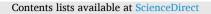
ELSEVIER



Journal of Ethnopharmacology



journal homepage: www.elsevier.com/locate/jethpharm

Analysis of historical changes in traditional Chinese medicine based on an Indonesian collection of Chinese materia medica from c. 1870

Yusheng Jia^{a,b,1}, Lei Lei^{e,1}, Xiao Luo^e, Zhongzhen Zhao^f, Mei Wang, PhD^{b,c,d,**}, Tinde van Andel, PhD^{a,c,*}

^a Naturalis Biodiversity Center, Darwinweg 2, 2333, CR, Leiden, the Netherlands

^b LU-European Center for Chinese Medicine and Natural Compounds, Institute of Biology, Leiden University, Sylviusweg 72, 2333, BE, Leiden, the Netherlands

^c Institute of Biology, Leiden University, Sylviusweg 72, 2333, BE, Leiden, the Netherlands

^d SU BioMedicine, Post Bus 546, 2300, AM, Leiden, the Netherlands

^e Chengdu Institute for Food and Drug Control, Key Laboratory for Quality Monitoring and Evaluation of Traditional Chinese Medicine (NMPA), Wuxing Erlu 10, Wuhou District, Chengdu, 610045, China

f School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, SAR

ARTICLE INFO

Keywords: C.H.A. westhoff collection Historical and contemporary comparison Authentication and medicinal processing Traditional Chinese medicine Chinese pharmacopoeia

ABSTRACT

Ethnopharmacological relevance: Traditional Chinese Medicine is subject to changes over time: product names, botanical ingredients, processing methods and uses have varied throughout the course of history. Historic collections of Chinese materia medica (CMM) are of great value for research on the evolvement, development and variability of Chinese herbal medicine over time. These changes may have a significant influence on the safety and efficiency of nowadays' clinical practice. Here we investigate a historic collection of Chinese medicinal products purchased in Indonesia in c. 1870, containing about 395 specimens.

Aim of the study: This study compares the specimens contained in late 19th century collection of CMM with contemporary marketed materials by investigating changes in vernacular names, botanical identity and processing methods which are important aspects for safety and clinical practice today.

Materials and methods: The contents and associated documentation of the CMM collection of Dr. C.H.A. Westhoff (University Museum Utrecht) were revised by means of morphological identification and study of the associated historic documentation. We compared this Westhoff collection with contemporary CMM, information from literature and various quality standards, including the official Chinese pharmacopoeia.

Results: The Westhoff collection represents a unique, well preserved collection of Chinese materia medica, with original uniform bottles, Chinese labels and a partly intact handwritten catalogue. Among the 395 specimens (bottles) of CMM surveyed, there are 387 contain a single component drug, while eight contain multiple components drugs. A total of 293 of the 395 specimens are mentioned in the modern Chinese pharmacopoeia. Ca. 25% of the specimens had been processed, such as stir-fried with or without adjuvants. Our analysis of local Chinese names, botanical content and processing methods indicate that this collection originates from southern part of China, possibly including in the region of Taiwan and was meant as a showcase for pharmaceutical education and/or as curiosity object.

Conclusion: Differences in vernacular names, plant parts and processing methods between the Westhoff collection and the current Chinese pharmacopoeia illustrate the regional variety of CMM and changes in CMM in the course of time. This work contributes to the understanding of the evolvement of CMM from a historic perspective.

¹ Authors contributed equally.

https://doi.org/10.1016/j.jep.2020.113714

Received 18 October 2020; Received in revised form 10 December 2020; Accepted 18 December 2020 Available online 25 December 2020

0378-8741/© 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Abbreviations: CMM, Chinese materia medica; TCM, traditional Chinese medicine; ChP 2015, Chinese Pharmacopoeia 2015 edition; INV., Inventory number; CDFDC, Chengdu Centre for Food and Drug Control; UMU, University Museum Utrecht.

^{*} Corresponding author. Naturalis Biodiversity Center, Darwinweg 2, 2333, CR, Leiden, the Netherlands.

^{**} Corresponding author. LU-European Center for Chinese Medicine and Natural Compounds, Institute of Biology, Leiden University, Sylviusweg 72, 2333, BE, Leiden, the Netherlands.

E-mail addresses: M.Wang@biology.leidenuniv.nl (M. Wang), tinde.vanandel@naturalis.nl (T. van Andel).



Fig. 1. Photographs of specimens in the Westhoff Collections in glass containers with original labels and original Dutch records. (a) mao gu shao (冇骨梢, INV. 0285-128602). (b) qian mu tong (钱木通, INV. 0285-133716). (c) four specimens with the same character huang on their labels. From left to right: ji gu huang (鸡 骨癀, INV. 0285-128554), cha shi huang (茶匙癀, INV. 2085-128555), xiang si huang (相思癀, INV. 0285-128556), zhen zhu huang (珍珠癀, INV. 0285-128557). (d) the corresponding original records of the specimens under c) (from top to bottom), text transcription (in Dutch) and translation (in English). The red dashed boxes indicate the same Chinese character huang (癀) and its phonetic name. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

1. Introduction

Chinese materia medica (CMM), an important part of traditional Chinese medicine (TCM), has been used for more than 2000 years and continuously plays an important role in complementary and alternative health care in the present. During the historic development of CMM, the vast majority of herbal medicine has been documented in medicinal monographs, from one of the earliest (reconstructed) materia medica texts, the *Divine Husbandman's Classic of Materia Medica* (Eastern Han Dynasty, 25-220 AD) and the earliest officially issued pharmacopoeia, the *Newly Revised Materia Medica* in 659 AD (Zhao et al., 2018), to the latest version of the Chinese Pharmacopoeia (ChP, 2015). During the thousands of years of practice, increasing numbers of herbal medicines were recorded, with detailed descriptions on their botanical identity, plant morphology, used parts, processing methods and therapeutic effects. Although most of these ancient practices are continued nowadays, some changes have also taken place over time, including regional nomenclature and substitutes. For example, *bai mao teng* refers to the herb *Solanum lyratum* Thunb., but in the annals of herbal medicine of the Jiangsu Province (Chinese Academy of Sciences, 1959), the herb *Aristolochia mollissima* Hance was also called *bai mao teng* (Zhao, G. et al., 2006). This nomenclatural inconsistency (one species with more than one common name) caused confusion and safety issues. The genus *Aristolochia* is known to contain toxic aristolochic acids, and in 2004, a case reported on account of *bai mao teng* confusion led to a 60-year-old patient who was diagnosed with kidney failure (Zhao, Z. et al., 2006).

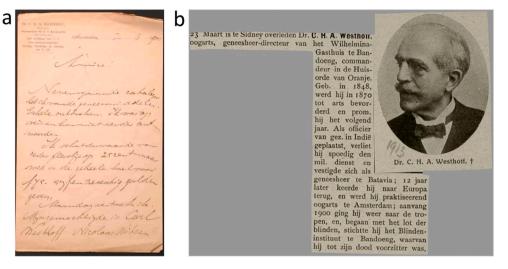


Fig. 2. Documents related to the Westhoff collection. (a) Letter by Westhoff (dated 1900) on the transaction of the collection to Nicolaas Witsen. Source: Utrecht University Museum (b) Brief biography of Dr. C.H.A Westhoff. Source: Collectie Veenhuijzen, Centraal Bureau voor Genealogie, the Hague.

Another example related to regional substitutes is *ban lan gen* (pharmaceutical name Isatidis radix). As described in the most recent Chinese and European Pharmacopoeia, Isatidis radix is the dried root of *Isatis indigotica* Fortune (ChP, 2015; European Pharmacopoeia, 2016). In Hong Kong, however, when *ban lan gen* is prescribed, the dried root of *Baphicacanthus cusia* (Nees.) Bremek. (pharmaceutical name Rhizoma et radix Baphicacanthis cusiae) is often given instead (Zhao, Z. et al., 2006).

Research on the development of herbal medicine over time, especially historical changes in medicinal plants, will lead toward a better understanding of confusions in nomenclature and botanical identity and therefore ensures the safe and effective use of CMM. Most previous research on historical changes has focused on CMM monographs and literature, which has been well summarized in Chinese publications (Chen and Huang, 2005; Xie, 2008). Historical changes revealed by examining physical samples are less often published. Zhao et al. (2015) studied ancient CMM specimens preserved at the Natural History Museum in London, where they found variations in medicinal plant parts and regional substitutes in this historic collection that spans approximately 300 years. The c. 100-year old CMM collection in the Royal Botanic Gardens Kew also differs from the modern Chinese pharmacopoeia with regard to species, plant parts, processing methods and regional substitutes, including commonly confused CMM, such as Aristolochia (Brand et al., 2017). These findings provide direct and strong evidence for historical changes in CMM, but studies based on historical CMM collections remain scarce.

The University Museum Utrecht (UMU), the Netherlands, houses a rare, well-preserved historical collection of CMM that has not been thoroughly studied. Approximately 400 specimens are included in this collection, each product stored individually in a square glass bottle labelled with its Chinese name in Chinese characters. The background information indicates that this collection was transported from the former Dutch East Indies (currently Indonesia) to the Netherlands in the late 19th century. At that time, between 73,900 and 90,000 Chinese immigrants lived in the former Dutch colony (Maddison, 1989). For this research, a thorough review was carried out of the botanical identity, Chinese nomenclature, plant part, processing method, and historic uses of this collection by comparing them to herbarium vouchers and modern monographs on CMM. This rare and previously uninvestigated collection provides new insights on historical changes and regional variety of Chinese materia medica.

2. Materials and methods

The historical CMM collection investigated is preserved in the depot of the UMU, the Netherlands. There are more than 400 specimens in this collection: every specimen is stored in a glass bottle ($10 \times 3.5 \times 3.5$ cm) with a lid (Fig. 1a). Except from a few specimens that were separately deposited because of minor damage to the container, the majority of the specimens (395) were opened and inspected. A red label with Chinese characters attached to each bottle contains the Chinese vernacular name of the corresponding medicine (Fig. 1a-c). Except from the original specimen's labels, parts of an original catalogue have been preserved, but unfortunately, only 183 of the 395 original records have survived to this day. The catalogue, handwritten on paper, begins with a serial number, followed by a Chinese name, a phonetic name, a small description and the medicinal use of the product written in Dutch (Fig. 1d). The specimens were first examined macroscopically at Utrecht University Museum by the first and second author. High resolution photographs of the specimens were further evaluated by all authors.

A preliminary survey of Westhoff collection was conducted by Dr. Willem van der Sluis around 2006, and his (unfinished) database kept at the UMU, with pictures, partial transcriptions of the original catalogue and tentative identifications, was used as the basis for our analysis. Vouchered reference specimens from Naturalis Biodiversity Center (Leiden, the Netherlands) and the Chengdu Centre for Food and Drug Control (Chengdu, China) were used to identify the specimens. The historical botanical identity, nomenclature, plant parts and processing methods were compared to the current specification of the Chinese Pharmacopoeia (ChP, 2015), Zhonghua Bencao (Zhonghua Bencao Edit Committee, 1999), Zhong Yao Da Ci Dian (Zhao, G. et al., 2006) and contemporary professional textbooks on CMM (Guo and Wang, 2011; Leon and Lin, 2017). For the accurate nomenclature of scientific name, we followed Plants of the World Online (http://powo.science.kew.org/). The geographic map used in this article was created using mapchart.net (https://mapchart.net/).

3. Results and discussion

3.1. General description of the Dr. C.H.A. Westhoff Collection

The earliest documented record of this collection was a transaction letter (Fig. 2a), which shows that Dr. C.H.A. Westhoff sold the collection to Mr. Nicolaas Witsen for 75 Dutch guilders in 1900 in Amsterdam. According to Dr. Westhoff's brief biography (Fig. 2b), he returned to Europe from Indonesia in 1882 and travelled back to Indonesia again in

Table 1

Specimens in the Westhoff collections and overlap with the Chinese Pharmacopeia (2015).

| Westhoff Collection | | | | | |
|-------------------------------|-----|--------------|-----|-----------|-----|
| Total amount of specimens 395 | | | | | |
| Categories | | ChP 2015 | | Material | |
| Single component drug | 387 | Included | 293 | Plant* | 314 |
| Multiple component drug | 8 | Not included | 102 | Animal * | 36 |
| | | | | Mineral * | 34 |
| | | | | Fungi | 2 |
| | | | | Other | 9 |

*and related substances.

1900. The background story is that Dr. Westhoff purchased this CMM collection in Indonesia and then brought it to the Netherlands in 1882. After he sold it in 1900, he set off for Indonesia again. This indicates that the Westhoff Collection is at least 138 years old. Of the 395 specimens investigated in this study, 387 are single component drugs and eight are multiple-species herbal drug preparations. The entire collection includes 316 botanical specimens, 36 zoological and 34 mineral substances, of which 293 drugs are also recorded in the ChP 2015 (Table 1). Details on scientific names, families, Chinese and pharmaceutical names of all specimens that were investigated are provided in Appendix 1.

3.2. Vernacular names

From a historical viewpoint, the nomenclatural system of CMM is quite complex and confusing. Vernacular names are often influenced by

historical and regional factors that are related to therapeutic effects or morphological features (Wu et al., 2007). For example, the dried stem and leaves of Sambucus javanica Blume (pharmaceutical name Caulis et Folium Sambuci Chinensis), is primarily produced in southern China and Taiwan. While it is called mao gu xiao (右骨消) in Taiwan (Huang et al., 2003), the common name is jie gu cao (接骨草) or lu ying (陆英) in mainland China (Xu and Wang, 1988). One valuable feature of the Westhoff collection is that the vernacular name of each specimen is well documented, both in the written text and preserved on the label, which allows us to find the meaning behind the given names and better understand the products within this collection. In the Westhoff collection, the label name mao gu shao (冇骨梢, INV. 0285-128602, Fig. 1a), is similar to the Taiwanese name for Sambucus javanica. The name gian mu tong (钱木通, INV. 0285-133716, Fig. 1b) is a typical vernacular name used in Taiwan and the Fujian Province of China for Akebiae Caulis (the stem(s) of Akebia quinata (Houtt.) Decne., A. trifoliata (Thunb.) Koidz. or A. trifoliata (Thunb.) Koidz. var. australis (Diels) Rehd.). There is also a batch of four bottles with the same character *huang* (癀) on their labels (Fig. 1c), a term mainly used in southeast China; its literal meaning is related to infection or inflammation. CMM indicated with huang generally has therapeutic effects such as activating blood circulation and anti-inflammation. Westhoff's handwritten record revealed that the phonetic name of huang (癀) is hong (Fig. 1d), which is typical for the Minnan dialect in southeast China (Lin, 2007). These local names demonstrate that the original source of the Westhoff collection is likely from southern China including the Taiwan region.

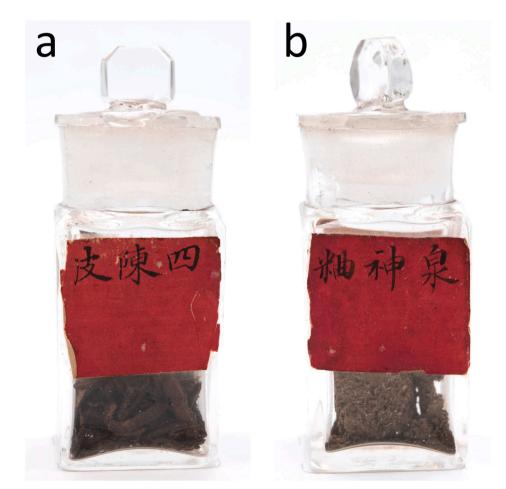


Fig. 3. Specimens with vernacular names that indicate provenance of the plant material. (a) si chen pi (四陈皮, INV. 0285-129297, pericarp of Citrus X reticulata Blanco and its different cultivars) and (b) quan shen qu (泉神粬, INV. 0285-133668, Massa Medicata Fermentata).



Fig. 4. Map of East Asia showing the geographical origin of some of the specimens in the Westhoff collection.

3.3. Provenance of plant materials

In the Westhoff collection, the label names of some specimens do not only indicate the type of medicine, but also contain information about its provenance. Some vernacular names reveal the geographic origin of the plant material. Citri Reticulatae Pericarpium is the pharmaceutical name for the dried pericarp of different cultivars of Citrus X reticulata Blanco (INV. 0285-129297, Fig. 3a). Its label name mentions si chen pi (四陈皮), in which si is the abbreviation for Sihui, a city located in the Guangzhou Province (Fig. 4). Citrus fruits cultivated in Sihui have a higher quality than those cultivated elsewhere and are considered as authentic drugs in CMM for a long time (Huang, 1997; Leon and Lin, 2017). Another example is shen qu, Massa Medicata Fermentata, a multi-herbal medicine comprised of Persicaria hydropiper (L.) Delarbre, Artemisia carvifolia Buch.-Ham. ex Roxb., apricot kernel and other ingredients, fermented with wheat flour and bran. This multi-herbal medicine is mainly used to promote digestion and increase appetite (Zhao, G. et al., 2006). In the Westhoff collection, Massa Medicata Fermentata was named quan shen qu (泉神粬, INV. 0285-133668, Fig. 3b), in which quan refers to Quanzhou, a port city in the Fujian Province (Fig. 4). According to the historic Supplement to Compendium of Materia Medica (Ben Cao Gang Mu Shi Yi, 1765), the Massa Medicata Fermentata produced in Quanzhou is famous for its top quality (Zhao, 1998). The vernacular names of the Westhoff collection also refer to the (good) quality of the medicines. This is in agreement with the concept of 'indigenous herbs' within Traditional Chinese medicine, in which growth conditions, latitude, altitude and environmental factors have a demonstrated impact on the quality of the herbal products (Chang et al., 2006; Sun et al., 2020).

3.4. Multiple interpretations of vernacular names

Within the Westhoff collection, the confusion of one vernacular name corresponding to multiple herbs is also reflected. One specimen was labelled as jin suo shi (金锁匙, INV. 0285-128620, Fig. 5a), which is not an official name for any CMM today, but in the past, it was a synonym for 19 different herbal medicines (Zhonghua Bencao Edit Committee, 1999). Based on the morphology, we identified the jin suo shi in the Westhoff collection as Striga asiatica (L.) Kuntze, an annual semi-parasitic herb native to Africa and Asia (Roskov et al., 2019; Zhong and Yang, 1979). As a folk medicine, S. asiatica is mainly used in southern China (Zhonghua Bencao Edit Committee, 1999). The vernacular name jin suo shi is only used in the Fujian Province, other regions have different local names for this herb. The Westhoff specimen labelled as yi zhi xiang (一枝香, INV. 0285-129288, Fig. 5b) was identified as Gerbera piloselloides (L.) Cass., while elsewhere in China, six different herbal medicines are using the name yi zhi xiang (Zhonghua Bencao Edit Committee, 1999).



Fig. 5. Specimens with vernacular names that correspond to multiple herb species. (a) *jin suo shi* (金锁匙, INV. 0285-128620, *Striga asiatica* (L.) Kuntze) and materials from the corresponding bottle. (b) *yi zhi xiang* (一枝香, INV. 0285-129288, *Gerbera piloselloides* (L.) Cass.) and materials from the corresponding bottle.

Table 2

| Historical changes in | vernacular | names | for | Natrii | Sulfas | Exsiccatus | and | Scro- |
|-----------------------|------------|-------|-----|--------|--------|------------|-----|-------|
| phulariae Radix. | | | | | | | | |

| Specimen number | Pharmaceutical name | Name in Compendium of Materia Medica (16th century) | Name in the Westhoff Collection (19th century) | Name in the ChP (2015) |
|----------------------|-----------------------------|--|--|-------------------------------|
| INV. 0285- 133907 | Natrii Sulfas Exsiccatus | xuan ming fen (玄 明粉) | yuan ming fen (元明粉) | xuan ming fen (玄明 粉) |
| INV. 0285- 133774 | Scrophulariae Radix | xuan shen (玄参) | jiu yuan shen (酒元参) | xuan shen (玄 参) |

3.5. Influence of Chinese dynasties on vernacular names

In the Westhoff collection, we found two special vernacular names of CMM for a particular period. The Chinese name is *xuan ming fen* (玄明粉) refers to the pharmaceutical name Natrii Sulfas Exsiccatus, which is obtained from Glauber's salt by efflorescencing, containing mainly sodium sulfate (Na₂SO₄). Scrophulariae Radix is the dried root of *Scrophularia ningpoensis* Hemsl. and its Chinese name is *xuan shen* (玄参) (元) (Table 2 and Fig. 6). The reason for this change was a Chinese emperor in the 17th century with the name *Xuan Ye* (玄烨). Using an identical term (*xuan*) for both a medicine and the emperor's name was a serious taboo in that time, so people changed the medicine's name to avoid it. These vernacular names in the Westhoff collection prove that the labels of the medicinal material were produced in the period of this taboo (the Qing Dynasty, 1644-1911). After 1911, *yuan ming fen* (元明粉) and *yuan shen* (元参) were changed back to *xuan ming fen* (玄明粉) and *xuan shen* (玄参). This finding is consistent with our estimation that the Westhoff collection is at least 138 years old.

(ChP2015). However, in the Westhoff collection, their label names

mention yuan ming fen (元明粉, INV. 0285-133907) and jiu yuan shen (酒元参, INV. 0285-133774), in which the word xuan (玄) changed to yuan

In the Westhoff collection, the medicinal plant parts of some prod-

ucts differ from the specification in the modern Chinese pharmacopoeia. Aristolochiae Fructus in the ChP 2015 is the dried ripe fruit of *Aristolochia contorta* Bunge or *A. debilis* Siebold & Zucc. However, in the Westhoff collection, the Aristolochiae Fructus (*ma dou ling*, 马兜铃, INV. 0285-133755, Fig. 7a) included only seeds, while the fruit itself had been removed (Fig. 7b). According to ancient medical monographs, various parts of the *Aristolochia* fruit were used: seeds, fruit without

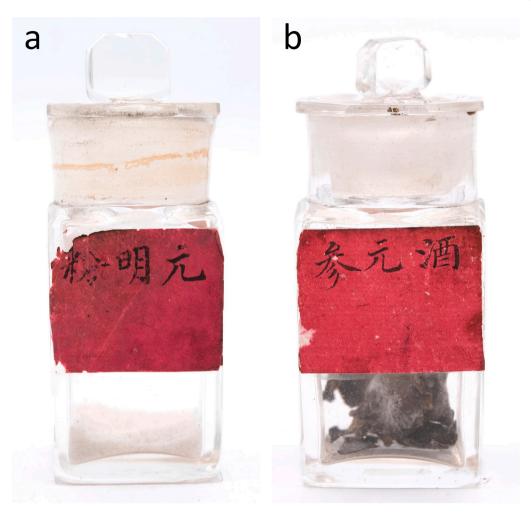


Fig. 6. Specimens with vernacular names that were changed over time. (a) yuan ming fen (元明粉, INV. 0285-133907, Natrii Sulfas Exsiccatus). (b) jiu yuan shen (酒元 参, INV. 0285-133774, Scrophulariae Radix, root of Scrophularia ningpoensis Hemsl.).

pericarp, and whole fruits (Mao et al., 2017). The specimen in the Westhoff collection proves that seeds alone were used as the medicinal part of Aristolochiae Fructus in the late nineteenth century. Moreover, the Westhoff *Aristolochia* seeds (Fig. 7c and d) are not obtusely triangular or fan-shaped like the seeds of the official species *A. contorta and A. debilis.* Therefore, *ma dou ling* in the Westhoff collection not only contains different medicinal parts, but also is an unofficial substitute compared to the species listed in the ChP 2015.

In certain cases, regional variation in herbal medicines explain the differences in medicinal plant parts between the Westhoff collection and the ChP 2015. Eriocauli Flos as described in ChP 2015 is the dried capitulum and peduncle of Eriocaulon buergerianum Koern. In the Westhoff collection, the specimen gu jing zhu (谷精珠, INV. 0285-129301, Fig. 8a) is the capitulum of Eriocaulon sexangulare L. In southeast China, this species is widely distributed and often used as an unofficial substitute for E. buergerianum (Zhonghua Bencao Edit Committee, 1999; Wu, 1997). Besides that, the use of the capitulum instead of the capitulum with peduncle is also a regional custom in south China. The Eriocauli Flos specimen in the 300-year old collection in the Natural History Museum in London and in the 100-year old collection in the Royal Botanic Gardens Kew both consisted of the capitulum of E. sexangulare (Brand et al., 2017; Zhao et al., 2015). The Westhoff collection proves that this unofficial substitute of Eriocauli Flos has a long history. This substitute is also widely accepted today in the marketed material often seen in Hong Kong (Zhao, 2016).

Another particularity in the Westhoff collection is the inconsistency between labels and contents. The label name of *jing jie sui* (荆芥穗) refers

to the fruit spike of *Schizonepeta tenuifolia* Briq., but the bottle of the specimen (IVN. 0285-129295, Fig. 8b) contains not only the fruit spike but also the stem and leaves. In specimen IVN. 0285-133884, the label *fen ou jie* (粉藕节) refers to the dried node of *Nelumbo nucifera* Gaertn., but the bottle contains slices of the rhizome (Fig. 8c).

3.7. Mixed collections in the Westhoff collection

In the practice of TCM, in most cases multi-herbal ingredients are used to make a formula for decoction. Thus single species or substances are usually considered as raw drug materials. When referring to a multiple component drug, its pharmaceutical name will indicate this, such as the previously mentioned quan shen qu (Fig. 3b). In the Westhoff collection, there are several bottles that contain multiple species while their labels do not explicitly specify this. For instance, Sinapis Semen (mustard seed) should, according to ChP 2015, be the ripe seed of Sinapis alba L. or Brassica juncea (L.) Czern. et Coss. The Westhoff specimen of Sinapis Semen is labelled bei jie zi (北芥子, INV. 0285-133878, Fig. 9a), which is a vernacular name specific for seed of S. alba, while the content of the bottle is a mixture of seeds of S. alba and B. juncea (Fig. 9b and c). The yellowish-white seeds of S. alba and pale brown seeds of B. juncea are relatively easy to distinguish. In the Chinese name bei jie zi, the literal meaning of the prefix "bei" is north. That is to say, the Sinapis Semen comes from northern China. In TCM, the seeds of S. alba that are cultivated in the northern Chinese Shanxi, Hebei and Shandong provinces are considered to be authentic and to have a higher therapeutic quality (Peng, 2011). It is a common practice in TCM that more than one plant

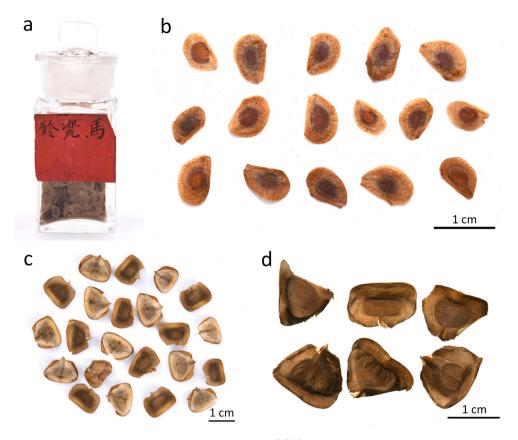


Fig. 7. Specimens with Aristolochia seeds in the Westhoff collection. (a) ma dou ling (马兜铃, INV. 0285-133755). (b) Seeds (Aristolochia sp.) from the corresponding bottle. (c) The reference specimen of Aristolochia contorta from the CDFDC. (d) Reference specimen of A. debilis from the CDFDC.

species is known under the same name for therapeutic application. The seeds of *B. juncea* have the same properties as *S. alba*, which allows both of them to be labelled as Sinapis Semen and interchangeably used in clinical use (ChP, 2015). While the Westhoff collection emphasizes the authenticity and therapeutic value of this herbal material by stressing its provenance from northern China, the collector was probably not intentionally adulterating, as seeds of both species have been used for thousand years as a source of Sinapis Semen (Peng, 2011). This mixed collection of Sinapis Semen in the Westhoff collection is an evidence that the collector was aware of the properties of the seeds of the two species.

The label dong kui zi (冬葵子, INV. 0285-133747, Fig. 10) refers to Malvae Semen, the seed of Malva verticillata L. (Zhao, G. et al., 2006). However, we identified the specimen as Abutilon theophrasti Medic., known officially as Abutili Semen (qing ma zi, 苘麻子, Fig. 10c). Malvae Semen was first recorded in The Divine Husbandman's Classic of Materia Medica (Shen Nong Ben Cao Jing) in the Eastern Han Dynasty (25-220 AD), while Abutili Semen was first recorded in the Newly Revised Materia Medica (Xin Xiu Ben Cao) in 659 AD. Both of them have a long history of medicinal use in China (Zhonghua Bencao Edit Committee, 1999), but the confusion between the two products occurs both in literature and clinical practices. In the ChP 1985, dong kui zi (Malvae Semen) was recorded as a synonym of qing ma zi (Abutili Semen). This confusion also appears in local pharmacopoeias. Cui et al. (1992) identified 39 samples labelled as Malvae Semen from all over the China that appeared to be A. theophrasti (Abutili Semen). Our finding confirms that this confusion has existed at least since the late 19th century. Moreover, the contents in this bottle are a mixture (Fig. 10b and c), as another seed is present that we identified as Trigonella foenum-graecum L. (fenugreek seed), which is commonly known as Trigonellae Semen and also included in the ChP 2015. Given the distinct morphological features of Abutili Semen and Trigonellae Semen, we speculate that this mixture is not an intentional adulteration for economic benefits, but evidence that these species were interchangeably used at that time.

3.8. Adulterated and misidentified specimens in the Westhoff collection

Adulteration is a long-standing problem in herbal medicine, which is not limited to China (Leon and Lin, 2017; Van der Valk et al., 2017; Zhao, Z. et al., 2006). Unsurprisingly, adulterations were also found in the Westhoff collection. For example, *chong wei zi* (茂蔚子, INV. 0285-129273) refers to the ripe fruit of *Leonurus japonicus* Houtt (Fig. 11a-c), but the specimen was contaminated with seeds or fruits of an unknown species that shared some features (e.g. shape pattern and size) with the Leonuri Fructus (Fig. 11c), but differenced in color and curvature of the pericarp.

Sha yuan zi (沙苑子, INV. 0285-133725) should refer to the seeds of Astragalus complanatus Bunge (ChP, 2015). Close inspection revealed that although all seeds in this specimen have highly similar features: somewhat reniform, slightly flattened and darkish brown, some seeds have more dented edges than the other (Fig. 11). Comparison with specimens from CDFDC revealed that the seeds with the strongly dented edge were Astragalus sinicus L. (Fig. 11f, indicated by dashed circle). The seeds with the slightly dented edge were similar but not identical to those of the reference voucher A. complanatus, and were identified as the closely related species A. complanatus (Fig. 11f, indicated by solid circle). Therefore, the specimen sha yuan zi in the Westhoff collection was both misidentified and adulterated at the same time.

Another example is *hai jin sha* (海金沙, INV. 0285-133829), which refers to Lygodii Spora, the dried ripe spores of *Lygodium japonicum* (Thunb.) Sw. (Fig. 11g–i). According to the ChP 2015, Lygodii Spora are brownish-yellow, tetrahedral or triangular conical, triphase conical in top view, subtriangular in lateral view, round-triangular in bottom view, 60-85 µm in diameter (ChP, 2015). The *hai jin sha* spores in the Westhoff collection are indeed brownish-yellow, but further observation through

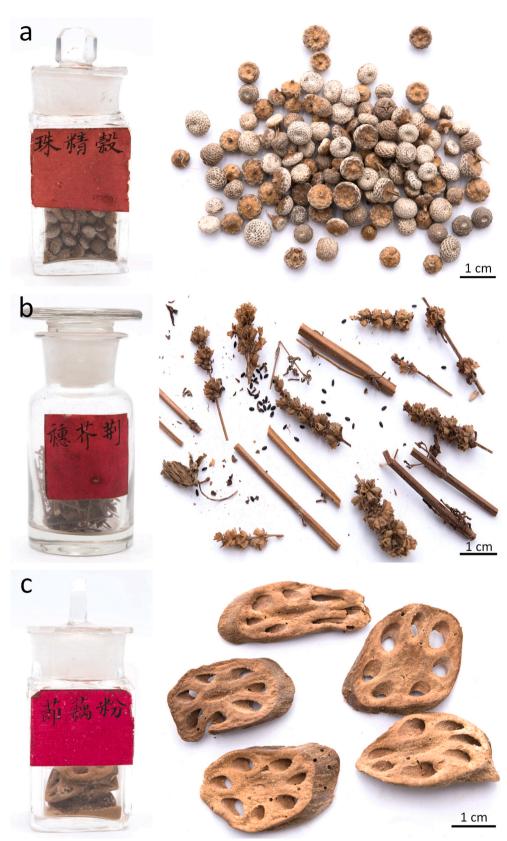


Fig. 8. Inconsistency between labels and contents in the Westhoff collection. (a) gu jing zhu (谷精珠, INV. 0285-129301, Eriocauli Flos, capitulum of Eriocaulon sexangulare L.) and materials from the corresponding bottle. (b) jing jie sui (荆芥穗, IVN. 0285-129295, Schizonepetae Spica, spikes of Schizonepeta tenuifolia Briq.) and materials from the corresponding bottle. (c) fen ou jie (粉藕节, IVN. 0285-133884, Nelumbinis Rhizomatis Nodus, node of Nelumbo nucifera Gaertn.) and materials from the corresponding bottle.

a microscope showed that they are oval-shaped with a short axis of ca. 100-300 μ m (Fig. 11i). Because of the different size and shape, the specimen *hai jin sha* in the Westhoff collection does not belong to *L. japonicum*, but its true botanical identity could not be verified. The

adulteration of these three samples seems primarily caused by the highly similar appearances of the products. Whether this adulteration was intentionally to earn more benefits or unintentionally because of lack of knowledge or identification tools remains unknown.

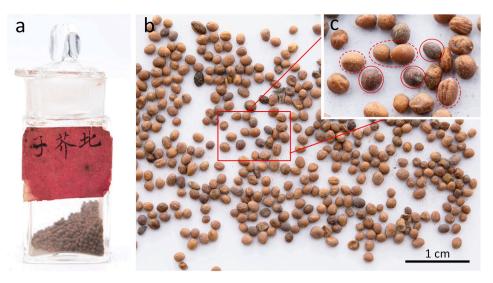


Fig. 9. Mixed specimens in the Westhoff collection. (a) bei jie zi (北芥子, INV. 0285-133878) and (b) contents. (c) Enlargement of (b). Dashed circles indicate the seeds of Brassica juncea, solid circles indicate the seeds of Sinapis alba.



Fig. 10. Mixed specimen in the Westhoff collection. (a) dong kui zi (冬葵子, INV. 0285-133747). (b) The contents (c) Left: seeds of Trigonella foenum-graecum; right: seeds of Abutilon theophrasti.

3.9. Medicinal processing

Chinese medicinal products are often processed to reduce their volume and enhance their therapeutic effects. For medicinal purpose, the dried roots, rhizomes, stems, leaves, flowers, fruits and seeds are mostly prepared as a decoction, but the herbal material is often processed before it is boiled in water (Wang and Franz, 2015, 2015; 2015; Guo et al., 2015). The processing of medicinal material has a history as long as TCM itself, and can be divided into simple preparations (such as cutting, crushing, calcination) and elaborate processing (such as frying with or without liquid adjuvants). The processing transforms raw medicinal materials into a stand-by status with the desired properties for their medical application, which enhance their efficacy, reduce toxicity, or alter some of their medicine properties (Sheridan et al., 2015; Wang and Franz, 2015).

In the Westhoff collection, ca. 25% of the specimens has been processed. Processing methods in modern times often differ from those applied in the past (Brand et al., 2017), and historical CMM can provide evidence for these changes. The sample of Phytolaccae Radix, the root of *Phytolacca acinosa* Roxb. or *P. americana* L. is labelled as *jiu shang lu* (酒 商陆, INV. 0285-133812), which indicates the root was stir-fried in wine. In the past, there were several processing methods: boiling, steaming, soaking, stir-frying, stir-frying in vinegar or stir-frying in wine (Zhonghua Bencao Edit Committee, 1999). Since the late Qing Dynasty



Fig. 11. Adulterated and misidentified material in the Westhoff collection. (a) *chong wei zi* (茺蔚子, INV. 0285-129273). (b) contents (c) Left: contaminants; right: fruit of *Leonurus japonicus* Houtt. (d) *sha yuan zi*, (沙苑子, INV. 0285-133725). (e) contents (f) Local enlargement of e. Dashed circle: seeds of *Astragalus sinicus*. Solid circle: seeds of *Astragalus* sp. (g) *hai jin sha* (海金沙, INV. 0285-133829, spores of *Lygodium japonicum* (Thunb.) Sw.). (h) contents. (i) Microscopic enlargement of h0.

(1644-1911), only the stir-frying in vinegar has continued, while other methods have gradually been abandoned. In the Westhoff collection, however, the stir-frying in wine is still practiced. Another example is Polyporus, the dried sclerotium of *Polyporus umbellatus* (Pers.) Fires, which is labelled as *xian zhu ling* (鹹猪苓, INV. 0285-133712), which means the fungus is stir-fried in salt water. According to the ChP 2015, the current processing methods of Polyporus are limited to cleaning and cutting and stir-frying with salt water is not mentioned in the literature. We speculate that this is an unofficial or regional preparation method, as Polyporus has been used in Chinese medicine for more than 2500 years. Because no side effects or toxicity has been reported for this fungus (Zhao, 2013), the unique processing method of Polyporus may enhance its efficacy or extend its storage time, but further chemical analysis is needed to verify these hypotheses.

One of the main purposes of these processing methods is to reduce the toxicity of the medicinal material, and the Westhoff collection demonstrates that Chinese physicians around 1870 were well aware of the processing methods to remove toxins. This is illustrated by the specimens of *dan nan xing* and *zhi nan xing*, both referring to Arisaematis Rhizoma (*tian nan xing*, Arisaema erubescens (Wall.) Schott., A. heterophyllum Bl. or A. amurense Maxim., INV. 0285-133730 and INV. 0285-133667). Dan nan xing (胆南星) refers to Arisaematis rhizome stirred or fermented in cow, sheep or pig bile, while the *zhi nan xing* (制 南星) refers to the same rhizome boiled with potassium alum and fresh ginger. The crude and processed Arisaematis rhizomes are included in the ChP 2015. Huang et al. (2011) reported that the processed rhizomes dan nan xing and *zhi nan xing* not only reduced neurotoxic effects, but also enhanced neuropharmacological efficacy.

The dried main tuber of *Aconitum carmichaelii* Debeaux is known as Aconiti Radix (*chuan wu*), while the processed lateral root of this species

is named Aconiti Lateralis Radix Praeparata (fu zi). In the Westhoff collection, both Aconiti Radix (INV. 0285-133685) and Aconiti Lateralis Radix Praeparata (INV. 0285-133704, INV. 0285-133863) are present (Table 3). The Aconiti Radix specimen's label name is zhi chuan wu (制川 乌), which means the drug is processed. In the past centuries, over ten different processing methods for Aconitum roots have been reported, varying from soaking, steaming, boiling or boiling with several adjuvants (Zhonghua Bencao Edit Committee, 1999). The Westhoff collection label name only indicates that root is processed, but does not specify which method was used. Chuan ming fu (川明附) and bei fu zi (焙附子) refer to the lateral root of A. carmichaelii and have similarly elaborate processing procedures. Despite their highly toxic effect, both root types are widely used in clinical practice in China today but only restricted to the processed herbal material (ChP, 2015). Research shows that several of the processing methods can greatly reduce the toxic diester diterpene alkaloids in Aconitum roots (Wang et al., 2009; Liu et al., 2017).

4. Conclusion

The Westhoff collection represents a unique, well preserved collection of Chinese materia medica, with its original uniform bottles, Chinese labels and handwritten catalogue largely intact. We assume that it was meant as a showcase for pharmaceutical education and/or as curiosity object. These 395 samples are a good representation of CMM at that time. Animal and mineral samples made up 9.1% and 8.6% of the total collection respectively. A large proportion of this collection was represented by processed medicine, which included not only cleaned and cut material, but also stir-fried with or without adjuvants. The local names, botanical species and processing methods of the Westhoff collection suggest that it was produced in a pharmacy in southern China

Table 3

Processed medicine from *Aconitum carmichaelii* Debeaux and preparation methods.

| Specimen number | Label name (pinyin name) | Pharmaceutical name | Medicinal part | Processing method |
|-------------------------|-----------------------------------|---------------------------------------|-------------------|---|
| INV. 0285- 133685 | 制川乌 (zhi chuan wu) | Aconiti radix | Main root | Macerated in water until the core is dry core, then taken out, boiled in only water or with other adjuvants (ginger, alumen and/or etc.) |
| INV. 0285- 133704 | 川明附 (chuan ming fu) | Aconiti lateralis radix praeparata | Lateral root | Cleaned, soaked in edible mother solution of mineral salts, boiled thoroughly, skin peeled, cut into slices, rinsed in water, steamed thoroughly and sun-dried |
| INV. 0285- 133863 | 焙附子 (bei fu zi) | Aconiti lateralis radix praeparata | Lateral root | Cleaned, soaked in edible mother solution of mineral salts, boiled thoroughly, skin peeled, cut into slices, rinsed in water, steamed thoroughly, sun- dried and stir-fried with sand |

and can be seen as a representative of south Chinese clinical practice towards the end of the 19th century.

Current issues of quality, confusion and safety issues in CMM appeared also present in this historic collection. Studying the actual specimens in pre-modern CMM collections shows that names, species and processing methods do not always coincide with the contemporary prescriptions and rules in official modern Chinese medicine handbooks. Historic CMM collections reflect the economic and cultural exchanges between China and the rest of the world. Several of these historic collections are still unexplored and are definitely worthy to be better investigated.

Declaration of competing interest

The authors declare that they have no conflicts of interest relevant to the publication of this document.

Acknowledgements

This research was supported by the "Single Cell Foundation"; We are grateful to Paul Lambers (Utrecht University Museum) for giving us access to the Westhoff CMM collection. We also thank the support from Chinese National Science and Technology Major Project for "Significant New Drugs Development" (2019ZX09201005-006-004) and Wang Mei Expert Workstation of Yunnan Province (201905AF150001).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2020.113714.

References

- Brand, E., Leon, C., Nesbitt, M., Guo, P., Huang, R., Chen, H., Liang, L., Zhao, Z., 2017. Economic botany collections: a source of material evidence for exploring historical changes in Chinese medicinal materials. J. Ethnopharmacol. 200, 209–227.
- Chang, W.-T., Thissen, U., Ehlert, K.A., Koek, M.M., Jellema, R.H., Hankemeier, T., van der Greef, J., Wang, M., 2006. Effects of growth conditions and processing on Rehmannia glutinosa using fingerprint strategy. Planta Med. 72, 458–467, 05.
- Chen, Z., Huang, S., 2005. Materia Medica Literature. Dongfang University Press, Naning.
- Chinese Pharmacopoeia Commission, 2015. Pharmacopoeia of the People's Republic of China 2015 Edition. China Medical Science Press, Beijing.
- Cui, X., Li, S., Wang, L., Zhang, J., Ma, A., 1992. Textual research of change of seed of Malva Crispa and seed of Abutilon theophrasti. China J. Tradit. Chin. Med. Pharm. 1, 19–21.
- European Pharmacopoeia Commission, 2016. European Pharmacopoeia, ninth ed. Council of Europe, Strasbourg.
- Guo, Q., Wang, C., 2011. The Illustrated Seeds of Chinese Medicinal Plants. Higher Education Press, Beijing.
- Guo, P., Brand, E., Zhao, Z., 2015. Chinese Medicinal Processing: a Characteristic Aspect of the Ethnopharmacology of Traditional Chinese Medicine. Ethnopharmacology. John Wiley & Sons, Inc., Chichester, pp. 303–316.
- Huang, C., 1997. Flora of China, vol. 43. Beijing Science Press, Beijing.
- Huang, T., Hsieh, C., Boufford, D.E., Kuoh, C., Ohashi, H., Peng, C., Tsai, J., Yang, K., Hsiao, A., Tsai, J., 2003. Flora of Taiwan, vol. 6. Department of Botany, National Taiwan University, Taipei.
- Huang, C.F., Yang, R.S., Liu, S.H., Hsieh, P.C., Lin-Shiau, S.Y., 2011. Evidence for improved neuropharmacological efficacy and decreased neurotoxicity in mice with traditional processing of Rhizoma Arisaematis. Am. J. Chin. Med. 39 (5), 981–998.
- Chinese Academy of Sciences, 1959. Jiang su sheng zhi wu yao cai zhi. Institute of Botany, CAS. Science Press, Beijing. https://www.biodiversitylibrary. org/item/158870#page/2/mode/1up.
- Leon, C., Lin, Y., 2017. Chinese Medicinal Plants, Herbal Drugs and Substitutes: an Identification Guide. Kew Publishing, Royal Botanic Gardens, Richmond, Surrey, United Kingdom.
- Lin, B., 2007. Pu Tong Hua Min Nan Fang Yan Chang Yong Ci Dian. Xiamen University Press, Xiamen.
- Liu, S., Li, F., Li, Y., Li, W., Xu, J., Du, H., 2017. A review of traditional and current methods used to potentially reduce toxicity of Aconitum roots in Traditional Chinese Medicine. J. Ethnopharmacol. 207, 237–250.
- Maddison, A., 1989. Dutch income in and from Indonesia 1700–1938. Mod. Asian Stud. 23 (4), 645–670.
- Mao, W., Gao, W., Liang, Z., Li, P., Zhao, Z., Li, H., 2017. Characterization and quantitation of aristolochic acid analogs in different parts of Aristolochiae Fructus, using UHPLC-Q/TOF-MS and UHPLC-QqQ-MS. Chin. J. Nat. Med. 15 (5), 392–400.
- Peng, C., 2011. Zhonghua Daodi Yaocai. China Press of Traditional Chinese Medicine Co. Ltd, Beijing.
- Roskov, Y., Ower, G., Orrell, T., Nicolson, D., Bailly, N., Kirk, P.M., Bourgoin, T., DeWalt, R.E., Decock, W., Nieukerken, E.v., Zarucchi, J., Penev, L. (Eds.), 2019. Species 2000 & ITIS Catalogue of Life, 2019 Annual Checklist. Species 2000. Naturalis, Leiden, the Netherlands.
- Sheridan, H., Kopp, B., Krenn, L., Guo, D., Sendker, J., 2015. Traditional Chinese herbal medicine preparation: invoking the butterfly effect. Science 350 (6262), S64–S66.
- Sun, M., Wu, H., Jia, Y.S., Wang, L., Liu, T., Hui, L.Q., Li, L., Wei, S.L., Van Wijk, E., Van Wijk, R., Tsim, K.W.K., Li, C., Wang, M., 2020. Integrated assessment of rhubarb herbal materials by combination of HPLC fingerprinting and delayed luminescence for a bioactivity-based quality control. Chin. Med. 15, 72.
- Van der Valk, J.M., Leon, C.J., Nesbitt, M., 2017. Macroscopic authentication of Chinese materia medica (CMM): a UK market study of seeds and fruits. J. Herb. Med. 8, 40–51.
- Wang, M., Franz, G., 2015. The role of the European pharmacopoeia (Ph Eur) in quality control of traditional Chinese herbal medicine in European member states. World J. Tradit. Chin. Med. 1 (1), 5–15.
- Wang, J., Van der Heijden, R., Spruit, S., Hankermeier, T., Chan, K., Van der Greef, J., Xu, G., Wang, M., 2009. Quality and safety of Chinese herbal medicines guided by a systems biology perspective. J. Ethnopharmacol. 126, 31–41.
- Wu, G., 1997. Flora of China, vol. 13. Beijing Science Press, Beijing.

 Wu, K.M., Farrelly, J.G., Upton, R., Chen, J., 2007. Complexities of the herbal nomenclature system in traditional Chinese medicine (TCM): lessons learned from the misuse of Aristolochia-related species and the importance of the pharmaceutical name during botanical drug product development. Phytomedicine 14 (4), 273–279.
Xie, Z., 2008. Chinese Medicinal Varieties: Theory and Use. People's Medical Publishing

- House, Beijing.
- Xu, B., Wang, H., 1988. Flora of China, vol. 72. Beijing Science Press, Beijing.
- Zhao, X., 1998. Supplement to Compendium of Materia Medica, Chinese Edition. China Press of Traditional Chinese Medicine Co.Ltd, Beijing.
- Zhao, Y.Y., 2013. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of Polyporus umbellatus (Pers.) Fries: a review. J. Ethnopharmacol. 149 (1), 35–48.
- Zhao, Z., 2016. Illustrated Identification of Chinese Materia Medica in Hong Kong. Hong Kong Baptist University, Hong Kong, pp. 10–21.
- Zhao, G., Dai, R., Chen, S., 2006. Dictionary of Chinese Traditional Medicine (Zhong Yao Da Ci Dian). Shanghai Scientific & Technical Publishers, Shanghai.
- Zhao, Z., Yuen, J.P., Wu, J., Yu, T., Huang, W., 2006. A systematic study on confused species of Chinese materia medica in the Hong Kong market. Ann. Acad. Med. Singapore 35 (11), 764–769.

Y. Jia et al.

Zhao, Z., Zhao, K., Brand, E., 2015. Identification of ancient Chinese medicinal specimens preserved at natural history Museum in London. China J. Chin. Mater. Med. 40 (24), 4923–4927.

 Med. 40 (24), 4923–4927.
Zhao, Z., Guo, P., Brand, E., 2018. A concise classification of bencao (materia medica). Chin. Med. 13 (1), 18. Zhong, B., Yang, H., 1979. Flora of China, vol. 67. Beijing Science Press, Beijing Zhonghua Bencao Edit Committee, 1999. Zhonghua Bencao. Shanghai Science and Technology Publications, Shanghai.