a bundle and cut into slices; drying and processing with wine</td>
<td>Upper part: cut lengthwise into thin slices; drying and processing with wine; simple steaming</td>
</tr>
<tr>
<td>Radix Notoginseng (Sanqi, 三七)</td>
<td>Cut or grind into fine powder</td>
<td>Color crude drug black and give the bark a polished look</td>
</tr>
<tr>
<td>Radix Salviae Miltiorrhizae (Danshen, 丹参)</td>
<td>Cross-cut into slices or cut into sections</td>
<td>Compress and cut lengthwise</td>
</tr>
<tr>
<td>Cortex Phellodendri (Huangbo, 黃柏)</td>
<td>Cut into fine sticks</td>
<td>Cut trunk bark into rectangular slats and then cut slats lengthwise into thin slices</td>
</tr>
<tr>
<td>Fructus Aurantii (Zhiqiao, 枳壳)</td>
<td>Moisten thoroughly, cut into slices</td>
<td>Pound flat with a hammer and cut</td>
</tr>
<tr>
<td>Radix Polygoni Multiflori (Heshouwu, 何首烏)</td>
<td>Cut into irregular, thick slices or sections; boiling in black bean juice</td>
<td>Mostly processed and then cut lengthwise into slices; drying; simple steaming; steaming with sugar; boiling with black beans; blanching in boiling water</td>
</tr>
</tbody>
</table>

Fig. 1 Decoction pieces of Radix Angelicae Sinensis as typically found in Mainland China (a) and Hong Kong (b).
cining and then dipping into vinegar is recorded in the Chinese pharmacopoeia. Similarly to the Korean pharmacopoeia, the Vietnamese pharmacopoeia also lists processed items, but the processing methods of some species are greatly different from those recorded in the Chinese pharmacopoeia (Table 4). Additionally, the Japanese pharmacopoeia also records the processing methods of some species under the item of plant source but not as a separated processing item. The processing methods are simple and also different from those of the Chinese pharmacopoeia (Table 4). In conclusion, there is no harmonized methodology for processing CMM between ancient practice methods and modern adopted procedure, within provincial regions or outside China.

Lack of objective quality control standards

Quality control is extremely important for the safety of CMM. However, the quality control standards of CMM processing practices are weak. The technology of CMM processing often depends on the practitioner’s experience which is strongly subjective and lacks objective criteria. For example, Radix Aconiti Preparata (Zhichuanwu) is processed until it has a slight numbing effect on the tongue; Radix Polygoni Multiflori Preparata is steamed until it is brown on all sides.

In the Chinese pharmacopoeia (2010 edition), the differences in actions between crude drugs and processed ones in many species have not been indicated. For example, under “Radix Aconiti Lateralis Preparata” (Fuzi) section, four kinds of processed products namely, “Heishunpian”, “Baifupian”, “Danfupian”, and “Paofupian” are listed and shared the same actions. In other cases, the crude drug and its different processed products are recorded under the same item. For example, under “Radix et Rhizoma Rhei Preparata” (Zhidahuang) section, besides the crude drugs, three kinds of processed products are listed: stir-fried with wine (Jiudahuang), stewed or steamed with wine (Shoudahuang), and carbonized (Dahuangtan), and all of them are called Radix et Rhizoma Rhei Preparata.

Current Situation and Progress in Research

Utilization of ancient documents

It is important to utilize and explore the ancient documents which record the valuable processing experiences. In the past thirty years, the processing practices recorded in many classics about CMM have been well summarized [21, 22]. Recently, the utilization and exploration of ancient documents has produced achievements. For example, in 2005, the colored drawings of the Ming Dynasty in “Buyi Leigong Paozhi Bianlan” (Buyi Lei Gong Processing Discussion Text) reappeared after having disappeared for four hundred years. This text contains fourteen volumes with 1193 beautiful colored figures including the rare 219 figures depicting herb processing, which provide precious data for the study of CMM processing [23]. Fig. 7a indicates the processing methods at that time, including the processing scenes, tools and instruments, such as chopper, mortar and pestle, boiler, cooking stove, jar, etc. Fig. 7b shows the scene of processing Radix Aconiti Lateralis involving the procedures of cutting, drying,
stir-frying, and burying. These figures depict a standard operation practice of illustrated CMM processing with a written record. Besides the monographs of CMM, almost four thousands books about medical records have been written by ancient Chinese medicine doctors. In these books, many valuable processing experiences have been recorded. These ancient documents about CMM processing need to be further organized, validated and implemented with scientific understanding of the procedures involved.

Comparative chemical studies
The main purposes of processing are reducing toxicity and enhancing the effects of crude drugs. The chemical components of crude drugs and processed products differ: new components may be formed or the relative contents of certain components may change; other components may disappear or their contents may decrease.

Difference of contents of some components between the crude drugs and processed products: In some herbal drugs, the contents of some compounds increase and others decrease at the same time. For example, for Radix Paeoniae Alba (Baishao), a study indicated that, gallic acid and pentagalloylglucose increased while the contents of catechin, albiflorin, paoniflorin, benzoic acid, and benzoylpaoniflorin decreased during decocting and boiling [24]. For Cortex Magnoliae Officinalis (Houpu), the contents of magnolol and honokiol increased by about 140% and 40%, respectively, after stir-frying with ginger [25]. A further study by HPLC fingerprint analysis indicated that the processed product of Cortex Magnoliae Officinalis contained a new component, gingerol, and the areas of some common peaks increased while some decreased in the chromatograms [26]. Comparing the chemicals of the crude drug of Fructus Corni (Shanzhuyu) and its processed product, which is steamed with yellow rice wine, the contents of iridoid glucosides, flavonoids, and saponins decreased, e.g., the contents of morroniside and loganin decreased from 1.85% to 1.57%, and 1.41% to 1.27%, respectively, while the content of polysaccharides increased [27]. A further comparative study on contents of amino acids and major and trace elements indicated that processing could lead to an increase in dissolved inorganic elements and change in the contents of amino acids. For example, the contents of some essential amino acids such as lysine, leucine, and valine increased [28]. Comparing the contents of three active components in raw and different processed products of Rhizoma Corydalis (Yanhusuo) showed that the contents of tetrahydropalmatine, protopine, and berberine in the products processed by stir-frying with vinegar and yellow rice wine were higher than those in the raw materials. However, the contents of tetrahydropalmatine and berberine hydrochloride decreased in the processed product boiled with vinegar [29].

The contents of toxic components in many toxic/potent CMM decreased after being processed. In Radix Aconiti Lateralis Preparata,
the processed daughter root of *Aconitum carmichaeli* Debx., the contents of the toxic constituents aconitine, mesaconitine, and hypanocitine are much lower than those in the raw materials [30, 31]. Recently, a market investigation on Radix Aconiti Lateralis Preparata was carried out in our group. We found that the sum of aconitine, mesaconitine, and hypanocitine in 8 types of Radix Aconiti Lateralis Preparata was only 3.91–34.8% of that in the raw slice. The amounts of toxic components in 8 types of Radix Aconiti Lateralis Preparata varied significantly, indicating that the dosage of these herbs prescribed for clinical use should be cautiously set in order to avoid poisoning incidents [32]. The case for processed Semen Strychni (Maqianzi) is similar; the content of strychnine, the toxic component, was found to be 0.411 (± 0.028) mg/g in the detoxified Semen Strychni, which was dramatically reduced 10 times in comparison to the unprocessed Semen Strychni. Additionally, the contents of brucine and vomicine were also greatly reduced in the processed seeds [33].

Beside the toxic/potent CMM, the contents of some active components may also decrease after processing. Investigation on the influences of different processing methods on the chemical components of Radix Polygoni Multiflori indicated that the content of (a) 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside changed as: raw materials > steamed with black bean juice at high pressure > steamed with black bean juice > steamed with black bean juice > steamed with water; (b) total free anthraquinones changed as: raw materials > steamed with black bean juice > stewed with black bean juice > steamed with water; (c) total anthraquinones changed as: raw materials > steamed with black bean juice > stewed with black bean juice > steamed with water; (d) total free anthraquinones changed as: raw materials > steamed with black bean juice > stewed with black bean juice > steamed with water. Also, during the course of stewing black bean juice, the content of 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside decreased with the increase of processing time; only 17% of the original levels remained at 48 h; the content of total free anthraquinones increased firstly and then decreased with longer processing; the contents of tannin, total anthraquinones, and total combined anthraquinones decreased with the increase of processing time [34]. Our recent studies showed in detail that two anthraquinones of emodin-8-O-(6′-O-malonyl)-glucoside and physcion-8-O-(6′-O-malonyl)-glucoside disappeared or greatly decreased and 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucopyranoside, emodin-8-O-β-D-glucopyranoside, and physcion-8-O-β-D-glucopyranoside decreased after raw Radix Polygoni Multiflori was processed. Conversely, the contents of emodin and physcion generally increased after processing [35].

Those changes in the contents of some components between crude drugs and processed products mostly are due to the transformation of chemical structures during processing. Sometimes, processing practice could increase the dissolving rate of chemicals which induces the change of chemical contents. For example, the analysis of the alkaloids of different processed products of *Rhzoma Coptidis* (Huanglian) indicated that the total contents of beberine, palmatin, and jatrorrhizine changed as: processed with wine > processed with vinegar > processed with ginger > processed with Fructus Evodiae > processed with salt > processed with bile > materials. The wine could benefit the dissolution of chemicals as well as the vinegar may transfer the free alkaloids into soluble alkaloids, which would increase the alkaloid contents [36].

**Change in the varieties of chemical components apart from the change in content:** Studies of the chemical changes in the constituents of *Radix Euphorbiae Kansui* (Cugansui, processed with vinegar) indicated that seven constituents disappeared and four new constituents were formed in the water extract of processed products while the contents of four other components decreased. In the methanol extract, two original constituents disappeared, two new constituents were produced, and the concentration of six other components increased obviously [37]. The change in quantity and quality of components in volatile oils of crude *Semen Myristicae* (Roudoulouk) and its processed product stir-fried with bran were observed. The results showed that thirteen new components were found and four components disappeared in volatile oils after processing. Also, the contents of the active components methyleugenol and methylosoeugenol increased. At the same time the contents of the toxic ingredients myristicin and safrol decreased [38].

A study of the chemical constituents of processed Radix Aconiti also found some new components, such as 14-O-acetyleneoline, foresaconitine, crassicauline A, and lipoforesaconitine [39, 40]. These norditerpenoid alkaloids may form from the diester diterpenoids during processing. Sometimes, there is no distinct change in chemical constituents during processing. For example, the chemical fingerprint analysis of *Semen Ziziphi Spinosae* (Suanzaoren) and its processed product indicated there were no distinct differences in the peak shape and numbers in their fingerprints [41].

In conclusion, the chemical constituents of crude drugs may change dramatically during processing. Sometimes, the change of chemical constituents is in accordance with the purpose of
Enhancing the pharmacological effects: Nowadays, many modern studies have confirmed that processing could enhance the pharmacological effects of crude drugs. However, the processing theory remains to be explored. Comparative study of pharmacological effects: In recent years, many investigations have been carried out on the different pharmacological effects of crude drugs and their processed products.

**Enhancing the pharmacological effects:** Modern studies have confirmed that processing could enhance the pharmacological effects of crude drugs. A comparative study on the pharmacological effects of Semen Armeniacae Amarum (Kuxingren) and its processed products indicated that all of them had the same effects of protecting the liver, lubricating the bowel, and promoting defecation [43]. The effect of resolving phlegm of different processed products of Radix Asteris (Ziwan) was evaluated. Results indicated that six different stir-fried slices had an expectorant effect and the stir-fried with honey sample was the most effective among all processed products [44].

**Reducing toxicity:** The acute toxicity in rats and long-term safety evaluation in mice were studied to compare the toxicity of crude Radix Aristolochiae (Qingmuxiang) and products processed with sodium bicarbonate and vinegar. The results indicated that the LD₅₀ values in mice of raw Radix Aristolochiae and processed products were 146.45 and 846.06 g materials/kg, respectively. The long-term safety evaluation in rats showed that processed products had a lower toxicity. The above results showed that the toxicity of processed products which were prepared with base and vinegar was much lower than that of the crude material. Further research indicated that there were no distinct differences in the pharmacodynamic actions of inhibiting gastrointestinal motility, relieving pain and anti-inflammation between the crude sample and processed ones [45, 46]. The experiment of acute toxicity of Semen Strychni (Maqianzi) and its processed product showed that the LD₅₀ values in the processed products were increased and the LD₅₀ of the processed product with vinegar was 387.7 mg/kg [47]. At the same time, the antinociceptive effect of processed Semen Strychni was distinct from the crude drugs, and the sand-processed products had the strongest analgesic potency [48]. Similar to Semen Strychni, the content of aconitine in processed Radix Aconiti Lateritis decreased with the reduction of toxicity.

<table>
<thead>
<tr>
<th>Decoction Pieces</th>
<th>Vietnam</th>
<th>Japan</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radix Angelicae Sinensis (stir-fried with wine)</td>
<td>Spray evenly with ethanol (40%) to slices of Radix Angelicae Sinensis, wrap up shortly then put in a pan, stir-fry by gentle heat to dryness, take out and allow to cool. Use 10 kg of ethanol (40%) for 100 kg of Radix Angelicae Sinensis.</td>
<td>Pass through hot water.</td>
<td>Mix the slices of Radix Angelicae Sinensis with wine thoroughly in a closed vessel until it is infused completely. Place the slices in a pot and roast with gentle heat to dry, take out and cool. Use 10 kg of yellow rice wine for each 100 kg of Radix Angelicae Sinensis.</td>
</tr>
<tr>
<td>Radix Rehmannia (熟地黃)</td>
<td>Three processing methods are recorded: Radix Rehmannia processed with wine and ginger water; Radix Rehmannia processed with ethanol; steamed Radix Rehmannia.</td>
<td>With or without the application of steaming.</td>
<td>Two processing methods are recorded: Radix Rehmannia processed with yellow rice wine; steamed Radix Rehmannia.</td>
</tr>
<tr>
<td>Rhizoma Zingiberis (乾薑)</td>
<td>Only preliminary processing is recorded: the over-mature zingiber rhizome is lifted from the soil, washed clean, and dried in the sun or at a low temperature.</td>
<td>Pass through hot water.</td>
<td>Besides the preliminary processing, two other methods are recorded: carbonizing; scalding with sand.</td>
</tr>
<tr>
<td>Fructus Corni (processed with wine) (山茱萸)</td>
<td>Mix clean crude drug with wine thoroughly. Place them in a suitable container, then close tightly, stew them thoroughly on a water bath or steaming until the liquid is absorbed entirely, cool, take them out and dry. Use 0.6–1 liter of wine for each 10 kg of clean crude drug.</td>
<td>Without record about processing content.</td>
<td>Mix clean crude drug with yellow rice wine thoroughly. Place them in a suitable container, then close tightly, stew them thoroughly on a water bath or steam until the liquid is absorbed entirely, cool, take them out and dry. Use 20 kg of yellow rice wine for 100 kg of clean crude drug.</td>
</tr>
<tr>
<td>Semen Strychni (馬錢子)</td>
<td>Clean Semen Strychni: Stir fry with clean sand until inflated and the color turns into deep brown or deep chestnut. When the outer bark is cracked or split, take out and sift out sand. The seeds are removed from burnt silky hairs in a turning machine. Semen Strychni (processed with sesame oil): Clean Semen Strychni is soaked in water or rice wash for 1 day and 1 night or soaked again in water several times until it becomes softened. The seed is removed from the shell and germs, cut into thin slices; dried at a low temperature, soaked in sesame oil for one night, then taken out and stir-fried until it becomes yellow. Allow to cool; preserve the seeds in a well-closed container.</td>
<td>Without record about processing content.</td>
<td>Semen Strychni (processed): Put the clean sand in a pot, heat at a high temperature, add the clean crude drugs, constantly stir until inflated and turns into brown or dark brown.</td>
</tr>
</tbody>
</table>
the procedure of steaming Fructus Schisandrae Chinensis (Wu-weizi). The results showed that the optimum condition was adding 20% wine in 100 kg Fructus Schisandrae Chinensis, moistening it in a cell container for an hour and steaming it for four hours [53]. The above reports mainly focused on the optimization of processing procedure using the contents of some components as evaluation markers.

Besides using chemical markers, the pharmacological effects were also considered in the optimization of processing technology, for instance, determination of coagulation time in mice was used for optimizing the best technology of charred Curcumae Platycladi Orientalis (Cebaiye) and Herba Cirsii Japonici (Daji) [54, 55]. Toxicological evaluation was also employed as a strategy to optimize processing technology of toxic CMM, such as Rhizoma Arisaemae, and the toxic reaction in experimental mice was used to attain the optimum amount of KAl(SO₄)₂ · 12H₂O for eliminating the toxic reaction of Rhizoma Arisaemae [56].

Improving traditional processing facilities or methods: The book Bencao Mengguan (Basic Knowledge of Materia Medica, 本草蒙筌), which was written in 1525 AD, divided processing methods into three kinds: preparations made with the help of water (Shui Zhi), preparations made with the aid of fire (Huo Zhi), and combined water and fire processes [57]. The intensity of fire used as a heat source for cooking was judged only by experience without objective parameters to evaluate. In recent years, some studies have reported about the use of a far-infrared oven for substituting the traditional processing method of stir-frying [58, 59]. The constant temperature oven was also applied to the study of the processing technology of charred Flos Sophorae (Chaohualhua); the results showed that the optimum condition of processing charred Flos Sophorae in a constant temperature oven was heating at 185°C ± 2°C for 30 minutes [60]. In recent years, the microwave technique has also been applied for processing CMM. A study on optimization of processing technology of Cortex Eucommiae (Duzhong) indicated that the content of chlorogenic acid in the products processed by microwave was higher than that of stir-fried and roasted products. Moreover, the external surface was entirely covered with charred and burnt spots [61]. The total contents of psoralen and isopsoralen were used as markers to optimize the processing technology of Fructus Psoraleae (Buguzi) by microwaves. The results indicated that the microwave technique was feasible for processing Fructus Psoraleae [62]. Through the microwaves, the salt solution can be fully absorbed by Fructus Psoraleae, and the controllable microwave strength and time make the processing procedure easily amenable. The above experimental studies indicate that the microwave technique could be used for processing CMM, besides having the advantages of saving time and labor as well as controlling technological parameters. However, this processing technique is so far only used for a few crude drugs and not yet applied to mass manufacture.

Studies on new processing technologies could provide scientific data for promoting the standardization of CMM processing. However, such research approaches are still not enough. Both chemical analysis and pharmacological evaluation should be used as markers for evaluating the science behind processing procedures and quality of processing.

Research on the quality standards of processed products
After processing, the constituents in crude drugs have changed and the chemical markers for quality control of crude drugs and of processed products should be different. Therefore, studies on

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the quality standards of processed products are also an important issue of processing research. For example, the study of the quality standard of processed products of Rhizoma Atractylodis Macrocephalae (Baizhu) indicated that atractylic acid could be oxidized as atractylolide I and atractylolide III. Therefore, the above three compounds should be selected as reference compounds to establish the quality standard of processed products [63]. At present, only twenty-five processed products can be found with their specific standards in the Chinese pharmacopoeia (2010 edition). However, most of the processed products recorded in the Chinese pharmacopoeia are lacking quality standards. Therefore, studies on the quality standards of processed products need to be strengthened.

Summary and Prospects

CMM processing, as a unique characteristic in the practice of Chinese medicine, has a close relationship with safety and efficacy of CMM. Modern research has indicated that chemical components may change and then induce different functions. Therefore, standards for CMM processing are urgently needed. Close collaboration with experts in academia, industry, and government both in Asia and throughout the world should be encouraged and developed. A summary of the most urgent work needed is as follows:

Investigation and arrangement: To make systematic investigations on folk experiences, ancient documents, and the current market situation, followed by a review of the corresponding information. This could provide useful references for further research of CMM processing.

Exploring the effects of processing: To reinforce the fundamental study on all processing methods used currently or recorded in ancient documents by modern pharmacological, toxicological, and chemical analysis as well as systems biology in order to clarify the effects and mechanisms of processing.

Standardizing the processing procedures: To carry out scientific studies on all kinds of processing procedures and optimizing them to establish the best ones.

Establishing the harmonized quality control standard: The decoction pieces used in clinic are commonly processed. Therefore, the quality control standard of the processed product has been separated from that of the crude drug under the item “crude drug” in the new version of the Chinese pharmacopoeia (2010 edition). The limitation in this approach is that the content of chemical marker in the processed product is mostly the same as that in the crude drug, and there are only a few processed products listed as separated items. This is not enough for the quality control of processed CMM. Therefore, the quality control standard of decoction pieces is the weak point in the current quality control of CMM and it is urgent to establish such standards.

Reinforcing good manufacture practice for processing and standardizing the names of processed products: Currently, State Food and Drug Administration in Mainland China has stipulated that all the manufacturing enterprises of decoction pieces must produce under the condition of “Good Manufacture Practice of Prepared Drug in Pieces” starting from January 1, 2008. Therefore, it is important to reinforce the quality management of producing decoction pieces and carry out the good manufacture practice in order to establish the standard processing procedures and safeguard the quality of decoction pieces. At the same time, it is necessary to propagate and advocate the standardization of the name of processed products, establish the related policy, and tighten up the management.

In conclusion, standardization of processing methods for Chinese herbal medicines is as important as authentication to maintain their quality and ensure their safe use. To build up the unified and scientific processing practices of CMM is important for the quality and safety control of CMM, and one of the key steps of standardization of CMM.

Supporting information

Current processing procedures of CMM are available as Supporting Information.

Acknowledgements

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