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* (Lei

Gong Processing Handbook, 雷公炮炙論) 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, charring, 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 (Jiangtan). 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-energizer, 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.

Zheng (蒸, steaming): Cleaned and cut crude drugs are put, with or without additive, into a suitable container and steamed. For example, in preparing Radix Polygoni Multiflori Preparata (Zhiheshouwu), Radix Polygoni Multiflori (Heshouwu) is thoroughly mixed with black bean juice and put into a suitable non-ferrous container, stewed until dry, or just steamed alone; or steamed to a brown color on all sides, dried in the sun partially, then cut into slices and dried. For each 100 kg of Radix Polygoni Multiflori (Heshouwu), 10 kg of black beans is used. Raw and processed Radix Polygoni Multiflori has different effects from the processed herb. The raw Radix Polygoni Multiflori (Heshouwu) counteracts toxicity, cures carbuncles and relaxes the bowels. The processed one has the actions of replenishing the *liver* and the *kidney* with vital *essence* and blood, blackening the hair, and strengthening the tendons and bones.

Duan (煅, Calcining): The crude drug is put into a smokeless flame or in a suitable container and calcined until it becomes crispy, brittle, or red-hot. This method is mainly used to process mineral crude drugs and others with hard texture. For example, Calcined Gypsum is the processed product of Gypsum; calcining renders the clean Gypsum porous. Gypsum can be used for removing "heat", quenching "fire", easing the mind, and relieving thirst while Calcined Gypsum has the effects of dispelling damp, promoting growth of muscles, curing sores, and arresting bleeding.

Among the 31 species of toxic and potent CMM described by the Department of Health of Hong Kong, most are crude drugs. Once processed, they become safe under prescription by qualified TCM practitioners for therapeutic use; these drugs include Radix Aconiti Lateralis Preparata, Rhizoma Pinelliae processed with alum, Rhizoma Pinelliae processed with ginger, processed Rhizoma Arisaematis, etc.

Many crude drugs can be processed in different ways. Some crude drugs under different processing methods will be used for producing different therapeutic effects. For example when Radix Angelicae Sinensis is processed by stir-frying with wine it has a different effect than when it is charred. For others, crude drugs processed in different ways may have the similar therapeutic qualities. For example Radix Aconiti Lateralis can be processed as *Heishunpian* (black slice), *Baifupian* (white slice), *Paofupian* (scalded) or *Danfupian* (processed with salt, Radix Glycyrrhizae, black bean), but *Heishunpian* and *Baifupian* have the same actions; the main purpose of the processing is to reduce toxicity (**Table 2**).

Table 1 Main methods of processing CMM as listed in the Chinese pharmacopoeia (2005).

Processing method	Additives	Example
Stir-frying without additional adjuvants (清炒)		Rhizoma Zingiberis (charred) 薑炭
Stir-frying with solid adjuvants (炒)	Fine powders of terra (土)	Rhizoma Atractylodis Macrocephalae (processed with terra) 土白朮
	Bran (麸)	Rhizoma Atractylodis (processed with bran) 麸炒蒼朮
	Rice (米)	Radix Codonopsis (processed with rice) 米黨參
	Sand (砂)	Rhizoma Zingiberis (processed with sand) 炮薑
Stir-frying with liquid adjuvants (炙)	Yellow rice wine (酒)	Radix Angelicae Sinensis (processed with wine) 酒當歸
	Vinegar (醋)	Radix Bupleuri (processed with vinegar) 醋柴胡
	Salt-water (鹽水)	Cortex Eucimmiae (processed with salt) 鹽杜仲
	Refined honey (煉蜜)	Radix et Rhizoma Glycyrrhizae (processed with refined honey) 蜜甘草
	Ginger juice (薑汁)	Rhizoma Coptidis (processed with ginger) 薑黃連
	Refined suet (羊脂油)	Herba Epimedii (processed with refined suet) 油淫羊藿
Steaming (蒸)	Only steaming (清蒸)	Radix et Rhizoma Ginseng Rurba 人參(紅參)
	Salt-water (鹽水)	Radix Morindae Officinalis (processed with salt) 鹽巴戟天
	Medicinal juice (藥汁)	Radix Polygoni Multiflori Praeparata (processed with black bean juice) 製何首烏
	Vinegar (醋)	Fructus Schisandrae Chinensis (processed with vinegar) 醋五味子
	Yellow rice wine (酒)	Rhizoma Polygonati (processed with wine) 酒黃精
Calcining (煅)		Gypsum Fibrosum Preparatum 煅石膏
Boiling (煮)		Radix Aconiti (processed) 製川烏
	Edible mother liquor of mineral salt preparation (食用膽巴)	Radix Aconiti Lateralis Praeparata 製附子
	Rhizoma Zingiberis Recens and alumen (薑汁、明礬)	Rhizoma Arisaematis (prepared) 天南星
	Rhizoma Zingiberis Recens and alumen (薑汁、明礬)	Rhizoma Pinelliae (processed with ginger) 薑半夏

Current Issues

In 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 Polygoni Multiflori included cleaning, cutting, and processing with or without additives. The *Bencaogangmu* (A.D. 1593) records the processing of Radix Polygoni 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 Polygoni Multiflori in the pot, repeat the layers, and then steam. When the black beans become cooked, take out the black bean and dry Radix Polygoni 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 Polygoni 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 Polygoni Multiflori are different from those in ancient times. As mentioned above, those

Table 2 Different processing methods and functions of Radix Angelicae Sinensis and Radix Aconiti Lateralis Preparata.

Decoction Pieces	Main Processing Methods	Action	Photos
Radix Angelicae Sinensis	Crude drug → remove foreign matter → clean → infuse slightly → slice → dry.	To enrich blood, regulate menstruation, relax bowels.	
Radix Angelicae Sinensis stir-fried with wine	Crude drug → slice → mix well with yellow rice wine → infuse slightly → put in a pot → heat and stir-fry until deep yellow → take out, cool.	To activate blood circulation and stimulate menstrual discharge.	
Charred Radix Angelicae Sinensis	Crude drug → slice → put in a pot → heat and stir-fry until slightly black → remove, cool.	To arrest bleeding.	
Heishunpian	Raw material of Radix Aconiti Lateralis → clean → soak in edible mother liquor of mineral salt preparation → boil the infusion thoroughly → take out → rinse in water → cut longitudinally → rinse in water again → stain the slices dark brown → steam → fry to half- dryness → sun-dry or fry to complete dryness.	To restore from collapse, supply body *fire* and reinforce *yang*, dispel *wind, cold* and *damp*.	
Baifupian	Raw material of Radix Aconiti Lateralis → clean → soak in edible mother liquor of mineral salt preparation → boil in the infusion thoroughly → peel away the bark → cut longitudinally → rinse in water → steam thoroughly → dry.	Same as *Heishunpian*.	
Paofupian	Put the sand in a pot → heat → add slices of Radix Aconiti Lateralis → stir-fry until slices are inflated and slightly discolored → sift out the sand → cool.	To warm the kidney and spleen.	
Danfupian	Raw material of Radix Aconiti Lateralis → clean → process as for salted Radix Aconiti Lateralis → rinse in water → boil thoroughly together with Radix Glycyrrhizae, black beans and water until the cut slice will not cause numbness to the tongue → cut slice → dry.	To restore from collapse, dispel *cold* and relieve pain.	

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, 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].

Table 3 Comparison of processing methods in Mainland China and Hong Kong.

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

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 aluminium 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* Tilesius 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-

Fig. 1 Decoction pieces of Radix Angelicae Sinensis as typically found in Mainland China (**a**) and Hong Kong (**b**).

Fig. 2 Decoction pieces of Radix Notoginseng as typically found in Mainland China (**a**) and Hong Kong (**b**).

Fig. 3 Decoction pieces of Radix Salviae Miltiorrhizae 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 Laterali involving the procedures of cutting, washing, drying,

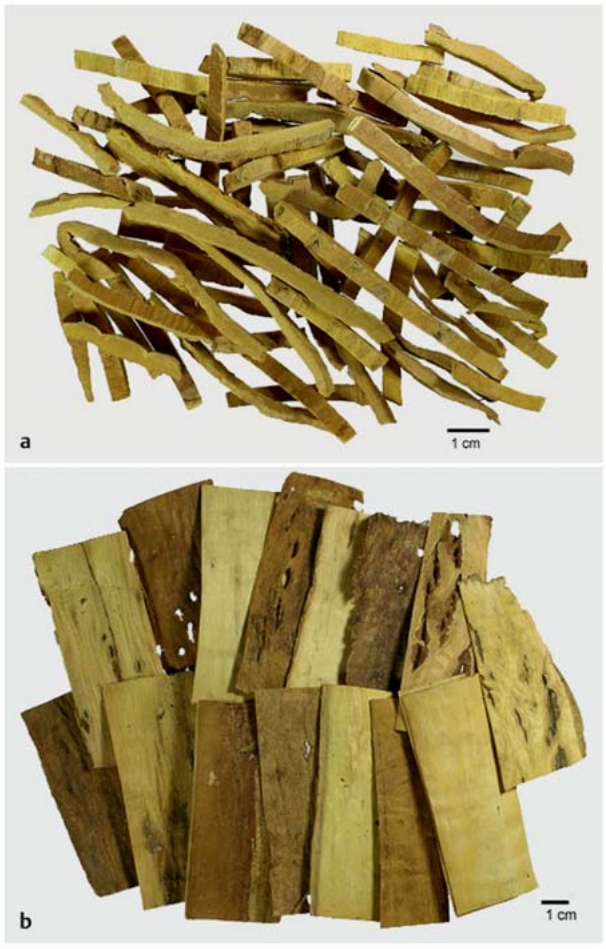

Fig. 4 Decoction pieces of Cortex Phellodendri as typically found in Mainland China (**a**) and Hong Kong (**b**).

Fig. 5 Decoction pieces of Fructus Aurantii as typically found in Mainland China (**a**) and Hong Kong (**b**).

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, paeoniflorin, benzoic acid, and benzoylpaeoniflorin decreased during decorticating 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 decrease after being processed. In Radix Aconiti Lateralis Preparata,

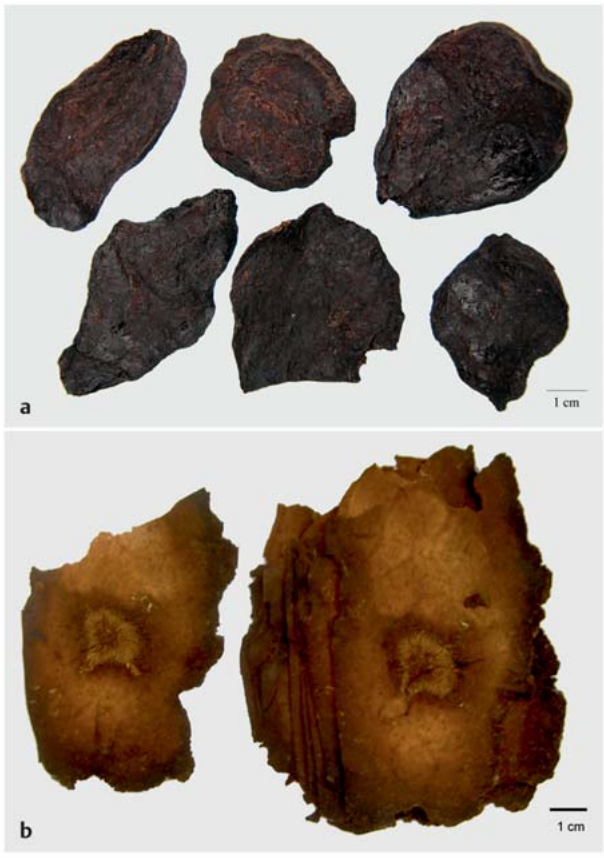

Fig. 6 Decoction pieces of Radix Polygoni Multiflori as typically found in Mainland China (**a**) and Hong Kong (**b**).

the processed daughter root of *Aconitum carmichaeli* Debx., the contents of the toxic constituents aconitine, mesaconitine, and hypaconitine 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 hypaconitine 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 uses 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 > stewed with black bean juice > steamed with black bean juice > steamed with water; (b) total free anthraquinones changed as: steamed with black bean juice at high pressure > steamed with black bean juice > stewed with black bean juice > steamed with water > raw materials; (c) total anthraquinones changed as: raw materials > steamed with black bean juice at high pressure > 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 Rhizoma 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 (Roudoukou) 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 methylisoeugenol 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-acetylneoline, foresaconitine, crassicauline A, and lipoforesaconitine [39, 40]. These norditerpenoid alkaloids may form from the diester diterpenoid alkaloids 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

Table 4 Comparison of processing methods described in Vietnamese and Chinese pharmacopoeias.

Decoction Pieces	Vietnam	Japan	China
Radix Angelicae Sinensis (stir-fried with wine) 當歸	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.	Pass through **hot water**.	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.
Radix Rehmanniae 熟地黃	Three processing methods are recorded: Radix Rehmanniae processed with **wine and ginger water**; Radix Rehmanniae processed with **ethanol**; steamed Radix Rehmanniae.	With or without the application of steaming.	Two processing methods are recorded: Radix Rehmanniae processed with **yellow rice wine**; steamed Radix Rehmanniae.
Rhizoma Zingiberis 乾薑	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.	Pass through **hot water**.	Besides the preliminary processing, two other methods are recorded: **carbonizing; scalding with sand**.
Fructus Corni (processed with wine) 山茱萸	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**.	Without record about processing content.	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**.
Semen Strychni 馬錢子	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.	Without record about processing content.	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**.

processing and can be documented by the modern research results. But sometimes 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: Many 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 different processed products indicated that all of them had the effect of relieving cough and asthma with decreasing strength in the following order; stir-fried, scalded, and crude samples. Acute toxicity tests showed that the toxicity was proportional to the pharmacological effects. Further exploration indicated that the emulsin was destroyed and the content of the active component (amygdalin) increased after Semen Armeniacae Amarum had been processed [42]. Investigations on the pharmacological effects related to therapeutic actions and indications of crude and stir-fried Semen Cassiae (Juemingzi) indicated that both of them had the effects of protecting the liver, lubricating the bowel, and promoting defecation. The stir-fried product, however, was more effective than the crude one in liver protection and decrease of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), but they had similar effects in 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 LD_{50} 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 LD_{50} values in the processed products were increased and the LD_{50} 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 Laterlis decreased with the reduction of tox-

Fig. 7 The processing chart (**a**) and processing method of Radix Aconiti Lateralis Preparata (**b** 1. Cutting; 2. Washing; 3. Stir-frying; 4. Drying; 5. Burying) recorded in the Ming Dynasty.

icity while the antinociceptive effect was still the same as in the crude sample [49]. In recent years, the systems biology has been explored for detection of *Aconitum* alkaloids induced toxicity by mapping the toxic chemicals into a biological pathway context. The results indicated that Aconitine has a direct link with 4 types of ion channels: Na(v) I Alpha, SCN 3A, SCN 2A, and tetrodotoxin-resistant Na(I) channel. Also, the results showed the activity to serotonin histamine and dopamine receptors to be the common bioactivities of *Aconitum* alkaloids [50].

The above studies confirm that processing can change the pharmacological effects and toxicity of CMM. Therefore, chemical analysis and pharmacological evaluation can be helpful to explain the theory of CMM processing.

Research on the reform of processing

Today there are no uniform practices for CMM processing. Manufacturers in different locations use different methods; and the procedures and standards of those local practices are different. At the same time, with the technical development of CMM processing, the traditional manual processing methods are gradually being replaced by modern instruments (see **Fig. 1S** in Supporting Information). Improvement and innovation in the technology of CMM processing help to industrialize the manufacture of decoction pieces. Thus, research on modern processing technologies is important and urgently needed.

Optimizing the best technology: The use of orthogonal design and the content of α-cyperone as a marker for choosing the most suitable processing practices for *Cyperus rotundus* (Xiangfu) were studied. The results indicated that the optimum condition of processing *Cyperus rotundus* with vinegar was adding the vinegar in the ratio of 60%, moistening it in a cell container for an hour, putting it into the pan at 150 °C and stir-frying it for 10 minutes [51]. The best temperature and time of charred stir-frying Radix Scutellariae (Huangqin) were optimized using the contents of baicalin and daicalein as well as the macroscopic description of decoction pieces for evaluation. The results showed that the optimum condition was stir-frying at 200 °C for 10–15 minutes [52]. The contents of schizandrol A and schizandrin B were used for optimizing the soaking and steaming time and wine dosage in the procedure of steaming Fructus Schisandrae Chinensis (Wuweizi). 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 Cacumen 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 $KAl(SO_4)_2 \cdot 12H_2O$ for eliminating the toxic reaction of Rhizoma Arisaemae [56].

Improving traditional processing facilities or methods: The book *Bencao Mengquan* (Basic Knowledge of Materia Medica, 本草蒙荃), 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 (Chaohuaihua); 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

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 atractylone 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.

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