Combining classic and novel tools in the study of Historical Collections of **Chinese *Materia Medica*** in the **Netherlands**

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Chapter One

General Introduction

History of Chinese *materia medica* (CMM)

Traditional Chinese medicine (TCM) is an experience-based healthcare system that has been practiced for thousands of years in China. It focuses on aspects of prevention and personalized treatment of human diseases and continues to hold significant relevance in the modern era (Hu, 2015). Chinese *materia medica* (CMM) refers to a significant component of TCM that consists of various natural substances, primarily derived from plants, animals, and minerals, for therapeutic purposes according to TCM principles. Based on Chinese philosophy and clinical experiences, the theories and methods of Chinese *materia medica* uses were gradually formed and recorded in written works (Zhang et al., 2010). The first treatise on Chinese *materia medica* is the *Shen nong ben cao jing* (*The Divine Husbandman's classic of materia medica*). The knowledge of *materia medica* presented in this treatise, which had been transmitted orally from ancient times (c. 6000 BC), was first written down in the Eastern Han Dynasty (25-220 AD). Although the original edition was lost, the contents of *The Divine Husbandman's classic of materia medica* were preserved and recreated as early as the Song dynasty (960-1280 AD) (Yang, 1998). The treatise records 365 types of CMM, which are classified into three categories (top grade, medium grade and low grade) based on their medicinal effects and toxicity (Teng, 2019; Zhao et al., 2018). The *Xin xiu ben cao* (*Newly revised materia medica*), completed in 659 AD by Su Jing et al., depended on the administrative power of the Tang dynasty, and became the earliest officially compiled treatise on *materia medica* in Chinese history. The treatise consists of 844 CMM, among which 144 are newly added (Teng, 2019). The monograph *Hai yao ben cao* (*Materia medica from overseas*), written by Li Xun in the 10th century, delves into the *materia medica* from the southern coastal area of China and from overseas regions. This demonstrates that traditional Chinese medicine has an inclusive and open-minded approach to the medicinal properties of natural substances, even when those substances originate outside of China. The *Ben cao gang mu* (*Compendium of materia medica*), a monumental masterpiece on CMM compiled by Li Shizhen in 1578, identified 1,892 medicinal drugs and listed 11,096 prescriptions. The book also covers discussion on topics such as botany, zoology, mineralogy, physics, astronomy, chemistry, metallurgy, geology, meteorology, etc. Charles Darwin, the British evolutionary biologist, hailed the book as an "ancient Chinese encyclopedia" (UNESCO, 2016). The *Ben cao gang mu shi yi* (*Supplement to Compendium of materia medica*) was written by Zhao Xuemin in 1765. In this work, 921 medicinal products were described, including 716 new additions not previously mentioned in older works. The treatise is compiled especially for the supplements and corrections of errors in the *Compendium of materia medica* (Li Shizhen, 1578). Furthermore, the work extensively documents folk herbal medicines and medicinal products from foreign lands (Teng, 2019). The *Zhong hua ben cao* (*Chinese materia medica*) was completed in 1999 with the efforts of more than 100 experts in China. It contains more than 20 million Chinese characters, records 8,980 types of CMM and adds such information as chemical components, pharmacological agents and clinical reports. This is a comprehensive work, reflecting the development of the CMM in the 20th century (Teng, 2019; Zhonghua Bencao Edit Committee, 1999). The Chinese Pharmacopoeia (ChP), compiled by the Pharmacopoeia Commission of the Ministry of Health of the People's Republic of China, is a legal code with the national legal authority that records drug standards and specifications. The first edition of the Chinese Pharmacopoeia was published in 1953, and since 1985, a new edition has been released every five years. The latest version currently available is the one issued in 2020.

Dynamic changes

Due to its long-standing history and extensive documentation, traditional Chinese medicine (TCM) still plays an important role in the Chinese healthcare system nowadays (Wang et al., 2017), and therefore Chinese *materia medica* (CMM) as well. The total output value of the pharmaceutical industry based on TCM was RMB 786.6 billion (approx. € 102.18 billion) in 2015, accounting for 29% of the total revenues generated by the country's pharmaceutical industry based on synthetic medicine (Xu and Xia, 2019). In 2017, the total fiscal appropriation in China's TCM agencies was c. € 5.98 billion. The number of students in TCM universities specializing in traditional Chinese medicine, was 693,267 in 2017, while the numbers of TCM agencies and practitioners were 54,243 and 217,118 respectively in the same year (Wang et al., 2021). The development of traditional Chinese medicine has received and will continue to receive, strong support from the Chinese government, such as evidenced by the *Outline of the Strategic Plan on the Development of Traditional Chinese Medicine (2016–2030)* and the *13th* and *14th Five-Year Traditional Chinese Medicine development plan* (Wang et al., 2021). Furthermore, the popularity of TCM and CMM is also increasing outside of China. For example, the import and export values of Chinese herbal medicine products to the European Union (EU) reached approximately 850 million USD in 2017 (Wang et al., 2022). With such massive support and worldwide demand, traditional Chinese medicine will continue to grow in the near future.

A pivotal aspect attributing to the remarkable success of TCM (and therefore its natural ingredients) is the continual inheritance of valuable historical experiences, accompanied by ongoing growth and changes. The majority of CMM are plant-based products (Leon and Lin, 2017). Through consistent testing and verification by Chinese practitioners and clients, certain plants have demonstrated their ability to cure diseases (Zhong, 2016). Consequently, essential information about species, such as the plant's vernacular name, place of origin, morphological characteristics, and other relevant details has been documented to ensure that future generations use the correct species for their medication (Zhonghua Bencao Edit Committee, 1999). Medicinal plants like *Panax ginseng* C.A.Mey., *Angelica sinensis* (Oliv.) Diels and *Astragalus mongholicus* Bunge have been used for more than 2000 years (Goldstein, 1975) and are still used today (Chinese Pharmacopoeia Commission, 2020). On the other hand, *Panax notoginseng* (Burkill) F.H.Chen, *Codonopsis pilosula* (Franch.) Nannf. and *Stellaria dichotoma* var. *lanceolata* Bunge, 'only' have a few hundred years of medicinal history, and remain in current usage (Xie, 2008). Chinese *materia medica* is not limited to the consistency of the taxonomic identity of the ingredients over time but also encompasses the persistence of accumulated knowledge. For instance, the entry of ginseng roots (*Panax ginseng*) in the *Divine Husbandman's classic of materia medica* (25-220 AD) comprises only 47 words, while the entry in the *Compendium of materia medica* (Li, 1578) contains nearly 10,000 words and more than 200,000 words in the modern treatise on *Chinese materia medica* (Zhonghua Bencao Edit Committee, 1999).

Based on both the positive and negative impact of certain CMM ingredients, certain changes have taken place in the course of history. An example is the goji berry (with the pharmaceutical name Lycii Fructus), which has been used as medicine to nourish the liver and kidney (according to the theory of TCM), and to improve vision since the 2nd-3rd century (Zhonghua Bencao Edit Committee, 1999). The morphological description in the *Ben cao tu jing* (*Illustrated Classics of materia medica*), compiled by Su Song in the 11th century, identified the biological origin of the goji berry as *Lycium chinense* Mill. (Xie, 2008). However, in the 16th century *Compendium of materia medica* (Li Shizhen, 1578), another species (*Lycium barbarum* L.) was also recognized as a source of goji berry. Due to the superior quality of *L. barbarum*, it became the only official species included in the 2000 edition of the Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2000; Xie, 2008; Zhonghua Bencao Edit Committee, 1999).

Another example of historic changes in TCM owing to later discoveries on quality is the root of *Lithospermum erythrorhizon* Siebold & Zucc., with the pharmaceutical name Arnebiae Radix, which has been used for over two millennia to clear heat, cool and activate the blood (Zhonghua Bencao Edit Committee, 1999). In recent decades, *Arnebia euchroma* (Royle ex Benth.) I.M.Johnst. and *A. guttata* Bunge have also been utilized for the same purposes. In the Chinese Pharmacopoeia 2000 edition (ChP 2000), all three species were acknowledged as botanical sources of Arnebiae Radix. With the release of ChP 2005, *L. erythrorhizon* was subsequently excluded from official sources. This decision was made after the discovery that *A. euchroma* and *A. gutata* exhibit superior quality attributes, rendering them more suitable candidates for anti-microbial applications because of their higher shikonin content (Kumar et al., 2021; Xie, 2008).

Historic change in Chinese *materia medica* can also be the result of negative side effects. Since the earliest records in *The Divine Husbandman's classic of materia medica* nearly 2000 years ago, *Akebia quinata* (Thunb. ex Houtt.) Decne. has consistently been recognized as the authentic species for the pharmaceutical product Akebiae Caulis. In modern times, caused by an increased demand for Akebiae Caulis, another plant with a similar appearance and higher yield, *Aristolochia manshuriensis* Kom., has been used as a substitute (Xie, 2008; Zhu, 2002). However, carcinogenic aristolochic acids have been discovered in species of the *Aristolochia* genus. The use of *A. manshuriensis* in TCM has raised serious health concerns due to its content of aristolochic acid I and II (Arlt et al., 2002). These compounds are responsible for causing interstitial renal fibrosis which can progress to end-stage renal failure in affected patients (Lord et al., 1999). In 2003, China's National Medical Products Administration banned *A. manshuriensis*, and the Chinese Pharmacopoeia removed it from the 2005 edition (Kim et al., 2013).

Changes in Chinese *materia medica* have been the result of the substitution of imported ingredients as well. Draconis Sanguis, commonly known as dragon's blood, refers to the prepared resin of the fruit of *Daemonorops draco* (Willd.) Blume. This resin has been utilized for nearly 1500 years as CMM. Due to its origin in Southeast Asia, Chinese consumers historically relied exclusively on resin imports. However, since the 1970s, Chinese researchers have actively sought alternatives because importing alone is no longer sufficient to meet consumer demands (Xie, 2008). In this pursuit, the ethanol extract obtained from the resinous wood of *Dracaena cochinchinensis* (Lour.) S.C.Chen emerged as a substitute for Draconis Sanguis (Xie, 2008). Until recently, there was an ongoing controversy regarding the potential use of *Dracaena cochinchinensis* as a substitute for *Daemonorops draco* to relieve pain, stop bleeding, and promote wound healing in traditional Chinese medicine (Xie, 2008; Zhang et al., 2019). Therefore, in the most recent edition of the Chinese Pharmacopoeia, *Daemonorops draco* remains the exclusive source of Draconis Sanguis, while *Dracaena cochinchinensis* is excluded as an ingredient (Chinese Pharmacopoeia Commission, 2020).

After undergoing extensive practice and verification, any beneficial improvements resulting from these changes in ingredients will eventually be acknowledged as positive changes. They will serve as supplements to the existing CMM, or gradually evolve into independent new drugs. Conversely, if any harmful shifts are identified, they will be classified as negative changes and will be prohibited and eventually eliminated.

Research on the dynamic changes in Chinese *materia medica*

An important reason for studying the dynamic changes of CMM use is to ensure the safety of medications (Zhao et al., 2006). There have been issues with drug safety caused by a change from *Akebia* species to *Aristolochia* species. Unfortunately, until 2006, herbal preparations made with the toxic *Aristolochia* species instead of the *Akebia* species could still be found in the Netherlands (Martena et al., 2007).

Another pivotal reason is to prevent the misdirection of new drug development. It is widely recognized that the 2015 Nobel laureate Dr. Youyou Tu, a Chinese pharmaceutical chemist who discovered artemisinin, drew inspiration from ancient Chinese medicine books, specifically the *Handbook of Prescriptions for Emergencies* by Ge Hong (284-346 AD). This led to the development of the effective antimalarial drug artemisinin, derived from *Artemisia annua* L. (Tu, 2011). The original text in this handbook states: "A handful of *qinghao* (sweet wormwood) immersed with two litres of water, wring out the juice and drink it all" (Ge Hong, 284-346 AD, p. 92). However, the text lacks additional details about the plant's botanical identity. Therefore, prior to initiating the antimalarial substance research, Tu conducted meticulous textual research to confirm the botanical identity of the *qinghao*. This was necessary due to historical confusion about the plant's Chinese name and five potential *Artemisia* species that could be meant by this name. Subsequent research results proved that the content of artemisinin in *Artemisia annua* L. was significantly higher than the five other species in the same genus (Tu, 2017).

The study of Chinese *materia medica*, as an independent discipline of a vital part of traditional Chinese medicine, has a history of over two thousand years. Investigating its dynamic changes can show a process of refinement, which helps prevent errors from accumulating over the extensive course of development. This endeavor ensures the sustainability of the discipline. However, research on the dynamic changes of Chinese *materia medica* heavily relies on textual research. Given the extensive history of traditional Chinese medicine, many treatises related to CMM from various historical periods have been preserved. Despite certain earlier works, such as *The Divine Husbandman's classic of materia medica*, providing overly simplistic descriptions of herbal medicine and lacking clear botanical characteristics of herbal ingredients, these valuable historical treatises still provide substantial foundations for the studying of the dynamic changes in CMM (Chen and Huang, 2005; Tu, 2017; Xie, 2008). Still, there remains quite some uncertainty on the plant species used in historic recipes documented in TCM herbals, as botanical descriptions are minimal and illustrations are lacking (Xie, 2008).

Historical collections of Chinese *materia medica*, which hold samples of medicinal specimens, offer tangible evidence of the dynamic changes within the field (Brand et al., 2017; Zhao et al., 2015). When compared to textual research on ancient Chinese herbals, these physical specimens present a more intuitive and compelling perspective, as they allow for scientific identification. As shown in Figure 1.1, both textual and specimen research provide substantial support for exploring the danymic changes in CMM. While each of these methods possesses distinct strengths and weaknesses, integrating these approaches has the potential to enrich our understanding of the ongoing 'evolution' of CMM.

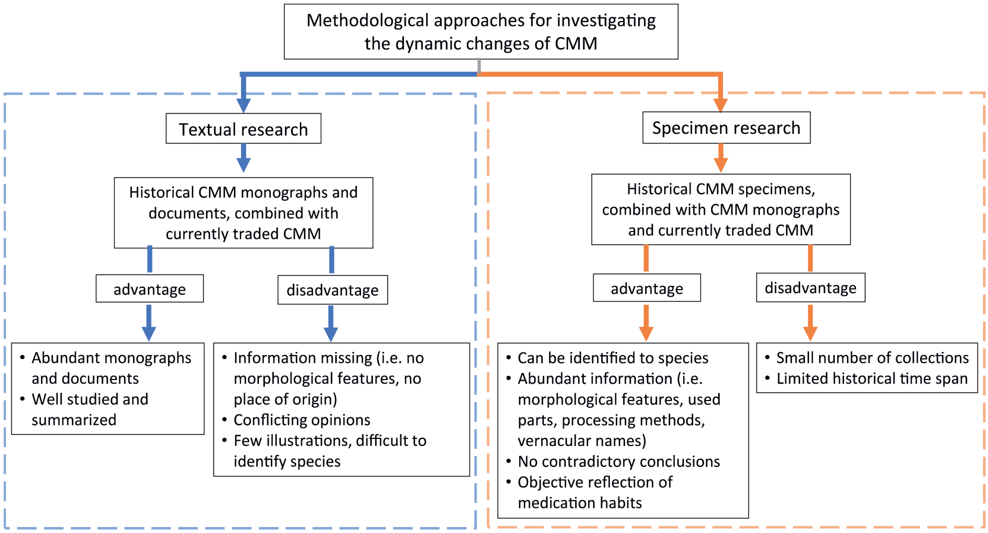

Figure 1.1 Flow chart of the methodology for investigating the dynamic changes of CMM.

Unfortunately, the investigation of the 'evolution' of CMM through historical specimens remains limited due to the scarcity of well-documented historical specimen collections, resulting in a considerable gap when compared to the findings derived from textual research.

Historical collections of Chinese *materia medica* in the Netherlands

The current Ph.D. thesis is built on research conducted on historical collections of Chinese *materia medica* in the Netherlands. A considerable number of CMM specimens are housed within the *materia medica* collections of Naturalis Biodiversity Center (Leiden), the Boerhaave Museum (Leiden), the Utrecht University Botanic Gardens, and the Utrecht University Museum. These specimens were transported from Southeast Asia to the Netherlands between the 1850s and the 1970s, facilitated by the trade in commercial plantation crops and other valuable goods, such as medicinal plant material, from Southeast Asia to the Netherlands that lasted for hundreds of years (Cook, 2007; van Andel et al., 2018). Some historic CMM specimens are held by private collectors in the Netherlands. Although these specimens have undergone preliminary identification and their basic classification has been established by either the vendors or the buyers of these collections, these historical specimens have never undergone systematic scientific research and remain inaccessible to the public. Studying these historical specimens of plants, animals and minerals will enable us to gain a deeper understanding on the dynamic changes in CMM over time, from a physical specimen perspective, bridging the gap between specimen research and textual studies, contributing to a comprehensive understanding of CMM in various aspects:

1. Identify the biological origin. The morphological descriptions of medicinal plants in historical CMM treatises are often generalized. For certain herbal medicines, the accurate biological source cannot be determined solely based on the descriptions provided in these treatises (Zhonghua Bencao Edit Committee, 1999). Furthermore, these comprehensive treatises tend to record the official species or widely accepted species of medicinal plants, but region-specific medicinal plants may be missing. By utilizing physical specimens, alternative methods such as microscopic and molecular identification can be employed to ascertain their biological origins if morphological characteristics are not visible to the naked eye (Han et al., 2018; Zhao et al., 2007). Certain CMM specimens may represent regional substitutions, which provide information about geographical variation in traditional Chinese medicine with regard to ingredients.

2. Examine the medicinal part. Although many recipes prescribe the whole plant as medicine, the majority of CMM consists of specific plant parts or related substances, such as resins or distilled extracts. The CMM specimens visually display the medicinal parts of plants. By examining specimens from different periods, it is possible to determine whether there have been any changes in the medicinal parts prescribed in herbal, zoological or mineral preparations.

3. Clarify confusing vernacular names. Historical CMM specimens usually have labels attached, bearing their common names, or the entire collection includes a catalogue containing the names of each medicine. The physical specimens, combined with the vernacular name(s), can help to clarify the confusion caused by multiple medicines sharing the same vernacular name or one medicine referred to by various names. Moreover, certain vernacular names that are region-specific also assist us in determining the area of origin for these historical specimens.

4. Determine the processing method. Some CMM are processed before being used in clinical applications, such as stir-frying. Historical specimens can directly demonstrate the processing methods used for the samples. By comparing specimens from different periods, it is possible to discover the dynamic changes in the processing methods.

5. Identify commonly used medicines from a physical specimen perspective. In general, the majority of CMM treatises are comprehensive, aiming to encompass as much pertinent information as possible (Zhonghua Bencao Edit Committee, 1999). Specimens in historical collections tend to consist of commonly used and easily obtainable items. By comparing specimens from different periods, it becomes possible to identify medicines that were commonly employed during specific timeframes, thus gaining insight into the dynamic changes of CMM.

Physical specimens represented in historical Chinese *materia medica* collections not only enhance understanding of its ‘evolution’ but also, owing to their time-honoured characteristics, offer valuable insights into other research fields. Delayed luminescence (DL), for instance, has been developed as a rapid, direct, sample loss-free technique to measure the decaying ultra-weak luminescence exhibited by material after being illuminated by light (Sun et al., 2016a). Recently, some studies of CMM using delayed luminescence have proven successful in detecting variations caused by variations in growth conditions (Sun et al., 2016a), different processing methods (Sun et al., 2018; Sun et al., 2016b), and in the determination of authenticity (Sun et al., 2019). Therefore, delayed luminescence is a promising new method to measure the dynamic changes of CMM. In addition, using historical CMM can verify whether DL is a suitable tool for discriminating CMM storage time and explore the potential of DL for use in CMM quality control.

Research aims and outline of the thesis

The primary aim of this Ph.D. thesis is to explore and research the lesser-known historical Chinese *materia medica* specimens and collections housed in the Netherlands, with a focus on their physical attributes, in order to comprehend the dynamic changes of CMM. This objective is pursued by investigating the specific research questions listed below.

Which historical CMM collections and specimens are currently preserved in the Netherlands, and what are the taxonomic identities of the specimens, the utilized parts (plants, minerals or animals), and the processing methods of the specimens?

1. What differences can be observed between these historical specimens and currently traded Chinese *materia medica* in China and the EU?
2. How were historical CMM utilized by people in the past; for which illnesses or symptoms they were used?
3. How can these new findings be used to understand the dynamic changes in time of Chinese *materia medica*?
4. Can historical CMM offer valuable insights into the application of delayed luminescence technique?

In **Chapter 2**, research was conducted on a historical collection of nearly 400 specimens of Chinese *materia medica*. These specimens were originally gathered in Indonesia and later transported to the Netherlands during the late 19th century. Currently, the collection is preserved at the Utrecht University Museum in the Netherlands. The taxonomic identity, Chinese vernacular names, medicinal plant parts, and processing methods of the specimens were examined and compared with the descriptions in modern treatises. The physical evidence regarding changes in botanical identities, medicinal plant parts, adulterations, misidentifications, and the history of CMM itself is presented. The new findings in this chapter demonstrate that historical specimens can expand knowledge of CMM variations in space and time, while also revealing related information through these physical specimens. Several of the herbal ingredients and product names point towards an origin in southern China.

Chapter 3, a continuation of Chapter 2, focuses on a handwritten catalogue corresponding to this historical CMM collection from the late 19th century. The catalogue comprises over 400 entries, each containing a Chinese name, a phonetic Dutch transcription of the Chinese name, a brief description of the medicine's natural origin, the preparation method, and the medical indication for symptom or illness. The catalogue not only serves as a valuable historical record of CMM, contributing to our understanding of its dynamic changes but also reflects an individual physician's interpretation of Chinese medicine in a specific time and space. It gives us new insight into social and cultural aspects related to traditional Chinese medicine, but also to misinterpretations of TCM concepts in the Dutch translation of the recipes.

In **Chapter 4**, five sets of CMM collections from various periods have been selected as subjects for investigating the dynamic changes of CMM from the perspective of physical specimens. The samples encompass four historical CMM collections (one of which is preserved in the Utrecht University Museum as previously mentioned; another is a private collection in Leiden, and two are housed in the UK, as described in previously published research). The fifth collection represents contemporary marketed CMM in Europe. Through the analysis of these CMM collections, which span over 300 years and comprise more than 1,700 specimens, Fabaceae and Asteraceae emerge as the major sources of medicinal plants. Root/rhizomes and fruits/seeds are the most dominant medicinal parts.

Chapter 5 explores the value and contribution of aged CMM specimens beyond the study of dynamic change. In this chapter, the delayed luminescence (DL) technique was applied to test aged CMM specimens and their corresponding modern samples. The objective was to ascertain whether the DL technique can differentiate between CMM samples from different time periods and whether there is potential for the technique to emerge as a novel method for identifying the storage duration and quality control of Chinese *materia medica*.

In **Chapter 6**, the answers to the overall research questions are provided, followed by a discussion of how these new findings address the current gap in science regarding CMM dynamic change. Furthermore, the limitations of these studies are discussed, accompanied by suggestions for future research.

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Chapter Two

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

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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 bottles of CMM surveyed, 387 contain a single component drug, eight contain multiple components drugs, of which 293 are also mentioned in the modern Chinese pharmacopeia. 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 pharmacopeia 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.

Keywords: C.H.A. Westhoff collection; historical and contemporary comparison; authentication and medicinal processing; traditional Chinese medicine; Chinese pharmacopoeia

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.

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 the earliest extant *materia medica* text The *Divine Husbandman's Classic of Materia Medica* (Han Dynasty, 25-220 AD) and the earliest national pharmacopoeia *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 (Institute of Botany, 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). 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 pharmacopeia 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 to 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*.

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 x 3.5 x 3.5 cm) with a lid (Figure 2.1a). 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 (Figure 2.1a-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 (Figure 2.1d). 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 Pharmacopeia (ChP, 2015), *Zhong hua ben cao* (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 The Plant List (http://www.theplantlist.org/) and 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/).

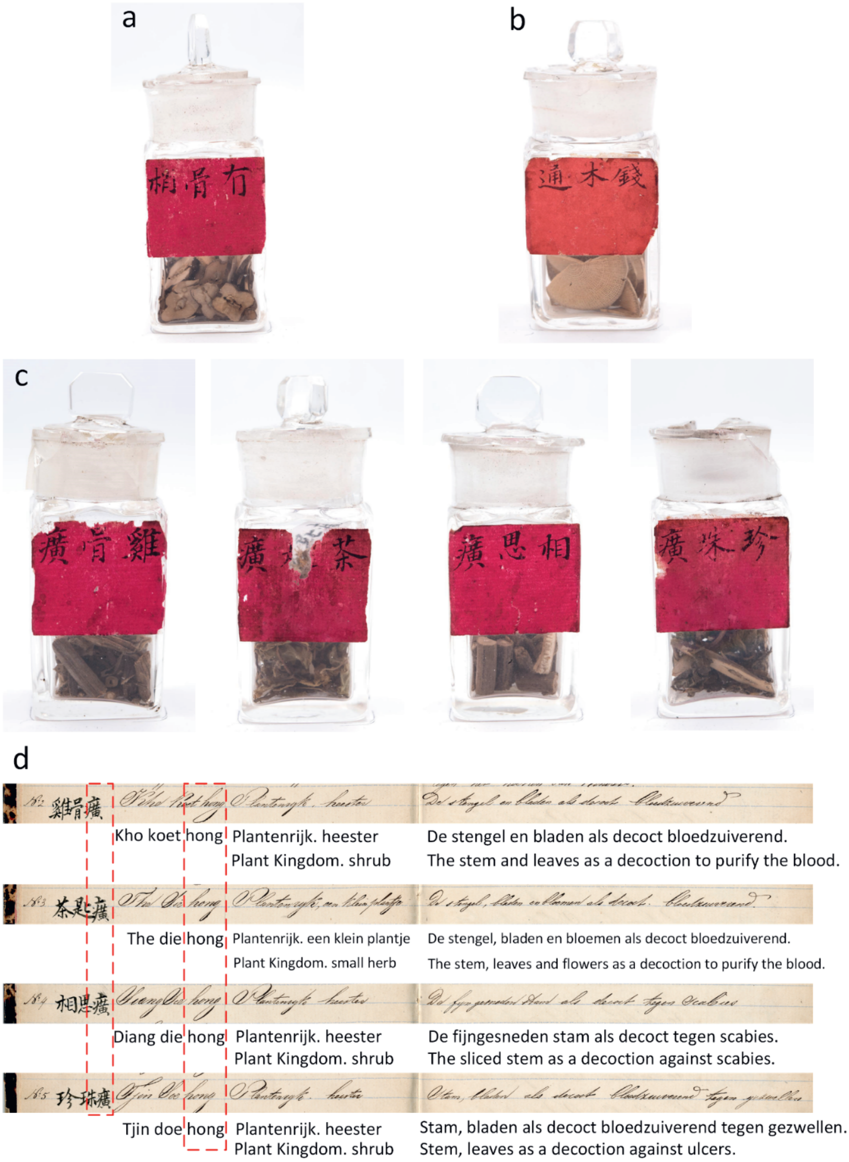
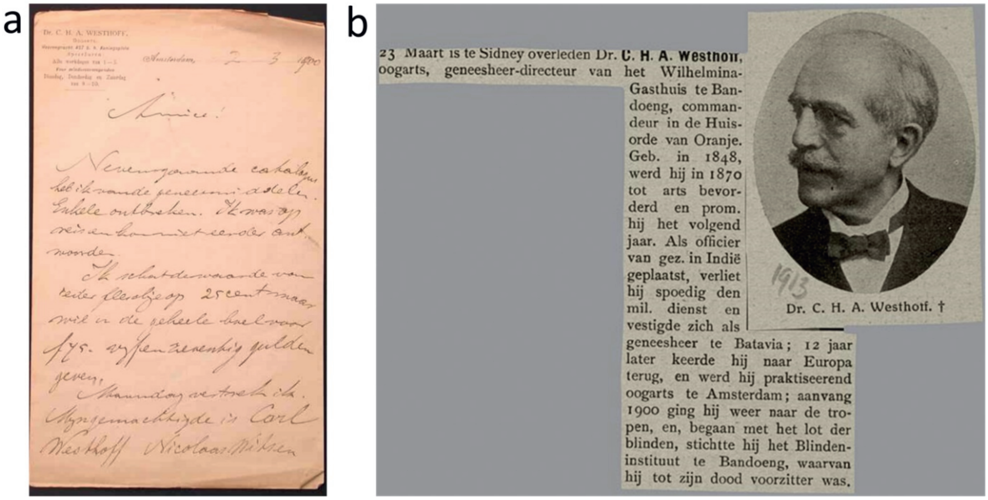


Figure 2.1 Photographs of specimens in the Westhoff Collection. (a) *mao gu shao* (冇骨梢, INV. 0285-128602). (b) *qian mu tong* (钱木通, INV. 0285-133716). (c) specimens with one same character *huang* on their labels. From left to right, *ji gu huang* (鸡骨癀, INV. 0285-128554), *cha shi huang* (茶匙癀, INV. 2085-128555), *xiang si huang* (相思癀, INV. 0285-128556), *zhen zhu huang* (珍珠癀, INV. 0285-128557) and (d) their corresponding origin records (from top to bottom), records text transcription (in Dutch) and translation (in English). The red dashed boxes indicate the same Chinese character *huang* (癀) and its phonetic name.

Results and Discussion

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

The earliest documented record of this collection was a transaction letter (Figure 2.2a), 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 (Figure 2.2b), he returned to Europe from Indonesia in 1882 and travelled back to Indonesia again in 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 2.1). Details on scientific names, families, Chinese and pharmaceutical names of all specimens that were investigated are provided in Appendix 1.



a

Dr. C. H. A. WESTHOFF.

Amsterdam, 2 3 1900

Amice!

Nevensgaande catalogus heb ik van de geneesmiddelen. Enkele ontbreken. Ik was op reis en kon niet eerder antwoorden.

Ik schat de waarde van ieder flesje op 25 cent maar wil u de geheele boel voor f 75.- vijf en zeventig gulden geven.

Maandag vertrek ik.

Uw genegen Carl Westhoff

Nicolaas Witsen

b

23 Maart is te Sidney overleden Dr. C. H. A. Westhoff, oogarts, geneesheer-directeur van het Wilhelmina-Gasthuis te Bandoeng, commandeur in de Huisorde van Oranje. Geb. in 1848, werd hij in 1870 tot arts bevorderd en prom. hij het volgend jaar. Als officier van gez. in Indië geplaatst, verliet hij spoedig den mil. dienst en vestigde zich als geneesheer te Batavia; 12 jaar later keerde hij naar Europa terug, en werd hij praktiseerend oogarts te Amsterdam; aanvang 1900 ging hij weer naar de tropen, en, begaan met het lot der blinden, stichtte hij het Blinden-instituut te Bandoeng, waarvan hij tot zijn dood voorzitter was.

1913

Dr. C. H. A. Westhoff. †

Figure 2.2 Documents related to the Westhoff collection. (a) Letter by Westhoff (1900) on the transaction of the collection to Witsen. Source: Utrecht University Museum (b) A brief biography of Dr. C. H A Westhoff. Source: Collectie Veenhuijzen, Centraal Bureau voor Genealogie, the Hague.

Table 2.1 Specimens in the Westhoff collections and overlap with the Chinese Pharmacopeia 2015.

Westhoff Collection Statistics					
Total amount specimen	395				
Categories		ChP 2015		Classifications	
Single component drug	387	Record	293	Plant *, **	316
Multiple component drug	8	Not record	102	Animal *	36
				Mineral *	34
				Other	9

*, and related substances; **, seaweeds and fungi are included

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* Reinw. ex Blume (pharmaceutical name Caulis et Folium Sambuci Chinensis), is primarily produced in southern China and Taiwan. While it is called *mao gu xiao* (有骨消) 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* (有骨梢, INV. 0285-128602, Figure 2.1a), is similar to the Taiwanese name for Sambucus chinensis. The name *qian mu tong* (钱木通, INV. 0285-133716, Figure 2.1b) 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 (Figure 2.1c), 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* (Figure 2.1d), 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.

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* × *reticulata* Blanco (INV. 0285-129297, Figure 2.3a).

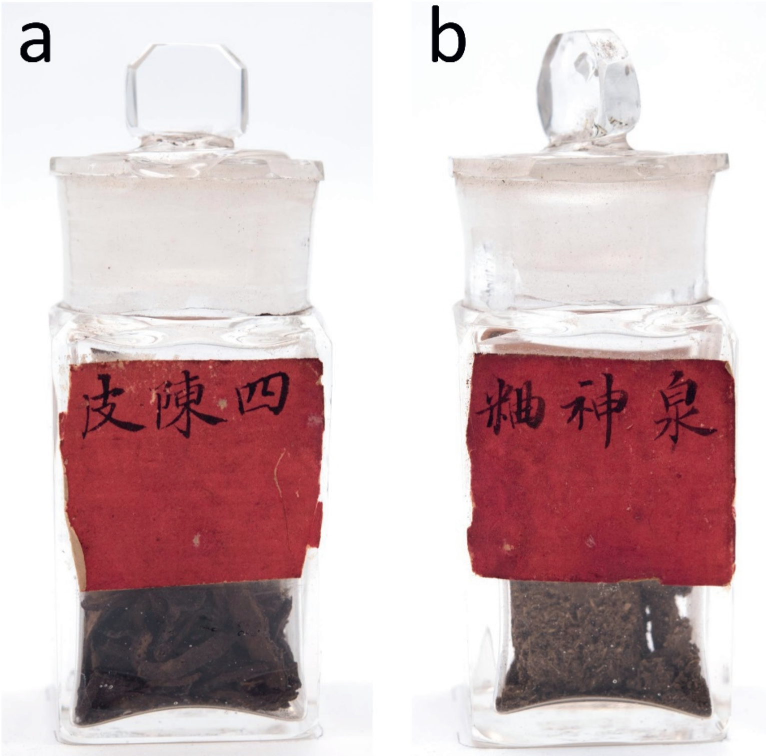


Figure 2.3 (a) *si chen pi* (四陈皮, INV. 0285-129297, pericarp of *Citrus X reticulata* Blanco and its different cultivars) and (b) *quan shen qu* (泉神粬, INV. 0285-133668, Massa Medicata Fermentata).

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 (Figure. 2.4). *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, Figure 2.3b), in which *quan* refers to Quanzhou, a port city in the Fujian Province (Figure 2.4). 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).

Figure 2.4 Map of East Asia showing the geographical locations relevant to the Westhoff collection.

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, Figure 2.5a), 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, Figure 2.5b) 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).

Figure 2.5 (a) *jin suo shi* (金锁匙, INV. 0285-128620, *Striga asiatica* (L.) Kuntze) and the materials from the corresponding bottle. (b) *yi zhi xiang* (一枝香, INV. 0285-129288, *Gerbera piloselloides* (L.) Cass.) and the materials from the corresponding bottle.

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 (Na_2SO_4). Scrophulariae Radix is the dried root of *Scrophularia ningpoensis* Hemsl. and its Chinese name is *xuan shen* (玄参) (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* (元) (Table 2.2 and Figure 2.6). 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.

Table 2.2 Historical changes in vernacular names for Natrii Sulfas Exsiccatus and Scrophulariae Radix.

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

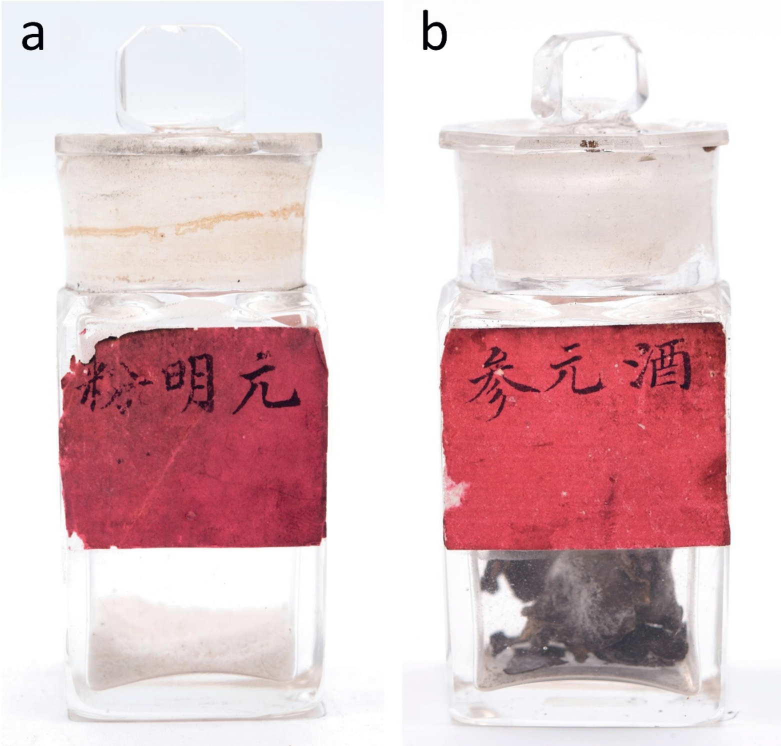


Figure 2.6 (a) *yuan ming fen* (元明粉, INV. 0285-133907, Natrii Sulfas Exsiccatus). (b) *jiu yuan shen* (酒元参, INV. 0285-133774, Scrophulariae Radix, root of *Scrophularia ningpoensis* Hemsl.).

6. Changes in plant parts

In the Westhoff collection, the medicinal plant parts of some products differ from the specification in the modern Chinese pharmacopeia. 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, Figure 2.7a) included only seeds, while the fruit itself had been removed (Figure 2.7b). According to ancient medical monographs, various parts of the *Aristolochia* fruit were used: seeds, fruit without 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 are not obtusely triangular or fan-shaped like the seeds of the official species *A. contorta and A. debilis* (Figure 2.7c and d). 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, Figure 2.8a) 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, Figure 2.8b) 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 (Figure 2.8c).

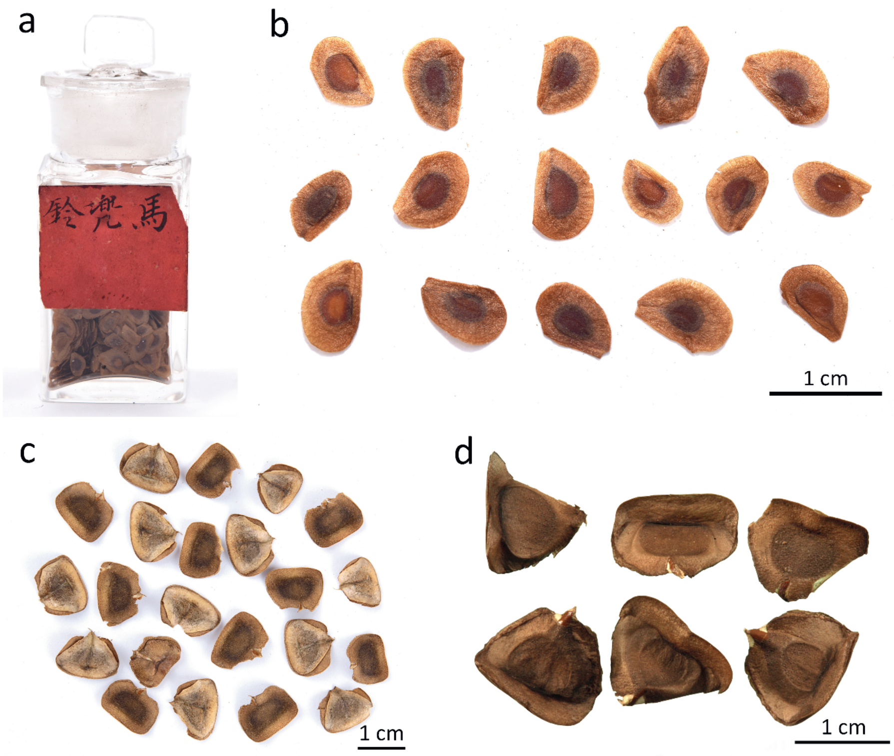


Figure 2.7 (a) *ma dou ling* (马兜铃, INV. 0285-133755). (b) The seeds (*Aristolochia* sp.) from the corresponding bottle. (c) The reference specimen of *Aristolochia contorta* from CDFDC. (d) The reference specimen of *A. debilis* from CDFDC.

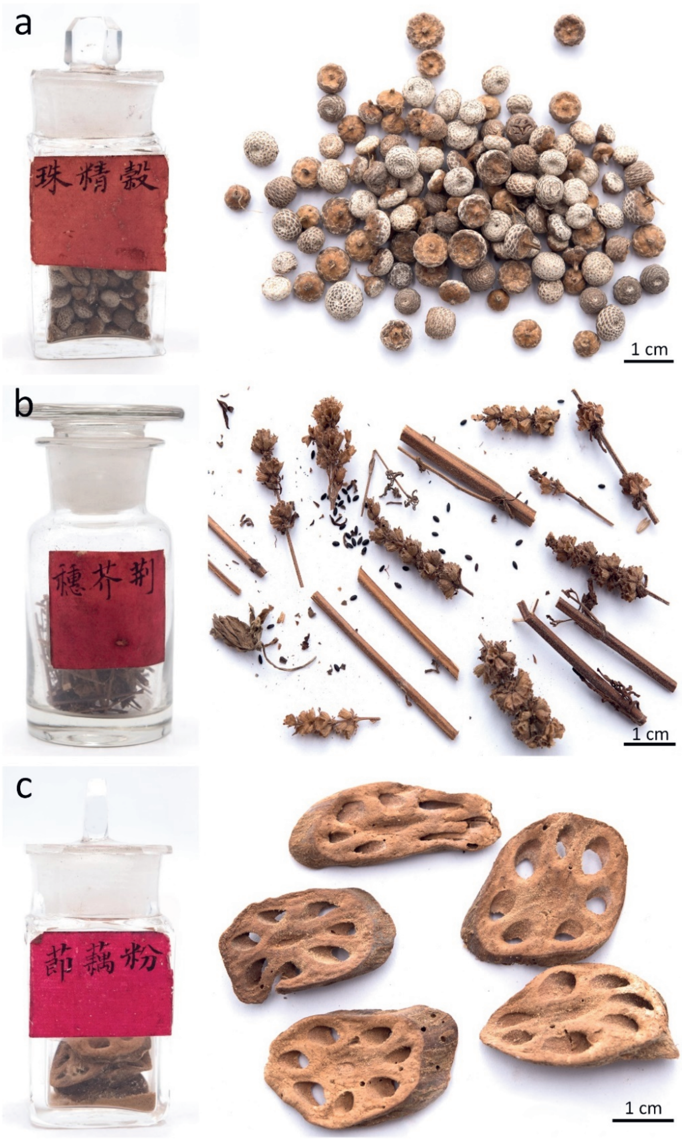


Figure 2.8 (a) *gu jing zhu* (谷精珠, INV. 0285-129301, Eriocauli Flos, capitulum of *Eriocaulon sexangulare* L.) and the materials from the corresponding bottle. (b) *jing jie sui* (荆芥穗, IVN. 0285-129295, Schizonepetae Spica, spike of *Schizonepeta tenuifolia* Briq.) and the materials from the corresponding bottle. (c) *fen ou jie* (粉藕节, IVN. 0285-133884, Nelumbinis Rhizomatis Nodus, node of *Nelumbo nucifera* Gaertn.) and the materials from the corresponding bottle.

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* (Figure 2.3b). 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, Figure 2.9a), 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* (Figure 2.9b 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 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 evidence that the collector was aware of the properties of the seeds of the two species.

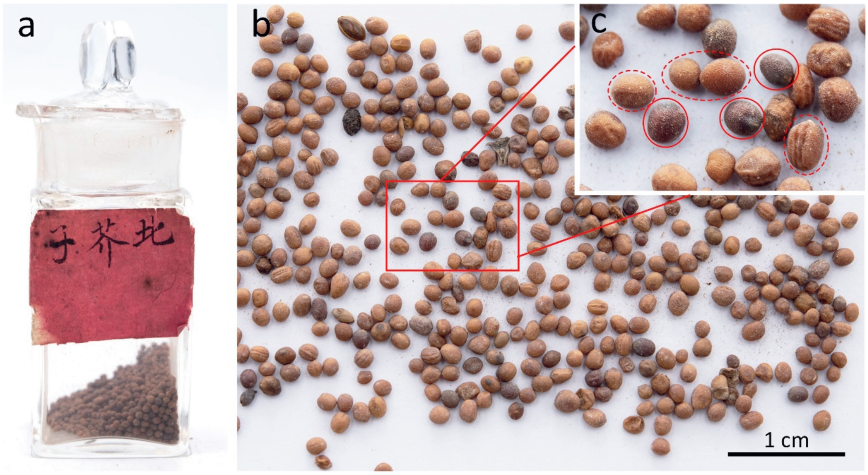


Figure 2.9 (a) *bei jie zi* (北芥子, INV. 0285-133878). (b) the contents. (c) Enlargement of (b). The dashed circles indicate the seeds of *Brassica juncea*, the solid circles indicate the seeds of *Sinapis alba*.

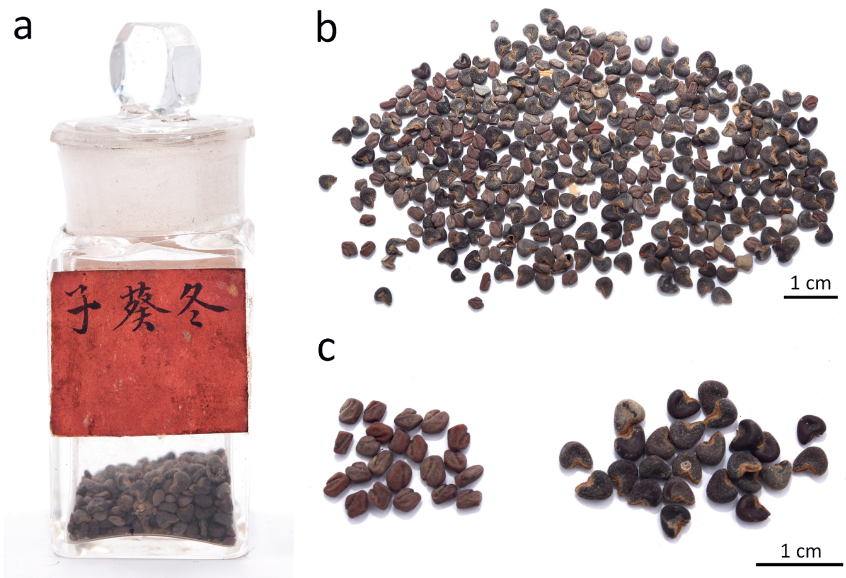


Figure 2.10 (a) *dong kui zi* (冬葵子, INV. 0285-133747). (b) The contents (c) Left are seeds of *Trigonella foenum-graecum*; right are seeds of *Abutilon theophrasti*.

The label *dong kui zi* (冬葵子, INV. 0285-133747, Figure 2.10) 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, Figure 2.10c). 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 (Figure 2.10b 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.

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* (茺蔚子, INV. 0285-129273) refers to the ripe fruit of *Leonurus japonicus* Houtt (Figure 2.11a-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 (Figure 2.11c), 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 (Figure 2.11). Comparison with specimens from CDFDC revealed that the seeds with the strongly dented edge were *Astragalus sinicus* L. (Figure 2.11f, 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* (Figure 2.11f, indicated by solid circle). Therefore, the specimen *sha yuan zi* in the Westhoff collection was both misidentified and adulterated at the same time.

Figure 2.11 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) microscope enlargement of h.

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. (Figure 2.11g-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 a microscope showed that they are oval-shaped with a short axis of ca. 100-300 µm (Figure 2.11i). 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.

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; 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 labeled 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 (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 2.3). 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).

Table 2.3 Processed medicine from *Aconitum carmichaelii* and preparation methods.

INV.	Label name (pinyin name)	Pharmaceutical name	Scientific name	Medicinal part	Processing method
0285-133685	制川乌 (*zhi chuan wu*)	Aconiti radix	*Aconitum carmichaelii* Debeaux	Main root	Macerated in water until there is no more dry core, then taken out, boiled in water or boiled with other adjuvants (ginger, alumen and/or etc.)
0285-133704	川明附 (*chuan ming fu*)	Aconiti lateralis radix praeparata	*Aconitum carmichaelii* Debeaux	Lateral root	Clean, soak in edible mother solution of mineral salts, boil thoroughly, peel the skin, cut into slices, rinse in water, steam thoroughly and sun-dry
0285-133863	焙附子 (*bei fu zi*)	Aconiti lateralis radix praeparata	*Aconitum carmichaelii* Debeaux	Lateral root	Clean, soak in edible mother solution of mineral salts, boil thoroughly, peel the skin, cut into slices, rinse in water, steam thoroughly, sun-dry and stir-frying with sand

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 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 TCM 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.

Conflict of interest:

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

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Appendix A. Supplement data:

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Chapter Three

The catalogue of the Westhoff Collection of Chinese *materia medica* (c. 1870): evidence of interaction between a Chinese medicine practitioner and the Dutch in Indonesia

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Abstract

Ethnopharmacological relevance: The Westhoff collection of Chinese *materia medica* (c. 1870) at the Utrecht University Museum in Utrecht, the Netherlands, contains an original, handwritten catalogue, which was putatively ascribed to a Chinese medicine practitioner. It provides a detailed record of the Chinese names, plant parts, preparations, and applications of the specimens contained in glass bottles, which probably reflects the physician's personal interpretation of Chinese medicine in Indonesia at the end of the 19th century. Such individual catalogues can reveal historical changes and regional variations in the use of traditional Chinese medicine, which can lead to a better understanding of the history and development of this field.

Aim of the study: We addressed the following questions: 1) What are the contents of the Westhoff catalogue? 2) What medicinal preparations and applications were recorded in the catalogue, and which ones are dominant? 3) How similar is the use of Chinese *materia medica* in Westhoff catalogue compared to the modern Chinese Pharmacopeia? 4) What other specific information is contained in the Westhoff catalogue?

Materials and methods: The catalogue had been digitized previously, and all handwritten Dutch text has been transcribed and translated into English. The information for each entry was summarized and analysed, the medicinal applications were compared to modern Chinese pharmacopeia or other monographs on Chinese *materia medica*.

Results: The catalogue contains 436 entries, for which 395 corresponding specimens still exist in the Westhoff collection of Chinese *materia medica*. Each entry contains a serial number, a Chinese name, a phonetic Dutch transcription of the Chinese name, a description of the plant, animal, or mineral origin of the medicinal product, the preparation method, and the medical indication for which it should be used. The dominant preparation method is decoction (79% of the entries). The most frequently mentioned applications are fever, skin diseases, strengthening and wounds. Around 80% of the medicinal applications in the catalogue were also listed for the same CMM in modern monographs. The catalogue also sheds light on typical characteristics of popular medicine, their geographic origin, and social aspects of traditional Chinese medicine in Indonesia around 1870.

Conclusion: The Westhoff catalogue is a valuable record of Chinese *materia medica* and its practice in a specific time and space. It reflects an individual physician's interpretation of Chinese medicine, shows the difficulties in the interpretation of cultural-bound health issues between the Dutch and the Chinese, and provides evidence that traditional Chinese medicine spread not only in East Asia but also to the distant Western world.

Abbreviations: CMM, Chinese *materia medica*; TCM, traditional Chinese medicine; ChP 2015, Chinese Pharmacopoeia 2015 edition.

Introduction

Traditional Chinese medicine (TCM) has a long history, with thousands of years of practice, experimentation and adaptation. Although most of these ancient practices are continued nowadays, Chinese *materia medica* (CMM), including product names, natural ingredients, processing methods and clinical applications have also changed over time (Brand et al., 2017; Jia et al., 2021; Jia et al., 2022; Zhao, Z. et al., 2006). A tremendous body of TCM treatises has been compiled in the past centuries, which not only recorded the medicinal materials' taxonomical identity, the place of origin but the methods of collection, processing, preservation and identification (Teng, 2019). One of the earliest monographs, the *Divine Husbandman's classic of materia medica* (Eastern Han Dynasty, 25-220 AD) contains 365 product names, their geographical origins, processing, preservation and identification methods. The *Collective commentaries on the classic of materia medica* (Tao Hongjing, c. 500 AD), recorded 730 medicinal products, established the concept of using the same medicine to treat varieties of diseases, and introduced more than 80 interchangeable *materia medica* (Teng, 2019). The *Newly revised materia medica* (Su Jing et al., 659 AD) was the first monograph to include illustrations, which were extremely important to identify the biological origin of the *materia medica*. These monographs were meant to be comprehensive, containing as much information as possible at that time, which meant that compiling these classic works was labor intensive and time-consuming. For instance, the *Newly revised materia medica* was written and revised by 23 persons and depended on the administrative power of the Tang dynasty (618-907 AD). Li Shizhen, the author of *Compendium of materia medica* (1578 AD), had read more than 800 medicinal books and spent 27 years compiling his monograph (Teng, 2019). With such a large body of documented knowledge, it is almost impossible for physicians who practice traditional Chinese medicine to precisely follow all the information and instructions provided in these monographs when making diagnoses and prescriptions. In addition, in various geographic regions, the use of Chinese *materia medica* is also influenced by the type of plants, animals and minerals that can be collected or grown locally. Therefore, there can be a gap between a physician's interpretation of TCM and the information in the professional monographs. Being aware of physician's personal interpretations of Chinese medicine in the past can help us discern the changes and developments over time with regard to ingredients, processing and application of Chinese medicine. However, there are few historical sources that reflect physicians' personal interpretations and viewpoints about Chinese *materia medica* and its application.

A unique, well-preserved historical collection of Chinese *materia medica* is housed at the Utrecht University Museum in Utrecht, the Netherlands. Almost 400 specimens of CMM are contained in this valuable collection, assumed to have been purchased by the Dutch ophthalmologist Dr. C.H.A Westhoff in Indonesia in c. 1870 and brought to the Netherlands in 1882. The botanical identity, Chinese nomenclature, plant parts, and processing methods of all specimens in this collection were studied previously and provided new insights into historic changes and local adaptations in Chinese medicine (Jia et al., 2021).

Along with the historic specimens, the Westhoff collection contains a handwritten catalogue that mentions not only the specimens' Chinese names but also their natural origin, the medicinal parts, preparation methods and medicinal applications. Over 400 entries in this document, written in Dutch, with detailed descriptions of each CMM product, indicate that this information may have been sourced from a local TCM physician or pharmacist. In other words, this handwritten catalogue may reflect an individual physician's interpretation of Chinese medicine and can provide unique information about the practices of TCM around 1870 in Indonesia.

By transcribing and translating this handwritten document, we aimed to identify the similarities and differences in the use of Chinese *materia medica* between this individual physician and modern Chinese pharmacopeia. We addressed the following questions:

1. What are the contents of the Westhoff catalogue?
2. What medicinal preparation methods and applications were recorded in the catalogue, and which ones are dominant?
3. How similar is the use of Chinese *materia medica* in the Westhoff catalogue compared to the modern Chinese Pharmacopeia and recent CMM treatises?
4. What other specific information is contained in the Westhoff catalogue?

Based on the medicinal applications in the Westhoff catalogue, we expected to detect historical changes and regional variation in CMM use. By analysing the patterns and frequency of the health issues mentioned in this handwritten source, we speculated on TCM practice in Indonesia in the late 19th century. We hope that our analysis gives more insight into the historical use of Chinese *materia medica* and the changes and variations that have occurred over time and space. Furthermore, the information obtained can be utilized to validate the modern Chinese medicine practice.

Materials and methods

The Westhoff catalogue is preserved as a handwritten table on paper, kept together with the boxes of Chinese *materia medica* in glass bottles by the Utrecht University Museum in Utrecht, the Netherlands. The catalogue had been digitized earlier by the museum, and TIFF images of partially separate records had previously been added to photographs of the corresponding CMM specimens in glass bottles in a digitized document.

The Dutch handwritten texts were transcribed into a spreadsheet and subsequently translated into English, as literally as possible. The Dutch phonetic transcription of the Chinese name of the material objects was transcribed, and the Chinese characters were typed. The identification of the botanical, animal, and mineral ingredients was already carried out during our previous study of this collection (Jia et al., 2021).

We compared the style and features of Dr. Westhoff's handwriting in the transaction letter of the CMM collection, reported in our previous study (Jia et al., 2021) with the catalogue of this collection. We compared the diseases recorded in the handwritten catalogue with those mentioned for the same CMM ingredients referenced in the 2015 edition of the Chinese Pharmacopoeia (ChP 2015) (Chinese Pharmacopoeia Commission, 2015). For those medicinal products in the Westhoff collection that were not included in the ChP 2015, we searched for corresponding indications in other CMM monographs (World Health Organization, 2007; Zhao, G. et al., 2006; Zhonghua Bencao Edit Committee, 1999). In order to evaluate the correspondence with contemporary uses of the medicinal indication in Westhoff catalogue, defined as the correspondence with the ChP 2015, we have established the following criteria: 1) the indications in Westhoff catalogue match completely or partially with at least one of the indications in the ChP 2015 or other modern works on TCM; 2) the words used to describe the indications in the catalogue are different, but the meaning of indications appears the same.

The complete transcriptions and translation of the handwritten catalogue are listed in Appendix 1, with scientific names, natural origins and product identifications, preparations and applications. For the current scientific names of plant products, we followed the Plants of the World Online (https://powo.science.kew.org/), and for animals the Global Biodiversity Information Facility (https://www.gbif.org/).

Results and discussion

1. General description of the handwritten catalogue of the Westhoff collection

The entire catalogue of the Westhoff collection comprises 436 entries for separate CMM specimens. Each entry contained abundant information in a fixed format. Figure 3.1 shows one entry selected from the handwritten catalogue, along with its transcription and English translation. The entry begins with a serial number (which is not present on the label of the glass bottle with the corresponding specimen), followed by the Chinese name of the *materia medica* represented by the specimen, the Dutch phonetic transcription of the Chinese name, a note whether the specimen belongs to the plant kingdom, the animal kingdom or whether it is a mineral, and type of plant, animal or mineral that produces the drug. The last part of the entry is the drug's medicinal use, which starts with its medicinal part, followed by the preparation method and indication or disease(s) for which it is used. In Appendix 1, we listed the serial numbers, the Chinese names, scientific names, pharmaceutical names, mineral or biological origins, the translated preparation methods and medical applications, and whether these are similar or different from the Chinese Pharmacopoeia 2015 edition or other published CMM monographs (Zhao, G. et al., 2006; Zhonghua Bencao Edit Committee, 1999).

It is worth noting that the Dutch transcription of the Chinese names for the *materia medica* is based on the Cantonese or Minnan pronunciation. This suggests that either the Westhoff collection or the Chinese physician who compiled this catalogue originated from southeast China, which is consistent with our previous conclusion (Jia et al., 2021).

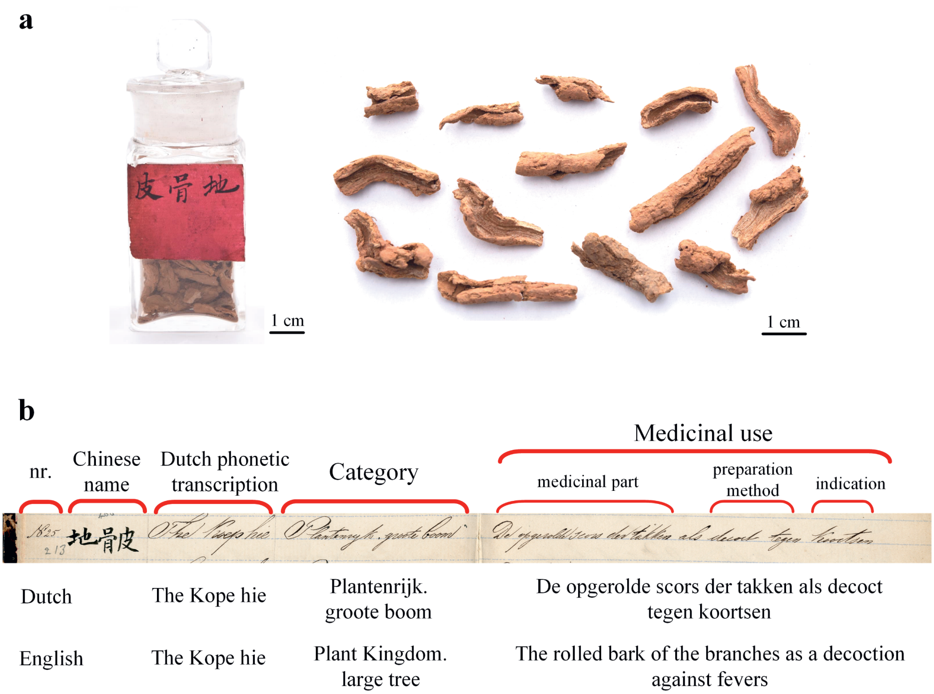


Figure 3.1 Specimen (a) and entry (b) of *Lycium chinense* Mill. in the Westhoff collection. The Dutch transcription and English translation are attached to the entry.

The handwritten catalogue consists of a total of 436 entries. The Westhoff CMM collection contains 395 specimens preserved in glass bottles, suggesting that 41 CMM specimens are no longer retained in the collection. Some of these CMM specimens were separated from the collection in the past due to damage to the glass bottles, but the remaining specimens were lost over the course of c. 150 years.

2. Medicinal preparation methods

All entries were analyzed for their preparation methods (Figure 3.2). The majority of the entries, which accounts for approximately 79% (346 out of 436), mention that the material should be taken in the form of a decoction. In the clinical practices of traditional Chinese medicine today, the practitioner usually prescribes multiple herbs to combine into one formula, instead of a single-species medicine (Jia et al., 2004; Qiu, 2007). Decoction of multiple herbs based on TCM formulae is the most important and most commonly used method, and more than 100,000 TCM formulae have been accumulated over the past 2000 years (Qiu, 2007).

Topical application was the second most frequent preparation method, with 46 entries (11%), most drugs were used in powdered form for open wounds and skin diseases (e.g., scabies, sore or itchy skin), such as Realgar (main component As_2S_2, entry nr. 218). Powdered medicinal material was sprinkled on infected parts (e.g., Haematitum, main component Fe_2O_3, nr. 415) or blown on the body part, in the case of the powder prepared from the leaf or stem of *Baphicacanthus cusia* (Nees) Bremek. or *Polygonum tinctorium* Ait or *Isatis tinctoria* L. (entry nr. 427). Powdered Calamina (main component $ZnCO_3$, nr. 429) was dissolved in water as an eyewash solution or eyedrops against eye disease. Only a few drugs were inhaled through the nose, such as the powdered fruit of *Gleditsia sinensis* Lam. (nr. 392) and the powdered flower of *Rhododendron molle* G.Don (nr. 400).

In the Westhoff catalogue, infusions were not often mentioned, comprising only 20 entries (approximately 5%) (Figure 3.2). Exceptions were the fruits of *Illicium verum* Hook.f. (nr. 96) and fruit of *Foeniculum vulgare* Mill. (nr. 97), used to treat testicular pain. The infusions above are all recorded in modern CMM monographs (ChP 2015, Zhao, G. et al., 2006; Zhonghua Bencao Edit Committee, 1999).

A total of 24 entries (approximately 5%) mentioned more than one application method, such as the intake of a decoction and a topical application, direct oral intake, fumigation or lacked specific preparation methods (Figure 3.2).

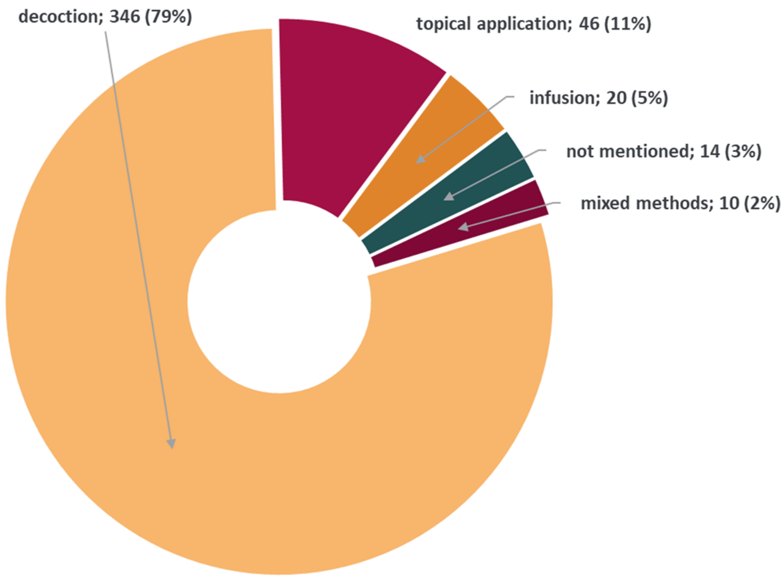


Figure 3.2 Proportion of preparation methods mentioned in the 436 entries in the handwritten catalogue of the Westhoff collection.

3. Medical applications

A valuable aspect of the Westhoff catalogue is that for each drug the medical indications and health issues are documented in detail. Most of the entries (79%) in the catalogue mention only one medical indication, and there are only a few multi-purpose medicines (Table 3.1).

Table 3.1 Versatility of medical applications per CMM entry in the Westhoff catalogue.

Number of health issues mentioned in each entry	Number of entries
1	343
2	79
3	7
4	1
not mentioned	6
Total number of entries	436

Among the 436 entries, there were a total of 526 mentions of diseases or health conditions. Fever was the most predominant indication of all drugs, with 49 entries recorded as appropriate medicines for fever treatment (Figure 3.3). These entries do not represent 49 taxonomically different CMM objects; the bark of *Phellodendron chinense* C.K.Schneid. was processed with salt in entry nr. 137, while the same bark was carbonized in entry nr. 292. From the perspective of TCM, these two are different drugs, as the processing method is not the same.

Fever is a common symptom of many diseases, such as parasitical, bacterial and viral infections, as well as neurologic injury and immune-mediated processes (Hines, 2021). Fever as a disease instead of a symptom has been documented from the beginning of recorded history (Moltz, 1993). Among the medicines listed in the Westhoff catalogue, 49 are documented as having fever-treating properties based on the handwritten records, while contemporary CMM treatises note that 53 of them possess properties that relieve fever. (ChP 2015; Zhao, G. et al., 2006; Zhonghua Bencao Edit Committee, 1999). This indicates that fever, either as a disease or symptom, has always been a major health concern addressed by traditional Chinese medicine, whether it was in the 19th century or now.

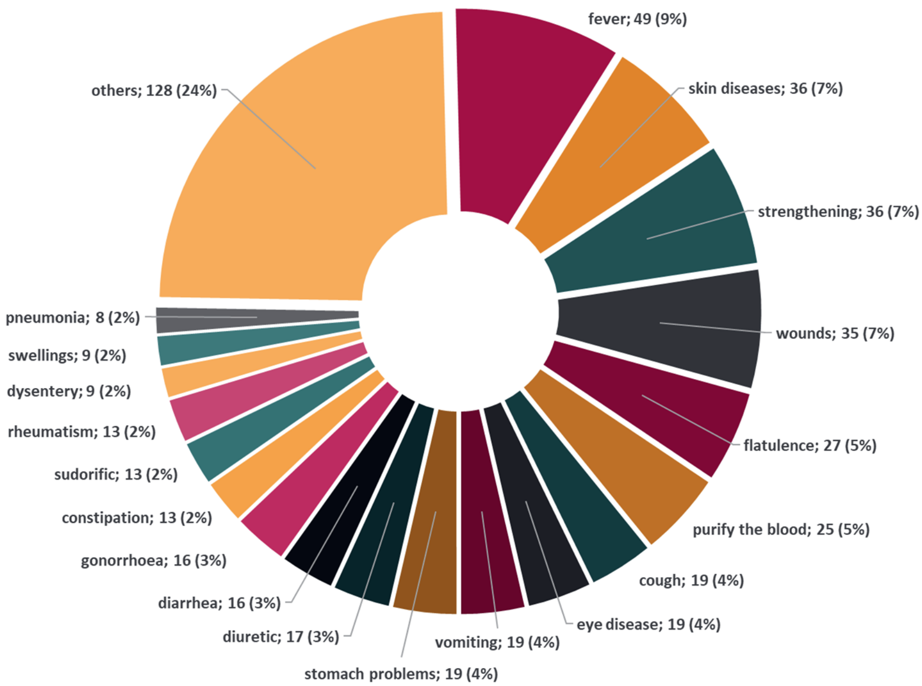


Figure 3.3 Proportion of corresponding medical indications according to the 436 entries in the Westhoff catalogue.

Indications related to skin diseases appeared 36 times in the catalogue. As one of the most common human illnesses (Hay et al., 2014), it is not surprising that skin diseases also occupy an important place in the catalogue of the Westhoff collection. Strengthening, another regular application in the catalogue, is not a frequently used health issue in Western medicine. In traditional Chinese medicine, however, strengthening is a fully recognized term. TCM aims to correct maladjustments and restore the self-regulatory ability of the body, and not solely to antagonize specific pathogenetic targets (Jiang, 2005). So *materia medica* applied within TCM is not only used to inhibit or kill pathogens but also to improve and enhance the body's resilience to adapt to environmental changes and prevent pathogen attacks. This theory is reflected in the catalogue of the Westhoff collection, which merely uses the word strengthening rather than specific symptoms.

The indication of flatulence is also repeatedly referenced, a medical condition characterized by excessive accumulation of air or gas in the stomach or intestines (Price et al., 1988). The corresponding Dutch words in the Westhoff catalogue are "winden" and "winderigheid", both of which have the meaning of flatulence. Meanwhile, "winden" also means "winds", which refers to the natural movement of the air. When comparing the 27 drugs recorded as against flatulence to their medical use in modern CMM books, none of them has the effect of treating flatulence. Instead, 24 of 27 drugs have the ability to dispel "wind" and/or to move "*qi*".

"Wind" in traditional Chinese medicine is an abstract concept of a disease pattern or pathogen. The ancient Chinese observed six different environmental conditions: wind, cold, summer heat, dampness, dryness and fire. When these environmental conditions cause sickness, they refer to six excesses or six climatic pathogenic factors (Wiseman and Ellis, 1996; World Health Organization, 2007). "Wind" as a pathogenic factor can be distinguished as external and internal wind. External wind causes disorders by the meteorologic phenomenon of wind entering the body, resulting in fever, aversion to wind, headache and facial paralysis. Internal wind arises from within the body, for instance, extreme heat engendering wind, which manifests in reversal and convulsion in the limbs (Wiseman and Ellis, 1996; Xie, 2003). The Chinese term "*qi*" can be literally translated as air or gas. The ancient Chinese believed that "*qi*" was the basic element that constituted the cosmos and, through its movements, changes and transformations, and produced everything in the world, including the human body and life activities. In the context of traditional Chinese medicine, "*qi*" refers both to the refined nutritive substance that flows within the human body and to its functional activities (Wiseman and Ellis, 1996; World Health Organization, 2007). "*Qi*" flows smoothly through the whole body under normal circumstances, but if its dynamic is disturbed, the result is a disorder known as "*qi*" stagnation. This is when medication with "*qi* moving effect" is given to restore the balance of the body.

By comparing the medicinal actions and indications in the Westhoff catalogue with the corresponding information in modern CMM treaties, it seems that there has been a misinterpretation by the Dutch author, who confused the physical meaning of gas or air with the traditional Chinese medicine concepts of "*qi*" and "wind". It is also possible that the Chinese doctor has tried to translate the term "*qi*" and "wind" to the Dutch author, but failed to convey the complexity of the concept.

The catalogue mentions recipes to "purify the blood" a total of 25 times. Possibly, the name of the medical indication that needed the blood to be purified was simplified or its connotation was lost during the translation by the author of the catalogue. Most herbal drugs (24 out of 25 entries) prescribed to purify the blood are said to have the ability of promoting blood circulation and removing blood stasis properties, as well as relieve (arthralgic) pain, regulate menstruation, heal wounds and relieve swelling (ChP 2015; Zhonghua Bencao Edit Committee, 1999). Nowadays, some of these ingredients are classified as blood-invigorating and stasis-dissolving medicines in traditional Chinese medicine (Teng, 2019). The need to purify the blood is also a frequently occurring concept in other traditional health care systems. Recipes to clean the blood are mentioned in historical documents from Sri Lanka (van Andel et al., 2018), and are still popular in African and the Caribbean (van Andel et al., 2012).

We have also observed that eye diseases are mentioned 19 times in the catalogue. Could it be that because Dr. Westhoff was an ophthalmologist, he was familiar with and interested in diseases related to eye? While the indications and efficacies of several ingredients include both oculopathy but also other diseases, the catalogue focused on the use for eye disease rather than for other medical applications, even if these were known at the time. For example, the fruits of *Leonurus japonicus* Houtt. (nr. 107) are prescribed for red eyes and nebula, but have also been used since the 2nd century AD for menstrual irregularities, dizziness, headache, and distention in the head (ChP 2015; Zhonghua Bencao Edit Committee, 1999), while these ailments are not mentioned in the catalogue. Additionally, the catalogue gives more details about some of eye diseases. For instance, a decoction of the seeds of *Celosia argentea* L. (nr. 101) is prescribed "against eye disease, especially when there is a veil in front of the iris" and the powder of the abalone shell (*Haliotis* sp., nr. 103) is stated as a remedy "against eye disease, especially when eyesight is weakened by age". The typical focus on eye diseases seems to indicate that the Chinese practitioner was aware of Westhoff's specialization and emphasized herbal remedies for eye diseases or that Westhoff specifically asked for such recipes.

4. Consistency between the catalogue and modern Chinese pharmacopeias

As we hypothesized before (Jia et al., 2021), the Westhoff collection and the associated catalogue seem to be compiled based on the knowledge and experiences of a TCM physician or merchant in Chinese medicine in Indonesia during the latter half of the 19th century. To what extent did the diseases and medical applications mentioned in the catalogue match the official Chinese Pharmacopeia or other classical works on Chinese *materia medica*?

The late 19th century Dutch terminology of diseases and health conditions differed substantially from the descriptions in the ChP 2015. However, many of the symptoms, diseases and applications mentioned in the catalogue had a similar meaning, even if using different words and expressions. The majority of the medicinal indications (339, accounting for 78%) in the catalogue matched with at least one of the definitions of symptoms and medicinal applications in the modern TCM literature (Figure 3.4). Considering that the knowledge documented in the catalogue could have come from a TCM physician or a Chinese medicine merchant, such a high similarity rate suggests that this person was very knowledgeable on both the ingredients and the application of traditional Chinese medicine.

A small proportion (53, accounting for 12%) of the medicinal indications did not match with any of the applications for the same drug mentioned in the pharmacopeias. We assume that the few inconsistencies between the catalogue records and the Chinese pharmacopeias were either caused by mistranslations from Chinese to Dutch or by regional differences in medicinal practices or personal preferences of the Chinese doctor by whom the collection of *materia medica* was compiled. This 12% does not exclude mismatches due to misunderstanding of the abstract TCM concepts.

Six of the 18 unidentified drugs were multi-component mixtures, whose indications could not be determined without further information on the CMM ingredients and therefore consistency with pharmacopeias could not be established.

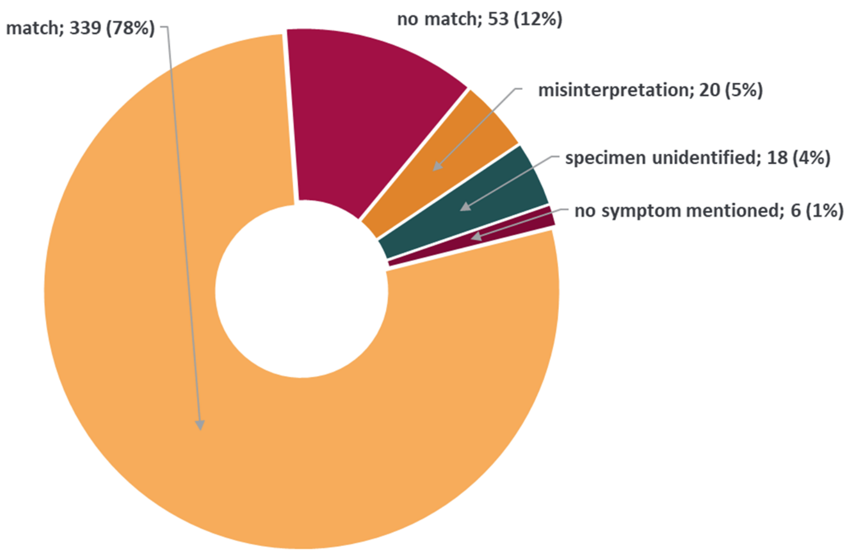


Figure 3.4 Consistency of medicinal application between the Westhoff catalogue and the modern Chinese pharmacopeia for identical natural ingredients.

5. Information beyond the medicinal actions and indications

The information contained in the catalogue of the Westhoff collection is not limited to ingredients, preparation methods and diseases, but also sheds light on typical characteristics of popular medicine, their geographic origin and social aspects. We illustrate this with such examples as licorice, ginseng and several mineral substances.

Licorice root, a drug with the pharmaceutical name Glycyrrhizae Radix et Rhizoma, is used for three different species: *Glycyrrhiza uralensis* Fisch. ex DC., *G. inflata* Batalin and *G. glabra* L. (ChP 2015). Licorice root is the most frequently-used herbal product in China. In the catalogue of the Westhoff collection, licorice root was mentioned in three different entries (nrs. 112, 205 and 237) that differed in processing methods and application (Figure 3.5).

Entry nr. 112 粉甘草 (fen gan cao) mentioned the removal of the bark of the licorice root. In this entry, no medicinal use or symptom is mentioned. The recipe just says it should be mixed with other herbal ingredients to alter its taste. Additionally, apart from acting as a flavoring agent, licorice root also possesses the ability to harmonize the actions of the other ingredients in traditional Chinese medicine theory (Jia et al., 2004). Modern research has demonstrated its effectiveness in enhancing the efficacy of other ingredients or reducing their toxicity (Wang et al., 2013). Just like in the Westhoff catalogue, historical TCM formulae also use debarked licorice roots (e.g., formula from *Complete works of jing yue* by Zhang Jiebin in c. 1640 AD).

One of the important characteristics of licorice root is described in a general and precise manner in the catalogue. Entry nr. 205 甘草梢 (gan cao shao) refers to licorice root tips and twigs of the plant, while entry nr. 237 甘草粉 (gan cao fen) describes powdered licorice root. Both recipes and their indications match exactly with the information in the modern Chinese pharmacopeias, which indicates the correspondence with contemporary uses of this catalogue. The specific species of licorice root, however, does not become clear from the catalogue. *G. glabra* is native to both China and Europe, while *G. uralensis* and *G. inflata* can be found in China but not in Europe (https://powo.science.kew.org). According to Xie (2008), *G. uralensis* is the authentic species of licorice root in TCM since the 2nd century BC, but *G. inflata* and *G. glabra* (known as European licorice in Chinese) have been increasingly used in the past 30 years due to the shortage of *G. uralensis*.

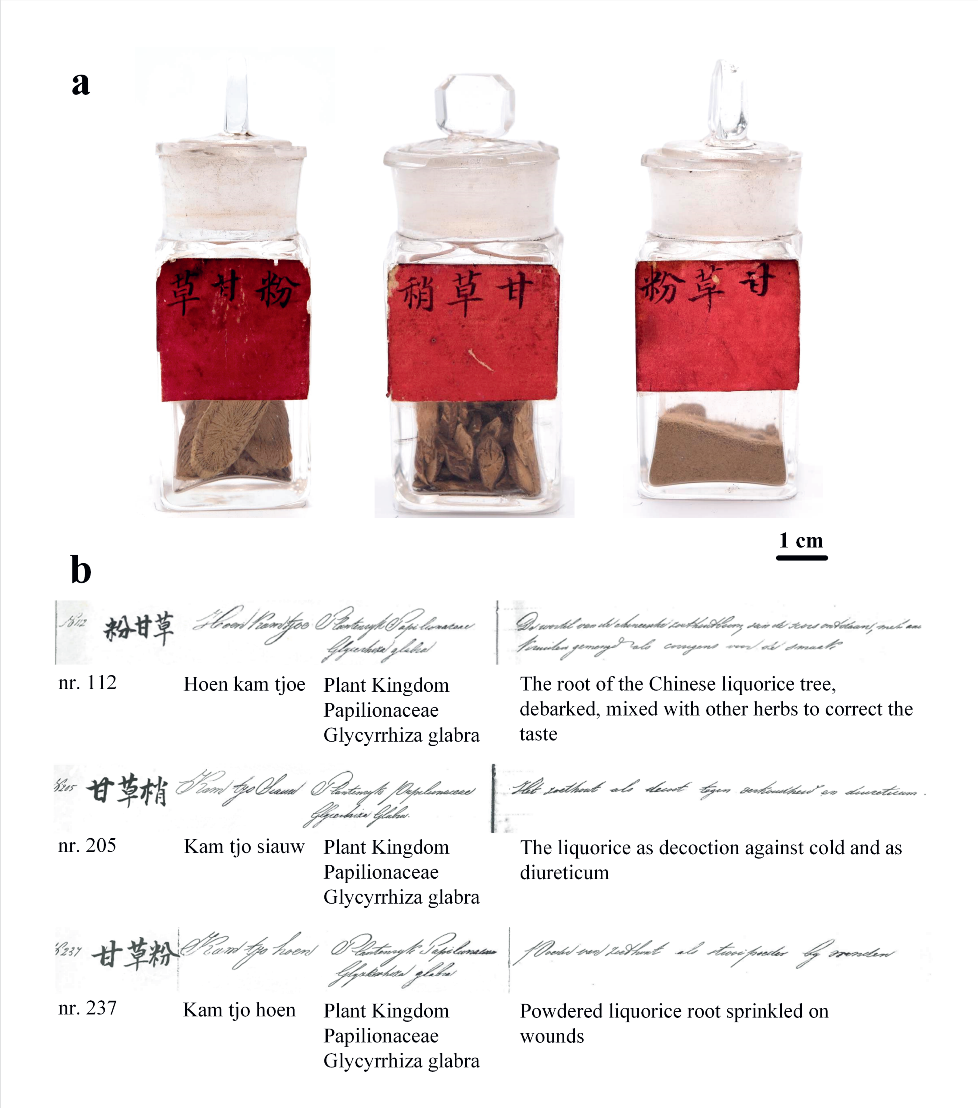
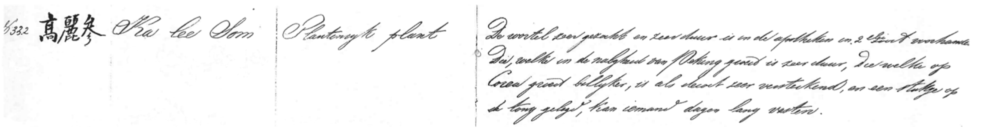


Figure 3.5 The specimens (a) and entries (b) on licorice root in the Westhoff collection, with their English translations. (a) from left to right: the debarked root, root tips and powdered root, with their corresponding entries (b), from top to bottom.

Ginseng root (*Panax ginseng* C.A.Mey.) is one of the most popular Chinese *materia medica* worldwide (Ernst, 2002; Xu et al., 2017). In the catalogue of the Westhoff collection, extra information is devoted to it (Figure 3.6). The entry gives a vivid description to illustrate the medicinal effects of ginseng, together with its geographic distribution and authenticity details of this product.



nr. 332	Ka lee som	Plant Kingdom herb	The root is very popular and very expensive in the apothecaries, a second species is available, which grows around Beijing, and is very expensive, the one growing in Korea is cheaper, as decoction very much strengthening, and with a piece on the tongue, a person can go without food for days.

Figure 3.6 Entry of the catalogue of the Westhoff collection on ginseng (nr. 332) with the English translation.

The entry confirms that there are different species of ginseng that differ in price and are sourced in either China or Korea. Unmistakably, the area near Beijing refers to the Shangdang area, which is historically famous for the high-quality production of ginseng roots (Xie, 2008). 'Korea' as mentioned here, implies the current country of North and South Korea and the neighboring northeastern region of China.

Many historical works on traditional Chinese and Japanese medicine mention that the Shangdang region produced better-quality ginseng (Xie, 2008; Zhonghua Bencao Edit Committee, 1999). However, from the 15th century onwards, due to the destruction of the local forests, the Shangdang region was no longer suitable for ginseng collection, as natural resources had been depleted (Xie, 2008). Therefore, some arguments questioning Shangdang as the authentic production region for ginseng have recently emerged (Peng, 2011; Xie, 2008). The catalogue of the Westhoff collection still supported the viewpoint that top-quality ginseng should come from Shangdang. In addition, this handwritten record also specified the method of verifying the authenticity of the ginseng: "With a piece on the tongue, a person can go without food for days". A similar verifying method was reported by Su Song (1061 AD) in his book *Ben cao tu jing* (*Illustrated Classics of materia medica*).

The 'minerals' Borneolum (nr. 293) and Camphora (nr. 348) are both included in the Westhoff collection of CMM and mentioned in the catalogue. Borneolum or natural Borneol ($C_{10}H_{18}O$) is the crystal produced from the fresh branches and leaves of *Dryobalanops aromatica* C.F.Gaertn. The handwritten text mentions that "Borneolum is very popular and expensive". *D. aromatica* is a tree native to west Malesia and therefore Borneolum can only be obtained by import (Zhonghua Bencao Edit Committee, 1999). The earliest written record of Borneolum is found in the *Newly revised materia medica* (Su Jing, 659 AD). The name "dragon brain" was given to Borneolum because of its rarity and preciousness (Zhonghua Bencao Edit Committee, 1999).

Natural camphor ($C_{10}H_{16}O$) is produced from the branches and leaves of *Cinnamomum camphora* (L.) J.Presl by steam distillation (Zhonghua Bencao Edit Committee, 1999). Trees of this species are widely distributed in southern China, and this is why the catalogue mentions that "Camphora is cheap". In order to meet the growing demand for Borneolum, China began to look for alternative sources in 1980s, rather than relying solely on imports. Around 2000, China succeeded in producing Borneolum from *C. camphora*. As a result, *C. camphora* has been included as source of Borneolum since 2005 (ChP 2005), so both substances now are produced from the same tree (Li et al., 2013).

Another interesting entry in the catalogue is cockscomb, the capitulum of *Celosia cristata* L. (nr. 16). Apart from the medicinal indication against leucorrhea, it states that the flowers on Java are often cultivated by "rich Chinese". *C. cristata* is indeed widely cultivated as a garden ornamental in China (Bao et al., 2003). It is associated with religious significance and ancestor worship by Indian, Burmese and Chinese people, who still plant cockscomb around their temple and in their gardens (Grant, 1954). The catalogue confirms that Chinese immigrants in the late 19th century had brought the tradition of cultivating cockscomb to Indonesia as well.

6. Who wrote the catalogue of the Westhoff collection?

The transaction letter of the Westhoff collection has quite different handwriting than the catalogue accompanying this collection (Figure 3.7). Therefore, we conclude that the catalogue was not written by Dr. Westhoff himself.

The catalogue may have been written by a Dutch clerk, maybe Westhoff's secretary. The Dutch text is written with a dip pen, while the Chinese words are written with a calligraphy brush. Moreover, to adapt to the Dutch writing habits (from left to right) and to keep the catalogue in a uniform format, the traditional Chinese writing direction was changed. Vertical columns written from right to left were replaced by horizontal lines written from left to right. Both the handwritten Dutch and Chinese texts in the catalogue are beautiful and neat. All these facts indicate that the catalogue must be compiled jointly by a Dutch and a Chinese person.

a b

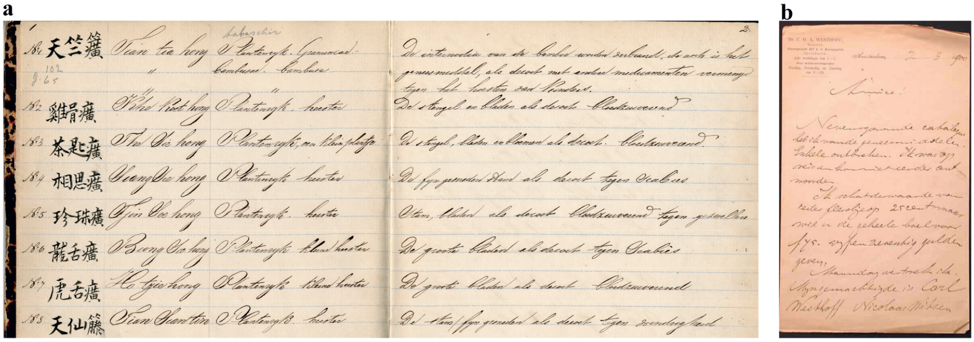


Figure 3.7 (a) section of Westhoff collection catalogue. (b) letter by Dr. Westhoff (dated 1900) on the transaction of the CMM collection. Source: Utrecht University Museum.

Conclusion

The Westhoff collection with nearly 400 specimens and even more medicinal recipes in the handwritten catalogue shows that an extensive and significant communication has taken place between two educated persons from the East and the West on the subject of traditional Chinese medicine in the late 19th century. There were language barriers, differences and misunderstandings of health concepts in Chinese and Western medicine. Still, more than 400 samples of Chinese *materia medica*, a wealth of information on their origin, medicinal parts, preparation method, application, and background knowledge have been recorded in a systematic way. The Dutch writer and the Chinese practitioner must have spent many hours together, meticulously organizing and discussing the CMM collection, its names, contents and uses. The catalogue shows a sincere interest in, and respect for traditional Chinese medicine from a Western-trained professional, but also a clear willingness to share information from the Chinese specialist.

This Westhoff collection, together with its catalogue, can be seen as a time capsule that has been preserved for over 150 years. It is not a perfect, but nevertheless a valuable record of Chinese *materia medica* and its practice in a specific time and space. Moreover, it provides strong evidence that traditional Chinese medicine, by the virtue of its unique charms, spread not only in East Asia but also could count on serious, professional interest from the distant Western world.

Declaration of competing interest

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

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Appendix A. Supplement data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2023.116987

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Chapter Four

Revisiting traditional Chinese *materia medica* from European historical collections and perspective for current use

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Abstract

Background and aim: Chinese *materia medica* (CMM) is subject to changes over time. Investigating changes in botanical ingredients, applications, plant parts used as well as name changes over time, contribute to the understanding of the history and development of CMM.

Materials and methods: This study compares four historic collections of CMM, located in Europe, compiled between 1700 and the late 19th century, with a list of contemporary CMM marketed in Europe.

Results: More than 1,700 specimens within these five collections. The dominant families are Fabaceae (5.3-7.2%) and Asteraceae (4.1-5.7%), while half of the medicinal parts are represented by roots or rhizomes and fruits and/or seeds. Their importance has been stable in a time span of 300 years. The proportion of animal and mineral drugs gradually decreased over time. 14 plant species appeared in all five collections. A total of 47 species are shared between the three more recent collections and the modern trade list. Among these common species, most medicinal parts remain unchanged, but for several species the used plant parts changed or new medicinal plant parts appeared. All common species have unanimously been used in ancient classical TCM formulae and/or Chinese patent medicines.

Conclusion: Over more than 300 years, the main body of CMM has hardly changed, with regard to plant taxa and plant parts used. The most prominent changes are related to conservation issues of threatened species, health safety and the discovery of new pharmacological applications of well-known species. Analyzing physical specimens from historic CMM collections complements literature-based research.

Keywords: Chinese *materia medica*; historical CMM collections; traditional Chinese medicine; medicinal plant parts; CMM development.

Abbreviations: CMM: Chinese *materia medica*; TCM: traditional Chinese medicine; ChP 2015: Chinese Pharmacopoeia 2015 edition.

Introduction

Chinese *materia medica* (CMM) has been used for thousands of years for traditional medicine in China. The nature and use of CMM have been extensively documented for centuries, with the first record dating from 1100 BC (*Formulae for 52 kinds of disorders,* 五十二病方 wǔ shí èr bìng fāng), followed by works such as *the Divine Husbandman's classic of materia medica* (神农本草经 shén nóng běn cǎo jīng) (200-250 AD), the *Newly revised materia medica* (新修本草 xīn xiū běn cǎo) (650 AD) and the *Compendium of materia medica* (本草纲目 běn cǎo gāng mù) from 1578 AD (Cragg and Newman, 2001; Zhao et al., 2018). During the millennia of practice, most CMM have remained the same, although some changes have taken place with regard to the botanical source material and medicinal parts (Brand et al., 2017; Jia et al., 2021). Research on the historical changes in CMM reveals the development of traditional Chinese medicine (TCM) and the habit of drug usage, which will lead toward a better understanding of the safe and effective use of CMM. Most previous research on historical changes has focused on CMM monographs and literature, and has been well summarized in Chinese publications (Chen and Huang, 2005; Xie, 2008). With the development of textual research on the history of CMM, the confusion of many frequently used drugs has been clarified. However, due to the excessive reliance on ancient literature, instead of on physical CMM samples, some conclusions are controversial, and confusion about botanical sources (Bing and Zhang, 2008) and vernacular names (Jia et al., 2021) of medicinal plants still exist.

Early CMM collections provide valuable material evidence on historical changes, which is more intuitive and persuasive than textual research. Besides, analyzing physical specimens from pre-modern CMM collections complement literature-based research. However, few studies based on historic CMM collections are published. One of the main reasons for this is that the number of well-preserved, early CMM collections is limited, especially in China, where most of the research on TCM is carried out.

In Europe, the use of herbal medicine also has a long history and has been relatively well documented in herbals and, since the 1550s, in herbaria. From ancient Greece and Rome, the works of Theophrastus's *Historia Plantarum* (c. 300 BC) and Dioscorides's *De Materia Medica* (c. 65 AD), and their many translations and additions, have served for centuries as the major sources of knowledge on herbal medicine. In the Renaissance, scholars reexamined these classical works and published high-quality manuals of medicinal plants (Dioscorides et al., 1544; Fuchs, 1542) and the first book herbaria with actual specimens (Stefanaki et al., 2019; Stefanaki et al., 2018). Since the 16th century, the European fleet reached southeast Asia and China, after which economic, cultural and material exchanges have increased significantly. The European interest in East Asian spices and medicine is represented by botanical voucher specimens (van Andel and Barth, 2018), published works (Orta and Camões, 1963) and illustrations of exotic *materia medica* (van Andel et al., 2018).

CMM was regarded as an exotic novelty, a promising source of medicine and a valuable object of scientific research, and transported to Europe on these merchant ships. One famous example is the “China root”, the tuber-like rhizomes of *Smilax glabra* Roxb. (Smilacis Glabrae Rhizoma, 土茯苓 tǔ fú líng). China root was described in 1535 as a wonder drug by the Dutch merchant, trader and historian Jan Linschoten, because of its effectiveness in ameliorating symptoms of syphilis (Winterbottom, 2015). For centuries, travelers and colonial staff stationed in the East collect Chinese medicinal plant products for curiosity, which has resulted in several pre-modern CMM collections preserved in museums in Europe, such as in the Sloane Collection in Natural History Museum in London (Zhao et al., 2015), the Westhoff Collection in the Utrecht University Museum (Jia et al., 2021) and the Hooper Collection in Royal Botanic Gardens Kew (Brand et al., 2017). These valuable historical CMM collections provide the most direct physical basis for research on the historical changes and development of CMM, and can fill the gap between the body of textual research and studies on physical specimens.

In this study, we compared several historical and contemporary CMM collections located in Europe with more than a 300-year time span (three pre-modern and one modern CMM collections) to a list of currently commercialized CMM by a Chinese company in the Netherlands. We posed the following research questions:

1. Is the botanical identity of CMM products stable over time?
2. Does the medicinal plant part of these species change over time?
3. Which species are shared by all CMM collections and why?
4. Are there CMM species that disappeared over time?
5. Are there species that recently emerged as CMM?

By comparing the similarities and differences in the five CMM collections, our research results will contribute to a better understanding of the ‘evolution’ of Chinese herbal medicine, which will help to better evaluate the safety and effective use of CMM use.

Materials and methods

1. Collections studied

We studied four historical CMM collections (Figure 4.1) and compared these to a list of CMM from the commercial trader Zhong Hua International Trading B.V. (https://www.zhonghua-trading.com), located in Utrecht, the Netherlands. This company is one of the major players in the import and export of Chinese herbal medicine on the European market.

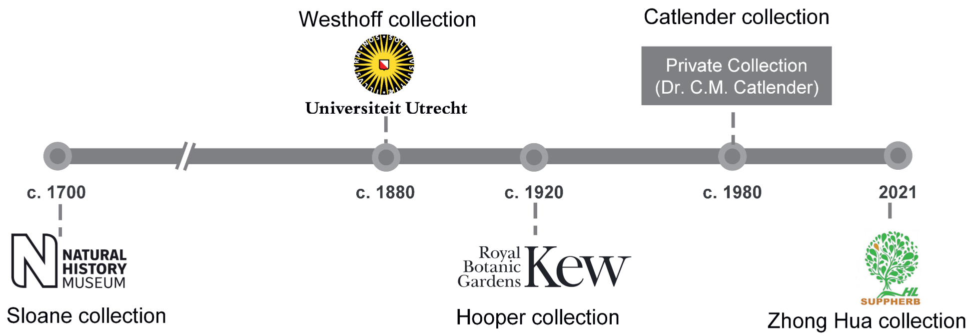

Figure 4.1 The four historical collections of Chinese *materia medica* in chronological order, and the collection of contemporary marketed CMM.

The oldest collection that we included in our analysis is preserved at the Natural History Museum in London, UK. It is part of the Hans Sloane Collection, and thus herein referred to as the 'Sloane collection', and is approximately 320 years old. This CMM collection has been studied in detail by Zhao et al. (2015), so for our analysis, we retrieved the pharmaceutical names, plant parts and scientific names from their published article. Zhao et al. (2015) counted 84 specimens in the Sloane Collection, of which 76 were plant materials, but several could not be identified to species level (Table 4.1, Appendices 1, tab 'Sloane').

The Westhoff Collection is housed by the Utrecht University Museum (Utrecht, the Netherlands). This collection was acquired from Indonesia by Dr. C.H.A Westhoff around 1882. It contains 395 specimens, of which 314 are plant-based (Table 4.1, Appendices 1, tab 'Westhoff'). Details about the species, plant parts and Chinese names of the Westhoff Collection were published previously by Jia et al. (2021). Similar to the Sloane collection, several specimens lost their identifiable characteristics due to long-term storage.

Table 4.1 Number of specimens and their natural origin in the five studied collections.

CMM collection		Sloane Collection (c. 1700)	Westhoff Collection (c. 1880)	Hooper Collection (1924)	Catlender Collection (c. 1980)	ZhongHua Trade list (2021)
Total amount of specimens		84	395	520	297	333
Material origin	Plant *	76	314	493	247	295
	Animal *	3	36	1	20	16
	Mineral *	1	34	2	15	11
	Fungi	2	2	13	10	8
	Other	2	9 **	11 **	5	3

* and related substances
** including unidentified specimens

The Hooper collection is stored in the Economic Botany Collection of the Royal Botanic Gardens Kew, UK. It was acquired from Chinese pharmacies in Malaya by the botanist Isaac Henry Burkill (1870-1965). Hooper conducted the first identifications of this collection, and therefore referred to as the Hooper Collection (Hooper, 1929). Brand et al. (2017) recently revised the specimen identifications within the Hooper Collection, and for our analysis, we used their results with regard to plant parts and botanical taxa. Among the 619 specimens identified by Brand et al. (2017), there were many duplicates (identical taxa and plant parts, for example EBC# 69076 and EBC# 69210, see Appendices 1, tab 'Hooper 619'). In this study, we wanted to compare the botanical composition, so these identical specimens were counted only once. After removing 99 redundancies, 520 specimens in Hooper Collection were included in our analysis. Of these 520 specimens, 493 are plant materials (Table 4.1, Appendices 1, tab 'Hooper 520').

The Catlender Collection is a private collection held by Dr. C.M. Catlender in Leiden, the Netherlands. It is between 20 and 30 years old and contains 297 specimens, of which 247 are plant-based materials (Table 4.1, Appendices 1, tab 'Catlender'). To see how many of the historically used Chinese plant taxa continue to be part of the commercialized body of CMM today, we compared the taxa in the historic collections to the 2021 species trade list obtained from Zhong Hua International Trading B.V. in Utrecht (https://www.zhonghua-trading.com), wholesaler in traditional Chinese medicine on the European market. Their product list contained 333 drug names, of which 295 represent plant-based medicine (Table 4.1, Appendices 1, tab 'Zhong Hua').

2. Species identification

Several selection criteria were applied in our comparison of botanical species within these five collections. Excluded from our analysis were 1) unidentified specimens; 2) CMM specimens with multiple botanical sources that could not be identified on species level based on morphological features; 3) zoological and mineral substances. If different parts of the same plant species were used as separate medicinal products, the species itself was only counted once.

To verify the botanical identity, nomenclature and plant parts represented by the specimens, we used the specification of the Chinese Pharmacopoeia 2015 edition (Chinese Pharmacopoeia Commission, 2015), Zhong Hua Ben Cao (中华本草 zhōng huá běn cǎo) (Zhonghua Bencao Edit Committee, 1999) and Zhong Yao Da Ci Dian (中药大辞典 zhōng yào dà cí diǎn) (Zhao et al., 2006). For current scientific names, we followed the Plants of the World Online database (http://powo.science.kew.org/) and the Flora of China (Flora of China Editorial Committee, 1994-2013). To verify the use of the species shared by the five CMM collections in TCM formulae, we consulted the formulae of Chinese patent medicine (Chinese Pharmacopoeia Commission, 2015) and the ancient classical TCM formulae list issued by the Chinese National Administration of Traditional Chinese Medicine (http://kjs.satcm.gov.cn/zhengcewenjian/2018-04-16/7107.html). A Venn diagram was created to show similarities and differences among the four collections and the currently traded CMM, using the webtool Venn (http://bioinformatics.psb.ugent.be/webtools/Venn/). The UpSet plots were made with the OECloud tools (https://cloud.oebiotech.cn).

Results and Discussion

1. Variation in natural origin of specimens

Our final database contained more than 1,700 specimens, retrieved from the publications on the three historical CMM collections, our revision of the Catlender collection and the Zhong Hua list of currently commercialized herbal medicine (Appendix 1). Although the age and provenances of the CMM collections were quite different, the largest proportion of the specimens was always plant-based (Table 4.1). Some clear differences were visible in the proportion of CMM of animal and mineral origin among the collections. The Sloane collection was small (84 specimens) and contained three animal-based and one mineral specimen, while the Hooper collection did not contain animal and mineral drug (Brand et al., 2017). In the other three collections, the number of animal-based drugs decreased over time: from 9.1% of the specimens in the Westhoff collection to 6.7% in the Catlender collection and 4.8% in the Zhong Hua list (Table 4.1). The mineral drugs also decreased from 8.6% of the specimens in the Westhoff collection to 5.1% in the Catlender collection and 3.3% in Zhong Hua's list. The reason for this may lie in the conservation issues concerning species of animals threatened by the trade in Chinese medicine. For example, pangolin scales

(Mantitis Squama, 穿山甲 chuān shān jiǎ, *Manis pentadactyla* L.) are commonly used in China to promote lactation in women and reduce swelling (ChP 2015). Pangolin scales were present in the Westhoff and Catlender collections, but absent from the Zhong Hua list in 2021, because pangolins are endangered and the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) transferred all eight species of pangolin from Appendix II to I in 2016 (Challender and Waterman, 2017). In 2020, the Chinese Pharmacopoeia Commission also removed pangolin scales from the Chinese Pharmacopoeia. Although pangolin scales are still illegally traded and consumed as medicine in China (Heinrich et al., 2017), the absence of pangolin scales in the list of commercial CMM in Europe illustrates the efforts of European environmental organizations, CITES and European law.

2. Variation in plant families

When we categorized the plant medicine on family level, the collections showed a clear tendency in botanical composition (Table 4.2). The most represented plant family in all five CMM collections was the Fabaceae, representing 5.3% to 7.2% of the specimens. The second largest family was the Asteraceae (4.1% to 5.7% of the specimens), except for the Sloane Collection, in which Rutaceae were more abundant than Asteraceae. Compared to the other four collections, the Sloane Collection was much smaller with only 84 specimens, so possible less representative of the botanical diversity in CMM used around 1700. The Asteraceae still accounted for 4.8% of the specimens. The families Apiaceae, Rosaceae, Lamiaceae and Rutaceae were relatively abundant in all five collections (Table 4.2). Fabaceae and Asteraceae are among the most species-rich plant families in the world. In China, there are 1673 species of Fabaceae and 2336 species of Asteraceae (Flora of China Editorial Committee, 1994-2013). Because of their high species diversity and their known pharmacological activity (He et al., 2015; Ma et al., 2011; Meng et al., 2009), more taxa within the Fabaceae and Asteraceae are used as medicine than in other plant families. The comprehensive CMM monograph of Zhong Hua Ben Cao lists 7921 plant-based drugs, 559 belong to the Fabaceae family (7.1% of all plant-based drugs) and 420 drugs from the Asteraceae family (5.3%) (Zhonghua Bencao Edit Committee, 1999). These percentages are similar in the CMM collections we studied: Fabaceae and Asteraceae are major sources of medicinal plants. However, these families are not dominant and never represent more than 10% of the floristic diversity: the low percentages indicate that the plant sources of CMM are highly diverse.

3. Plant parts represented in CMM collections

With regard to the medicinal parts, roots and/or rhizomes, fruits and/or seeds are the dominant plant organs in all collections (Table 4.3). This has been stable in a time span of 300 years, as roots/rhizomes, fruits and seeds together account for about 50% of the specimens in all collections. CMM that is represented by entire herbs account for 8-11% of the specimens in each collection, except for Hooper collection, where only 2.9% of the specimens are whole herbs. This may be caused by the considerable number of unidentified specimens, which were left out of our analysis. No leaf-based drugs were found in the Sloane Collection, but this can be explained by the small size of this collection.

From an overall perspective, the composition of botanical families and medicinal parts show a remarkable continuity over a 300-year time span.

Table 4.2 Comparison of 5 CMM collections in plant family. Similar colours represent similar families.

Sloane (84 specimens) (c. 1700)		Westhoff (395 specimens) (c. 1880)		Hooper (520 specimens) (1924)		Catlender (297 specimens) (c. 1980)		Zhong Hua (333 specimens) (2021)	
Family	Quantity (%)	Family	Quantity (%)	Family	Quantity (%)	Family	Quantity (%)	Family	Quantity (%)
Fabaceae	6 (7.1%)	Zoological substance	36 (9.1%)	Fabaceae	31 (6.0%)	Fabaceae	20 (6.7%)	Fabaceae	24 (7.2%)
Rutaceae	5 (6.0%)	Mineral	34 (8.6%)	Asteraceae	28 (5.4%)	Zoological substance	20 (6.7%)	Asteraceae	19 (5.7%)
Asteraceae	4 (4.8%)	Fabaceae	21 (5.3%)	Apiaceae	27 (5.2%)	Asteraceae	17 (5.7%)	Rosaceae	16 (4.8%)
Lamiaceae	4 (4.8%)	Asteraceae	16 (4.1%)	Rosaceae	20 (3.8%)	Mineral	15 (5,1%)	Zoological substance	16 (4.8%)
Apiaceae	3 (3.6%)	Lamiaceae	16 (4.1%)	Rutaceae	20 (3.8%)	Apiaceae	14 (4.7%)	Lamiaceae	15 (4.5%)
Brassicaceae	3 (3.6%)	Unidentified	16 (4.1%)	Zingiberaceae	16 (3.1%)	Lamiaceae	13 (4.4%)	Apiaceae	13 (3.9%)
Cucurbitaceae	3 (3.6%)	Apiaceae	13 (3.3%)	Lamiaceae	16 (3.1%)	Rosaceae	11 (3.7%)	Poaceae	13 (3.9%)
Liliaceae	3 (3.6%)	Rosaceae	13 (3.3%)	Araceae	14 (2.7%)	Rutaceae	11 (3.7%)	Rutaceae	12 (3.6%)
Zingiberaceae	3 (3.6%)	Rutaceae	13 (3.3%)	Fungi, seaweeds	13 (2.5%)	Fungi, seaweeds	10 (3.4%)	Mineral	11 (3.3%)
Zoological substance	3 (3.6%)	Zingiberaceae	11 (2.8%)			Poaceae	9 (3.0%)		
Other	47 (56.0%)	Other	206 (52.2%)	Other	335 (64,4%)	Other	157 (52,9%)	Other	194 (58.3%)

Table 4.3 Medicinal plant parts in the 4 CMM collections and the modern trade list. Similar colours represent the same plant organ.

Sloane (84 specimens) (c. 1700)		Westhoff (395 specimens) (c. 1880)		Hooper (520 specimens) (1924)		Catlender (297 specimens) (c. 1980)		Zhong Hua (333 specimens) (2021)	
Medicinal part	Quantity (%)	Medicinal part	Quantity (%)	Medicinal part	Quantity (%)	Medicinal part	Quantity (%)	Medicinal part	Quantity (%)
Fruits / seeds	32 (38.1%)	Roots / rhizomes	108 (27.3%)	Roots / rhizomes	135 (26.0%)	Roots / rhizomes	89 (30.0%)	Roots / rhizomes	101 (30.3%)
Roots / rhizomes	21 (25.0%)	Fruits / seeds	86 (21.8%)	Fruits / seeds	121 (23.3%)	Fruits / seeds	77 (25.9%)	Fruits / seeds	90 (27.0%)
Whole herbs	7 (8.3%)	Whole herbs	38 (9.6%)	Unidentified	81 (15.6%)	Whole herbs	29 (9.8%)	Whole herbs	38 (11.4%)
Flowers	5 (6.0%)	Zoological substance	36 (9.1%)	Stems / wood	66 (12.7%)	Zoological substance	20 (6.7%)	Flowers	18 (5.4%)
Stems / wood	5 (6.0%)	Minerals	34 (8.6%)	Flowers	37 (7.1%)	Minerals	15 (5.1%)	Stems / wood	18 (5.4%)
Bark	4 (4.8%)	Stems and woods	25 (6.3%)	Bark	23 (4.4%)	Stems / wood	14 (4.7%)	Bark	16 (4.8%)
Zoological substance	3 (3.6%)	Flowers	19 (4.8%)	Leaves	18 (3.5%)	Bark	13 (4.4%)	Zoological substance	16 (4.8%)
Resins	2 (2.4%)	Bark	14 (3.5%)	Whole herb	15 (2.9%)	Flowers	13 (4.4%)	Leaves	12 (3.6%)
Fungi, seaweeds	2 (2.4%)	Leaves	6 (1.5%)	Fungi, seaweeds	13 (2.5%)	Fungi, seaweeds	10 (3.4%)	Minerals	11 (3.3%)
Minerals	1 (1.2%)	Fungi, seaweeds	4 (1.0%)	Resins	6 (1.2%)	Leaves	8 (2.7%)	Fungi, seaweeds	8 (2.4%)
Other	2 (2.4%)	Other	25 (6.3%)	Other	5 (1.0%)	Other	9 (3.0%)	Other	5 (1.5%)

4. Changes and continuities in species over time

With regard to plant families and medicinal parts, the CMM collections clearly show continuity, but differences in botanical species could indicate subtle changes in Chinese herbal medicine use over time. Species that are present in all four studied collections and the modern trade list could be considered as stable elements in Chinese medicine over the past centuries. In contrast, plant taxa that only appear in one or two of the historic collections may have lost their importance in Chinese medicine today. Figure 4.2 shows the number of common and unique species among the four collections and the modern trade list. As not all specimens were identified to species level in the collections, the number of species that we could compare was considerably lower than the number of specimens in each collection.

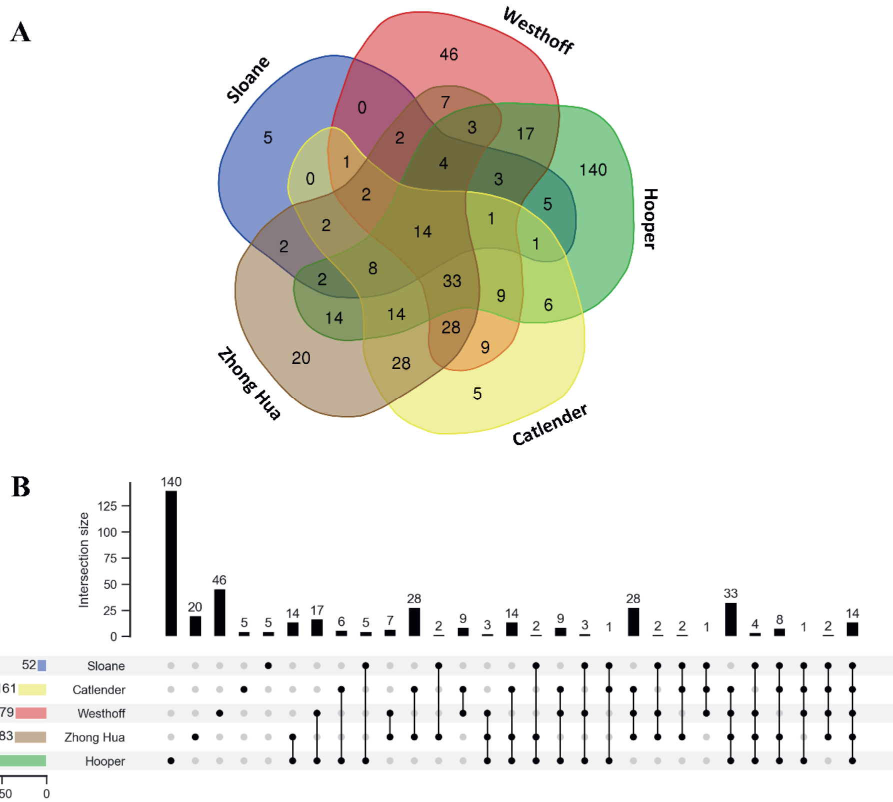

Figure 4.2 Similarities and differences in species between the four CMM collections and the modern trade list. A. Venn diagram showing the number of overlapping species. B. UpSet plots: single dots without connecting lines representing unique species in each corresponding collection. The upper column indicates the number of unique species. Dots connected with line indicate overlapping species between these specific collections, with the number of overlapping species.

5. Popular CMM species over time

There are 14 plant species that appeared in all five collections (Figure 4.2B, far right). Their Chinese pharmaceutical and scientific names, medicinal parts and pharmaceutical names are listed in Table 4.4. Although the medicines have identical botanical sources, the used parts are not always the same: the root of *Reynoutria multiflora* (Thunb.) Moldenke (Polygoni Multiflori Radix, 何首乌 hé shǒu wū) is always present, but the vine with leaves of this species is only included in the modern Catlender collection and Zhong Hua trade list. The use of the root (Polygoni Multiflori Radix) and the stem with leaves (Polygoni Multiflori Caulis, 夜交藤 yè jiāo téng) of this species as medicine can be traced back to the 10th century (*Ri Hua Zi Materia Medica*, 日华子本草 rì huá zǐ běn cǎo) and the 17th century (*Ben Jing Feng Yuan*, 本经逢原 běn jīng féng yuán). Records on the use of these roots in traditional Chinese medicine formulae also date back to the 15th century (*Prescriptions for Universal Relief*, 普济方 pǔ jì fāng, 1406). In contrast, most formulae that use the vine with leaves as an ingredient have only appeared in the 1970s-1980s (Zhong Yao Da Ci Dian Edit Committee, 2006; Zhonghua Bencao Edit Committee, 1999). The appearance of the stem and leaves of *R. multiflora* in the Catlender collection demonstrates the recent changes in use of this frequently employed plant, which is again confirmed by the modern trade list. Table 4.4 also shows that for the species *Citrus* × *aurantium* L. and *Nelumbo nucifera* Gaertn., much more parts are used nowadays than in the past. For the other shared species, the plant parts employed in medicine did not change over time.

As the Sloane Collection is dissimilar to other collections due to its small sample size, we made another comparison on species overlap within the other three collections (Westhoff, Hooper and Catlender) and the Zhong Hua 2021 trade list. The number of common species increased to 47 (Table 4.5), but the exact uses of the species showed some variation over time. One interesting example is *Dimocarpus longan* Lour. In the Westhoff and Hooper collections, the flowers (Longan Flos, 龙眼花 lóng yǎn huā) are used as medicine, but in the Catlender collection and Zhong Hua list, the medicinal part is the aril around the seed (Longan Arillus, 龙眼肉 lóng yǎn ròu). The aril, however, has a long history of medicinal use in China, appearing as one of the main ingredients in various TCM formulae (*Ji Sheng Fang*, 济生方 jì shēng fāng, 1253; *Jing Yue Quan Shu*, 景岳全书 jǐng yuè quán shū, 1624) as well as in present Chinese patent medicine (Chinese Pharmacopoeia Commission, 2015; Zhonghua Bencao Edit Committee, 1999). The references on the use of the flowers as medicine are very limited and all come from local monographs of the Fujian province (Zhong Yao Da Ci Dian Edit Committee, 2006; Zhonghua Bencao Edit Committee, 1999). These findings again support the previous conclusions that the Sloane and Westhoff collections are originally from southeast China (Brand et al., 2017; Jia et al., 2021). These differences in used plant parts among the collections reflect alterations in herbal medicine applications but also show regional variation in traditional Chinese medicine.

Table 4.4 Common species appeared in 5 collections.

	Sloane Collection (c. 1700)		Westhoff Collection (c. 1880)		Hooper Collection (1924)		Catlender Collection (c. 1980)		Zhong Hua Collection (2021)	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Achyranthes bidentata Blume	Root	Achyranthis Bidentatae Radix (牛膝)	Root	Achyranthis Bidentatae Radix Praeparata (酒淮膝)	Root	Achyranthis Bidentatae Radix (牛膝)	Root	Achyranthis Bidentatae Radix (牛膝)	Root	Achyranthis Bidentatae Radix (牛膝)
					Stem	unknow				
Areca catechu L.	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)
			Pericarp	Arecae Pericarpium (大腹皮)			Pericarp	Arecae Pericarpium (大腹皮)	Pericarp	Arecae Pericarpium (大腹皮)
Citrus × aurantium L.	Fruit	Aurantii Fructus (枳壳)	Fruit	Aurantii Fructus Immaturus Praeparata (炒枳实)	Sliced peel	unknow	Fruit	Aurantii Fructus (枳壳)	Fruit	Aurantii Fructus (枳壳)
	Pericarp	Citri Reticulatae Pericarpium (陈皮)	Exocarp	Citri Reticulatae Exocarpium (橘红)	Flower	Citri Aurantii Flos (玳玳花)	Fruit	Aurantii Fructus Immaturus (枳实)	Fruit	Aurantii Fructus Immaturus (枳实)
			Pericarp	Citri Reticulatae Pericarpium Viride (青皮)			Seed	Citri Reticulatae Semen (橘核)	Seed	Citri Reticulatae Semen (橘核)
			Pericarp	Citri Reticulatae Pericarpium (四陈皮)			Exocarp	Citri Reticulatae Exocarpium (橘红)	Exocarp	Citri Reticulatae Exocarpium (橘红)
							Pericarp	Citri Reticulatae Pericarpium Viride (青皮)	Pericarp	Citri Reticulatae Pericarpium Viride (青皮)
							Pericarp	Citri Reticulatae Pericarpium (陈皮)	Pericarp	Citri Reticulatae Pericarpium (陈皮)
Gardenia jasminoides J.Ellis	Fruit	Gardeniae Fructus (栀子)	Fruit	Gardeniae Fructus (山栀子)	Fruit	Gardeniae Fructus (栀子)	Fruit	Gardeniae Fructus (栀子)	Fruit	Gardeniae Fructus (生栀子)
			Fruit	Gardeniae Fructus Praeparata (黑枝仁)					Fruit	Gardeniae Fructus Praeparata (炒栀子)

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Table 4.4 Common species appeared in 5 collections. *(continued)*

	Sloane Collection (c. 1700)		Westhoff Collection (c. 1880)		Hooper Collection (1924)		Catlender Collection (c. 1980)		Zhong Hua Collection (2021)	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Leonurus japonicus Houtt.	Whole herb	Leonuri Herba (益母草)	Fruit	Leonuri Fructus (茺蔚子)	Whole herb	Leonuri Herba (益母草)	Whole herb	Leonuri Herba (益母草)	Whole herb	Leonuri Herba (益母草)
					Fruit	Leonuri Fructus (茺蔚子)			Fruit	Leonuri Fructus (茺蔚子)
Lonicera japonica Thunb.	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)
			Vine	Lonicerae Japonicae Caulis (忍冬藤)					Vine	Lonicerae Japonicae Caulis (忍冬藤)
Nelumbo nucifera Gaertn.	Rhizome	Nelumbinis Rhizomatis Nodus (藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (粉藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (生藕节)
			Rhizome	Nelumbinis Nodus Rhizomatis Praeparata (黑藕节)	Stamen	Nelumbinis Stamen (莲须)	Stamen	Nelumbinis Stamen (莲须)	Rhizome	Nelumbinis Nodus Rhizomatis Praeparata (炭藕节)
			Stamen	Nelumbinis Stamen (金莲须)	Seed	Nelumbinis Semen (莲子)	Seed	Nelumbinis Semen (莲子)	Seed	Nelumbinis Semen (莲子)
			Seed	Nelumbinis Semen (莲子)	Flower	Nelumbinis Flos (莲花)	Leaf	Nelumbinis Folium (荷叶)	Leaf	Nelumbinis Folium (荷叶)
									Receptacle	Nelumbinis Receptaculum (莲房)
									Plumule	Nelumbinis Plumuia (莲子芯)
Nepeta tenuifolia Benth.	Whole herb	Schizonepetae Herba (荆芥)	Whole herb	Schizonepetae Herba (荆芥)	Flower	Schizonepetae Spica (荆芥穗)	Whole herb	Schizonepetae Herba (荆芥)	Whole herb	Schizonepetae Herba (荆芥)
			Whole herb	Schizonepetae Herba Praeparata (黑荆芥)						
Polygonatum odoratum (Mill.) Druce	Rhizome	Polygonati Odorati Rhizoma (玉竹)	Rhizome	Polygonati Odorati Rhizoma (明玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)

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Table 4.4 Common species appeared in 5 collections. *(continued)*

	Sloane Collection (c. 1700)		Westhoff Collection (c. 1880)		Hooper Collection (1924)		Catlender Collection (c. 1980)		Zhong Hua Collection (2021)	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Prunus mume (Siebold) Siebold & Zucc.	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)
					Kernel	Mume Semen (梅核仁)				
Raphanus raphanistrum subsp. *sativus* (L.) Domin	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)
Reynoutria multiflora (Thunb.) Moldenke	Root	Polygoni Multiflori Radix (何首乌)	Root	Polygoni Multiflori Radix Praeparata (制首乌)	Root	Polygoni Multiflori Radix (何首乌)	Root	Polygoni Multiflori Radix (何首乌)	Root	Polygoni Multiflori Radix (何首乌)
							Vine with leaves	Polygoni Multiflori Caulis (夜交藤)	Root	Polygoni Multiflori Radix Praeparata (制首乌)
									Vine with leaves	Polygoni Multiflori Caulis (夜交藤)
Salvia miltiorrhiza Bunge	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma Praeparata (酒丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)
Syzygium aromaticum (L.) Merr. & L.M.Perry	Flower	Caryophylli Flos (丁香)	Flower	Caryophylli Flos (丁香末)	Flower	Caryophylli Flos (丁香)	Flower	Caryophylli Flos (丁香)	Flower	Caryophylli Flos (公丁香)

Chapter 4

Table 4.5 Common species appeared in 4 collections.

	Westhoff Collection (c. 1880)		Hooper Collection (1924)		Catlender Collection (c. 1980)		Zhong Hua Collection (2021)	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Achyranthes bidentata Blume	Root	Achyranthis Bidentatae Radix Praeparata (酒淮膝)	Root	Achyranthis Bidentatae Radix (牛膝)	Root	Achyranthis Bidentatae Radix (牛膝)	Root	Achyranthis Bidentatae Radix (牛膝)
			Stem	unknow				
Areca catechu L.	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)	Seed	Arecae Semen (槟榔)
	Pericarp	Arecae Pericarpium (大腹皮)			Pericarp	Arecae Pericarpium (大腹皮)	Pericarp	Arecae Pericarpium (大腹皮)
Citrus × *aurantium* L.	Fruit	Aurantii Fructus Immaturus Praeparata (炒枳实)	Sliced peel	unknow	Fruit	Aurantii Fructus (枳壳)	Fruit	Aurantii Fructus (枳壳)
	Exocarp	Citri Reticulatae Exocarpium (橘红)	Flower	Citri Aurantii Flos (玳玳花)	Fruit	Aurantii Fructus Immaturus (枳实)	Fruit	Aurantii Fructus Immaturus (枳实)
	Pericarp	Citri Reticulatae Pericarpium Viride (青皮)			Seed	Citri Reticulatae Semen (橘核)	Seed	Citri Reticulatae Semen (橘核)
	Pericarp	Citri Reticulatae Pericarpium (四陈皮)			Exocarp	Citri Reticulatae Exocarpium (橘红)	Exocarp	Citri Reticulatae Exocarpium (橘红)
					Pericarp	Citri Reticulatae Pericarpium Viride (青皮)	Pericarp	Citri Reticulatae Pericarpium Viride (青皮)
					Pericarp	Citri Reticulatae Pericarpium (陈皮)	Pericarp	Citri Reticulatae Pericarpium (陈皮)

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Table 4.5 Common species appeared in 4 collections. (*continued*)

	Westhoff Collection (c. 1880)		Hooper Collection (1924)		Catlender Collection (c. 1980)		Zhong Hua Collection (2021)	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Gardenia jasminoides J.Ellis	Fruit	Gardeniae Fructus (山栀子)	Fruit	Gardeniae Fructus (栀子)	Fruit	Gardeniae Fructus (栀子)	Fruit	Gardeniae Fructus (生栀子)
	Fruit	Gardeniae Fructus Praeparata (黑枝仁)					Fruit	Gardeniae Fructus Praeparata (炒栀子)
Leonurus japonicus Houtt.	Fruit	Leonuri Fructus (茺蔚子)	Whole herb	Leonuri Herba (益母草)	Whole herb	Leonuri Herba (益母草)	Whole herb	Leonuri Herba (益母草)
			Fruit	Leonuri Fructus (茺蔚子)			Fruit	Leonuri Fructus (茺蔚子)
Lonicera japonica Thunb.	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)	Flower	Lonicerae Japonicae Flos (金银花)
	Vine	Lonicerae Japonicae Caulis (忍冬藤)					Vine	Lonicerae Japonicae Caulis (忍冬藤)
Nelumbo nucifera Gaertn.	Rhizome	Nelumbinis Rhizomatis Nodus (粉藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (藕节)	Rhizome	Nelumbinis Rhizomatis Nodus (生藕节)
	Rhizome	Nelumbinis Nodus Rhizomatis Praeparata (黑藕节)	Stamen	Nelumbinis Stamen (莲须)	Stamen	Nelumbinis Stamen (莲须)	Rhizome	Nelumbinis Nodus Rhizomatis Praeparata (炭藕节)
	Stamen	Nelumbinis Stamen (金莲须)	Seed	Nelumbinis Semen (莲子)	Seed	Nelumbinis Semen (莲子)	Seed	Nelumbinis Semen (莲子)
	Seed	Nelumbinis Semen (莲子)	Flower	Nelumbinis Flos (莲花)	Leaf	Nelumbinis Folium (荷叶)	Leaf	Nelumbinis Folium (荷叶)
							Receptacle	Nelumbinis Receptaculum (莲房)
							Plumule	Nelumbinis Plumuia (莲子芯)

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Table 4.5 Common species appeared in 4 collections. (*continued*)

	Westhoff Collection (c. 1880)		**Hooper Collection (1924)**		**Catlender Collection (c. 1980)**		**Zhong Hua Collection (2021)**	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Nepeta tenuifolia Benth.	Whole herb	Schizonepetae Herba (荆芥)	Flower	Schizonepetae Spica (荆芥穗)	Whole herb	Schizonepetae Herba (荆芥)	Whole herb	Schizonepetae Herba (荆芥)
	Whole herb	Schizonepetae Herba Praeparata (黑荆芥)						
Polygonatum odoratum (Mill.) Druce	Rhizome	Polygonati Odorati Rhizoma (明玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)	Rhizome	Polygonati Odorati Rhizoma (玉竹)
Prunus mume (Siebold) Siebold & Zucc.	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)	Fruit	Mume Fructus (乌梅)
			Kernel	Mume Semen (梅核仁)				
Raphanus raphanistrum subsp. *sativus* (L.) Domin	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)	Seed	Raphani Semen (莱菔子)
Reynoutria multiflora (Thunb.) Moldenke	Root	Polygoni Multiflori Radix Praeparata (制首乌)	Root	Polygoni Multiflori Radix (何首乌)	Root	Polygoni Multiflori Radix (何首乌)	Root	Polygoni Multiflori Radix (何首乌)
					Vine with leaves	Polygoni Multiflori Caulis (夜交藤)	Root	Polygoni Multiflori Radix Praeparata (制首乌)
							Vine with leaves	Polygoni Multiflori Caulis (夜交藤)
Salvia miltiorrhiza Bunge	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma Praeparata (酒丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)	Root and rhizome	Salviae Miltiorrhizae Radix et Rhizoma (丹参)

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Table 4.5 Common species appeared in 4 collections. (*continued*)

	Westhoff Collection (c. 1880)		**Hooper Collection (1924)**		**Catlender Collection (c. 1980)**		**Zhong Hua Collection (2021)**	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Syzygium aromaticum (L.) Merr. & L.M.Perry	Flower	Caryophylli Flos (丁香末)	Flower	Caryophylli Flos (丁香)	Flower	Caryophylli Flos (丁香)	Flower	Caryophylli Flos (公丁香)
Acorus calamus L.	Rhizome	Acori Tatarinowii Rhizoma (石菖蒲)	Rhizome	Acori Tatarinowii Rhizoma (石菖蒲)	Rhizome	Acori Tatarinowii Rhizoma (石菖蒲)	Rhizome	Acori Tatarinowii Rhizoma (石菖蒲)
Alisma plantago-aquatica L.	Rhizome	Alismatis Rhizoma Praeparata (鹹泽泻)	Rhizome	Alismatis Rhizoma (泽泻)	Rhizome	Alismatis Rhizoma (泽泻)	Rhizome	Alismatis Rhizoma (泽泻)
Alpinia oxyphylla Miq.	Fruit	Alpiniae Oxyphyllae Fructus (益智仁)	Fruit	Alpiniae Oxyphyllae Fructus (益智仁)	Fruit	Alpiniae Oxyphyllae Fructus (益智仁)	Fruit	Alpiniae Oxyphyllae Fructus (益智仁)
Anemarrhena asphodeloides Bunge	Rhizome	Anemarrhenae Rhizoma Praeparata (鹹知母)	Rhizome	Anemarrhenae Rhizoma Praeparata (知母)	Rhizome	Anemarrhenae Rhizoma Praeparata (知母)	Rhizome	Anemarrhenae Rhizoma Praeparata (知母)
Artemisia annua L.	Whole herb	Artemisiae Annuae Herba Praeparata (醋青蒿)	Whole herb	Artemisiae Annuae Herba (青蒿)	Whole herb	Artemisiae Annuae Herba (青蒿)	Whole herb	Artemisiae Annuae Herba (青蒿)
Asparagus cochinchinensis (Lour.) Merr.	Root	Asparagi Radix (天文冬)	Root	Asparagi Radix (天门冬)	Root	Asparagi Radix (天门冬)	Root	Asparagi Radix (天门冬)
Carthamus tinctorius L.	Flower	Carthami Flos Praeparata (酒红花)	Flower	Carthami Flos (红花)	Flower	Carthami Flos (红花)	Flower	Carthami Flos (红花)
Citrus medica L.	Pericarp	Citri Sarcodactylis Pericarpium (佛手柑)	Pericarp	Citri Sarcodactylis Pericarpium	Pericarp	Citri Sarcodactylis Fructus (佛手柑)	Fruit	Citri Sarcodactylis Fructus (佛手)
			Flower	Citri Sarcodactylis Flos (佛手花)			Fruit	Citri Fructus (香橼)
Cornus officinalis Siebold & Zucc.	Fruit	Corni Fructus (山茱萸)	Fruit	Corni Fructus (山茱萸)	Fruit	Corni Fructus (山茱萸)	Fruit	Corni Fructus (山茱萸)

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Table 4.5 Common species appeared in 4 collections. (*continued*)

	Westhoff Collection (c. 1880)		**Hooper Collection (1924)**		**Catlender Collection (c. 1980)**		**Zhong Hua Collection (2021)**	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Crataegus pinnatifida Bunge	Fruit	Crataegi Fructus (山楂肉)	Fruit	Crataegi Fructus (山楂肉)	Fruit	Crataegi Fructus (山楂)	Fruit	Crataegi Fructus (山楂-生)
							Fruit	Crataegi Fructus Preparata (山楂-焦)
Cullen corylifolium (L.) Medik.	Fruit	Psoraleae Fructus (破故纸)	Fruit	Psoraleae Fructus (补骨脂)	Fruit	Psoraleae Fructus (补骨脂)	Fruit	Psoraleae Fructus (补骨脂)
Curcuma longa L.	Rhizome	Curcumae Longae Rhizoma (姜黄)	Rhizome	Curcumae Longae Rhizoma (姜黄)	Rhizome	Curcumae Longae Rhizoma (姜黄)	Rhizome	Curcumae Longae Rhizoma (姜黄)
			Fruit slices	unknow				
Cyperus rotundus L.	Rhizome	Cyperi Rhizoma Praeparata (四香附)	Rhizome	Cyperi Rhizoma (香附)	Rhizome	Cyperi Rhizoma (香附)	Rhizome	Cyperi Rhizoma (香附)
Dimocarpus longan Lour.	Flower	Longan Flos (龙眼花)	Flower	Longan Flos (龙眼花)	Aril	Longan Arillus (龙眼肉)	Aril	Longan Arillus (龙眼肉)
Eclipta prostrata (L.) L.	Whole herb	Ecliptae Herba (旱莲草)	Whole herb	Ecliptae Herba (旱莲草)	Whole herb	Ecliptae Herba (旱莲草)	Whole herb	Ecliptae Herba (旱莲草)
Foeniculum vulgare Mill.	Fruit	Foeniculi Fructus (小茴香)	Fruit	Foeniculi Fructus (小茴香)	Fruit	Foeniculi Fructus (小茴香)	Fruit	Foeniculi Fructus (小茴香)
Forsythia suspensa (Thunb.) Vahl	Fruit	Forsythiae Fructus (赤连翘)	Fruit	Forsythiae Fructus (连翘)	Fruit	Forsythiae Fructus (连翘)	Fruit	Forsythiae Fructus (连翘)
Gleditsia sinensis Lam.	Thorns	Gleditsiae Spina (皂角刺)	Thorns	Gleditsiae Spina (皂角刺)	Thorns	Gleditsiae Spina (皂角刺)	Thorns	Gleditsiae Spina (皂角刺)
	Fruit	Gleditsiae Fructus (皂荚)	Fruit	Gleditsiae Fructus (皂荚)	Fruit	Gleditsiae Fructus (皂荚)		

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Table 4.5 Common species appeared in 4 collections. (*continued*)

Scientific name	Westhoff Collection (c. 1880) Medicinal part	Westhoff Collection (c. 1880) Pharmaceutical name (Chinese name)	Hooper Collection (1924) Medicinal part	Hooper Collection (1924) Pharmaceutical name (Chinese name)	Catlender Collection (c. 1980) Medicinal part	Catlender Collection (c. 1980) Pharmaceutical name (Chinese name)	Zhong Hua Collection (2021) Medicinal part	Zhong Hua Collection (2021) Pharmaceutical name (Chinese name)
Morus alba L.	Root bark	Mori Cortex (桑白皮)	Root bark	Mori Cortex (桑白皮)	Root bark	Mori Cortex (桑白皮)	Root bark	Mori Cortex (桑白皮)
			unknow	unknow	Fruits	Mori Fructus (桑惿)	Root bark	Mori Cortex Praeparata (炙桑白皮)
					Leaves	Mori Folium (桑叶)	Fruits	Mori Fructus (桑惿)
					Branch	Mori Ramulus (桑枝)	Leaves	Mori Folium (桑叶)
							Branch	Mori Ramulus (桑枝)
Myristica fragrans Houtt.	Seed	Myristicae Semen (肉豆蔻)	Seed	Myristicae Semen (肉豆蔻)	Seed	Myristicae Semen (肉豆蔻)	Seed	Myristicae Semen (肉豆蔻)
Ophiopogon japonicus (Thunb.) Ker Gawl.	Root	Ophiopogonis Radix (麦门冬)	Root	Ophiopogonis Radix (麦门冬)	Root	Ophiopogonis Radix (麦门冬)	Root	Ophiopogonis Radix (麦门冬)
Perilla frutescens (L.) Britton	Fruit	Perillae Fructus (紫苏子)	Fruit	Perillae Fructus (紫苏子)	Fruit	Perillae Fructus (紫苏子)	Fruit	Perillae Fructus (紫苏子)
			Stem	Perillae Caulis (紫苏梗)	Stem	Perillae Caulis (紫苏梗)	Stem	Perillae Caulis (紫苏梗)
			Leaf	Perillae Folium (紫苏叶)	Leaf	Perillae Folium (紫苏叶)	Leaf	Perillae Folium (紫苏叶)
Pinellia ternata (Thunb.) Makino	Rhizome	Pinelliae Rhizoma Praeparata (姜半夏)	Rhizome	Pinelliae Rhizoma (半夏)	Rhizome	Pinelliae Rhizoma (半夏)	Rhizome	Pinelliae Rhizoma (半夏)
Platycladus orientalis (L.) Franco	Leaf	Platycladi Cacumen Praeparata (黑扁柏)	Leaf	Platycladi Cacumen (侧柏叶)	Seed	Platycladi Semen (柏子仁)	Leaf	Platycladi Cacumen (侧柏叶-生)
			Seed	Platycladi Semen (柏子仁)			Leaf	Platycladi Cacumen Praeparata (侧柏叶-炒)
							Seed	Platycladi Semen (柏子仁)

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Table 4.5 Common species appeared in 4 collections. (*continued*)

	Westhoff Collection (c. 1880)		**Hooper Collection (1924)**		**Catlender Collection (c. 1980)**		**Zhong Hua Collection (2021)**	
Scientific name	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**	**Medicinal part**	**Pharmaceutical name (Chinese name)**
Platycodon grandiflorus (Jacq.) A.DC.	Root	Platycodonis Radix Praeparata (蜜橘梗)	Root	Platycodonis Radix (桔梗)	Root	Platycodonis Radix (桔梗)	Root	Platycodonis Radix (桔梗)
Polygonum aviculare L.	Whole herb	Polygoni Avicularis Herba (萹蓄)	Whole herb	Polygoni Avicularis Herba (萹蓄)	Whole herb	Polygoni Avicularis Herba (萹蓄)	Whole herb	Polygoni Avicularis Herba (萹蓄)
Prunella vulgaris L.	Spike	Prunellae Spica (夏枯草)	Spike	Prunellae Spica (夏枯草)	Spike	Prunellae Spica (夏枯草)	Spike	Prunellae Spica (夏枯草)
Rehmannia glutinosa (Gaertn.) DC.	Root	Rehmanniae Radix (地黄)	Root	Rehmanniae Radix (地黄)	Root	Rehmanniae Radix (地黄)	Root	Rehmanniae Radix (地黄)
	Root	Rehmanniae Radix Praeparata (老熟地)			Root	Rehmanniae Radix Praeparata (熟地黄)	Root	Rehmanniae Radix Praeparata (熟地黄)
Rosa laevigata Michx.	Fruit	Rosae Laevigatae Fructus (大金英)	Fruit	Rosae Laevigatae Fructus (金樱子)	Fruit	Rosae Laevigatae Fructus (金樱子)	Root	Rosae Laevigatae Radix (金樱根)
							Fruit	Rosae Laevigatae Fructus (金樱子)
Saposhnikovia divaricata (Turcz. ex Ledeb.) Schischk.	Root	Saposhnikoviae Radix (软防风)	Root	Saposhnikoviae Radix (防风)	Root	Saposhnikoviae Radix (防风)	Root	Saposhnikoviae Radix (防风)
Xanthium strumarium L.	Fruit	Xanthii Fructus (苍耳子)	Fruit	Xanthii Fructus (苍耳子)	Fruit	Xanthii Fructus (苍耳子)	Fruit	Xanthii Fructus (苍耳子)
Zingiber officinale Roscoe	Rhizome	Zingiberis Rhizoma Praeparata (泡干姜)	Rhizome	Zingiberis Rhizoma (干姜)	Rhizome	Zingiberis Rhizoma (干姜)	Rhizome	Zingiberis Rhizoma (干姜)
Ziziphus jujuba Mill.	Fruit	Jujubae Fructus Praeparata (大乌枣)	Fruit	Jujubae Fructus (大枣)	Fruit	Jujubae Fructus (大枣)	Fruit	Jujubae Fructus (红枣)

Another species that all four collections have in common, *Rosa laevigata* Michx., also witnessed an extension of its medicinal parts. The fruit of *R. laevigata* (Rosae Laevigatae Fructus, 金樱子 jīn yīng zǐ) is included in the three collections, but in the Zhong Hua 2021 trade list, not only the fruit but also the root of *R. laevigata* (Rosae Laevigatae Radix, 金樱根 jīn yīng gēn) is present. *R. laevigata* roots only recently appeared in TCM formulae and Chinese patent medicines (Chinese Pharmacopoeia Commission, 2015; Zhong Yao Da Ci Dian Edit Committee, 2006; Zhonghua Bencao Edit Committee, 1999), which is reflected in our comparative study as the CMM collection of the 1980s did not yet show this change.

China root, *Smilax glabra* Roxb. (Smilacis Glabrae Rhizoma, 土茯苓 tǔ fú líng), as we mentioned in Introduction part, was quite popular in Europe since 16th century (Winterbottom, 2015). Unsurprisingly, it has been found in historical collections and Zhong Hua list (except Westhoff collection), which supports the conclusion drew from textual research and complement them from physical specimen aspect.

Except for the common species discussed before, there are several common drugs in the five collections that are likely to come from multiple botanical sources. Glycyrrhizae Radix et Rhizoma (甘草 gān cǎo) can be obtained from *Glycyrrhiza uralensis* Fisch., *G. glabra* L. and *G. inflata* Batal. Ligustici Rhizoma et Radix (藁本 gǎo běn) has two possible botanical sources: *Ligusticum sinense* Oliv. and *L. jeholense* (Nakai & Kitag.) Nakai & Kitag. Gentianae Macrophyllae Radix (秦艽 qín jiāo) has three botanical sources: *Gentiana macrophylla* Pall., *G. straminea* Maxim., *G. crassicaulis* Duthie ex Burk. and *G. dahurica* Fisch. Finally, Gentianae Radix et Rhizoma (龙胆 lóng dǎn) can be harvested from *Gentiana manshurica* Kitag., *G. scabra* Bge., *G. triflora* Pall. and G. rigescens Franch (Chinese Pharmacopoeia Commission, 2015). These CMM products all appear over more than 300 years, but as the exact species from which they were harvested is not known or visible in the morphology of the product, we could not include these species in our comparative analysis.

If we focused on the large collections and exclude the smallest and oldest Sloane collection, more common drugs emerge. Bupleuri Radix (柴胡 chái hú, botanical sources: *Bupleurum chinense* DC. and *B. scorzonerifolium* Willd.), Dianthi Herba (瞿麦 qú mài, botanical sources: *Dianthus chinensis* L. and *D. superbus* L.) and Cassiae Semen (决明子 jué míng zǐ, botanical sources: *Senna obtusifolia* (L.) H.S.Irwin & Barneby and *S. tora* (L.) Roxb.) are shared between the remaining three collections and the modern trade list. These drugs have been used for thousands of years and are still very frequently used in China (Chinese Pharmacopoeia Commission, 2015; Zhong Yao Da Ci Dian Edit Committee, 2006; Zhonghua Bencao Edit Committee, 1999).

Among the studied collections, two common drugs, Aristolochiae Fructus (马兜铃 mǎ dōu líng, botanical sources: *Aristolochia contorta* Bunge and *A. debilis* Siebold & Zucc.) and Asari Radix et Rhizoma (细辛 xì xīn, botanical sources: *Asarum heterotropoides* F.Schmidt and *A. sieboldii* Miq.) also attracted our attention. These two products are present in four historical collections but disappeared from the list of currently commercialized CMM (Zhong Hua collection 2021). *Aristolochia* fruits and *Asarum* roots belong to the Aristolochiaceae family, well known because of its toxic aristolochic acids (Michl et al., 2014; Shibutani et al., 2007). These components are reported to stimulate defense mechanisms against infections and inflammation in several mammalian species, including humans (European Medicines Evaluation Agency, 2005). In the past, *Aristolochia* fruits and *Asarum* roots were frequently used in traditional Chinese medicine. After several accidents with poisoning (Lord et al., 1999; Vanherweghem et al., 1993), there is a better understanding of the toxicity of aristolochic acids, and species within the Aristolochiaceae family have been restricted or prohibited as herbal medicine in Europe (European Medicines Evaluation Agency, 2005). The recent exclusion of Aristolochiaceae species in CMM traded in Europe is also reflected in our comparative analysis.

6. Common species used in TCM formulae

In TCM, instead of single component medicines, combinations of multiple herbs are generally used for clinical treatment. These multi-herbal mixtures are known as formulae. More than 100,000 different TCM formulae have been documented over the past 2000 years (Qiu, 2007). Many of these classic formulae of Chinese patent medicine documented in the ChP 2015 have been extensively studied for efficacy and safety, and are widely used by the general public as over-the-counter (OTC) drugs in China today. The ancient classical TCM formulae are described in well-known historical CMM monographs, such as *Treatise on febrile diseases* (伤寒论 shāng hán lùn) and *Synopsis of the golden chamber* (金匮要略 jīn guì yào lüè) compiled by Zhang Zhongjing, *Thousand ducat formulas for emergencies* (备急千金要方 bèi jí qiān jīn yào fāng) compiled by Sun Simiao (Chen and Xie, 1999). Formulae from the Chinese patent medicine in the ChP 2015 and the ancient classical TCM formulae list issued by the Chinese National Administration of Traditional Chinese Medicine can indicate which ingredients were commonly used in the past and present.

The 14 species shared among all four studied collections and the modern trade list are all ingredients of TCM formulae that appear in the modern and/or classical lists. This means that the shared species in the five collections reflect the common species used in both historical TCM formulae and modern Chinese patent medicine. When we exclude the Sloane collection, all 47 shared species appeared in the formulae in the two lists. The high degree of consistency indicates that the shared species as ingredients for the traditional formulae have been used with high frequency in the past and present.

What is worth mentioning is that the flowers of *Lonicera japonica* Thunb. (Lonicerae Japonicae Flos, 金银花 jīn yín huā), appearing in all four collections and the modern trade list, are used as a major ingredient of TCM formulae in both the classical and the modern lists. *Lonicera* flowers are included in more than 420 TCM formulae, and have always been a frequently used medicine throughout Chinese history (Chinese Pharmacopoeia Commission, 2015; Zhonghua Bencao Edit Committee, 1999). In 2020, Lianhua Qingwen granules, which contain *Lonicera* flowers, were widely used in the treatment of Covid-19 in China (Li et al., 2020). This vivid example of continuity in CMM from ancient times to today was also shown in the physical specimens in the historic collections.

Currently, the European Union has demanded analytical and pharmaco-toxicological tests and clinical trials since the Directive 65/65/EEC in 1965 and the amended directive 2001/83/EC before Chinese herbal products can be legally registered as medicines in EU member states (Verma, 2016). A systematic regulatory framework was established after the enforcement of the traditional herbal medicinal products directive (Directive 2004/24/EC), which registered herbal products with long-standing use in a simplified way, with respect to the proof of efficacy and data on safety. In the directive 2004/24/EC, any non-European herbal medicinal product is required to have at least 30 years of traditional use evidence, and evidence of 15 years of traditional use in the EU (Qu et al., 2018). Our current research provides new information on the traditional use of multiple species and plant parts over time, as we know that the herbal materials analyzed in this study can be traced back to China (Sloane and Catlender collections, Zhong Hua trade list) or Chinese pharmacies in the Malay peninsula (Hooper collection) or Indonesia (Westhoff collection).

Conclusion

In the four historical collections of CMM included in our analysis, we can witness great continuity but also subtle changes in traditional Chinese medicine in a time span of 300 years. In general, the proportion of plant families and medicinal plant parts remain similar. Fabaceae and Asteraceae were the most represented plant families but did not dominate the floristic diversity. A total of 14 species were present in all studied collections, and 47 were shared by all but the oldest (and least complete) Sloane collection. Still, several new medicinal parts appeared in younger collections, while some toxic CMM (Aristolochiaceae products) and endangered animals disappeared from the most recent collection and the modern trade list due to the safety issues. These four historical CMM collections have been personal showcase collections and preserved in museums or scientific institutions in Europe. These materials have not been used as medicines in Europe, however they may have indirectly influenced the European view of herbal medicine. In addition, changes of CMM in these historical collections, particularly the Westhoff and Hooper collections, which originate from outside of China, may have been influenced by local medicinal practices or the availability of certain plant resources. To prove this hypothesis, further investigation is needed on regional variation in TCM. Identification problems hindered a full comparison among all specimens in the collection. Our investigation contributes to a better understanding of time dependent changes in CMM use, either caused by safety concerns, conservation issues or innovation in traditional Chinese medicine.

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Conflicts of interest

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

Appendix 1. Supplementary data

Supplementary data to this article can be found on line at
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Chapter Five

A comparative study of aged and contemporary Chinese herbal materials by using delayed luminescence technique

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Abstract

Background: Investigation of aged Chinese herbal materials will help us to understand their use and sources in ancient time and broaden the historical perspective of Chinese material medica. To reach this aim, the basic understanding of aged herbal materials, including physical and chemical characters, is of great importance. Delayed luminescence (DL) technique was developed as a rapid, direct, systemic, objective and sample loss-free tool to characterize the properties of Chinese herbal materials. In this study, we measured DL values in aged Chinese herbal materials that were transported from Asia to Europe during the 20th century and stored in Naturalis Biodiversity Center and the Utrecht University Museum, and compared these with modern material of the same species.

Methods: A hyperbolic function was used to extract four properties from the DL curves of Chinese herbal material from 1900, the 1950s and recently harvested products. Statistical tools, including the Student's t test, One-way analysis of variance and Principal Component Analysis, were used to differentiate the DL properties of aged and contemporary collections of *Glycyrrhiza* spp. *Curcuma aromatica* Salisb., *Zingiber officinale* Roscoe, *Alpinia officinarum* Hance and *Acorus calamus* L.

Results: Our results showed that DL properties were significantly different between historical and contemporary Chinese herbal materials. Changes in DL values were species-dependent: the effects of storage time of DL properties were specific for each species. These outcomes help us not only in the identification of historical Chinese medicine products but also provides valuable data of the effect of storage time on herbal materials.

Conclusion: The simple, direct, rapid, and inexpensive measurements offered by DL provide a novel tool to assess the taxonomic identity of Chinese and other herbal materials and assess the differences in chemical properties with increasing storage time. Our results contribute to the further development of novel digital tools for the quality control of herbal materials.

Keywords: delayed luminescence; Chinese herbal medicine; aged herbal materials, quality control.

Abbreviations: DL: delayed luminescence; PCA: Principal component analysis; ANOVA: Analysis of variance

Background

Herbal medicine has been used for millennia in China to maintain good health and for the treatment of diseases, and during the last decades it's global popularity is increasing (He et al., 2018; Scheid, 1999). Recently, the World Health Organization has included traditional Chinese medicine (TCM) in its medical compendium as a recognition of its significant acceptance worldwide (Cyranoski, 2018). As early as the Chinese Han Dynasty (202 BCE-

220 BE), the exchange of herbal medicine between China and the outside world has begun through the Silk Road (Heyadri et al., 2015). Around the beginning of the 10th century, Xun Li wrote his work *Extrinsic Materia Medica*, summarizing information on more than 120 herbs introduced into China from abroad (Zhang, 2013). In the same period, due to the gradual development of maritime trade, China began exporting herbal medicines to its surrounding countries and regions. From the Ming Dynasty (1368-1644 AD) onwards, Chinese herbal medicines were shipped to Europe in large quantities through maritime trade, first with Portuguese and later with the Dutch. One of the famous and popular herbal medicines at that time was "China root" (Smilacis Glabrae Rhizoma, the rhizome of *Smilax glabra* Roxb.). It was used to treat syphilis and as a result of increasing global movements and trade, the product became rapidly popular worldwide (Winterbottom, 2015). From the 17th century onwards, European scientists and explorers collected Chinese herbs progressively for the aim of curiosity, the study of different medical cultures and the interest in exotic medicinal plants. Several European museums and private persons hold collections of historical Chinese herbal medicine, some more than 100 years old, such as the ancient Chinese medicinal material collection in the Natural History Museum in London (Zhao et al., 2015). Several historic TCM collections are housed by the Utrecht University Museum and Naturalis Biodiversity Center in Leiden in the Netherlands (Figure 5.1).

Historic collections of Chinese herbal materials are valuable objects for the scientific study of Chinese culture, trade and ethnopharmacology. Investigation of ancient herbal materials will help us to understand how the use of TCM has changed through history. Centuries ago, the global demand in Chinese herbal materials was not as high as in the present. In the course of time, some of the original plant species were replaced by others. Wild plants are now grown in high production systems (Wang et al., 2019), while rare plants have gone extinct (Chen et al., 2016; Hamilton, 2004). For example, Lignum sinensis resinatum, the resinous wood of *Aquilaria sinensis* (Lour.) Spreng., was substituted by Lignum aquilariae resinatum (*Aquilaria agallocha* (Lour.) Roxb.) (Zhao et al., 2006). According to *Zhonghua Bencao*, *A. sinensis* and *A. agallocha* have similar active constituents and the same clinical effect (Zhonghua Bencao Edit Committee, 1999). In addition, historic local names of herbs have changed or are confused with different plant species with similar names elsewhere in China (Zhao et al., 2006). All these variations and changes in names and species over time may lead to mistakes in recipes and the use of the wrong herbal materials with potential risks to consumers (Lord et al., 2001). Most previous studies that evaluate historical changes in TCM have largely focused on literature research (Brand et al., 2017), but many of their conclusions have not yet been confirmed by the revision of physical samples from premodern collections of Chinese herbal materials. Therefore, it is critical to have an objective analytic tool for the assessment of these ancient collections of herbal materials (Brand et al., 2017).

Figure 5.1 Historic herbal materials used in this study. A) Display cabinets of historical herbal medicine in Utrecht Botanical Gardens. B) Historic collections of *Zingiber officinale* (Sample ID Z.o_1900) in Utrecht Botanical Gardens. C) Historic *Curcuma aromatica* collection (Sample ID C.a_1900) in Utrecht Botanical Gardens. D) Historic *Alpinia officinarum* rhizome (Sample ID A.o_1900) at Utrecht Botanical Gardens. E) Historic *Glycyrrhiza glabra* root (Sample ID G.g_1929) in Naturalis Biodiversity Center.

The identification of historic collections of TCM is challenging, as the amount of stored material per species is often very small and fragile. Due to the distinctiveness of these historic collections, we are constrained to perform analytic studies with limited amounts of herbal materials. Instead of destructive methods such as DNA analysis and chemical profiling studies, non-destructive techniques are preferred to identify ancient and very valuable TCM collections. Delayed luminescence (DL) was developed as a rapid, direct, systemic tool to measure the decaying ultra-weak luminescence (up to seconds or minutes) exhibited by materials after being illuminated with light. As a sample loss-free technique, DL is a sensitive approach and widely applied in determining food quality (Chen et al., 2005), seed germination (Costanzo et al., 2008) and cancerous cells (Scordino et al., 2014b). DL is a photo-induced ultra-weak photon emission (Scordino et al., 2014a), of which the properties are influenced by molecular structures and interactions (Barenboĭm et al., 2013), in particular the long chain molecules (He et al., 2019; Li et al., 2019). The molecular absorption of excitation energy determines the dynamics of the subsequent DL emission (Barenboĭm et al., 2013). Compared with other existing methods, DL has the following advantages: 1) Simplicity. Herbal material only needs be ground to powder, no other complicated treatment is required; 2) Sample loss-free. Powdered medicinal material is exposed to light for 10 seconds, then the photon released from the sample is recorded by the instrument. There will be no chemical or biological changes in the samples, and they can be used again for other analytical research; 3) Rapidity. The whole experiment process is simple and fast: it only takes several seconds for the measurement and ca. 10 minutes from sample pre-processing to obtaining the data for one sample; 4) Reduced costs. Compared to chromatography and DNA-barcoding, DL experimental instruments are very cheap and no kits are required for sample preparation.

Recently, various researchers have successfully applied DL in herbal medicine to identify specific properties of herbal materials or to detect variations in the material due to variation in environmental growth conditions (Sun et al., 2016a), different processing methods (Sun et al., 2018; Sun et al., 2016b) and determination of authenticity (Sun et al., 2019b). Differences detected by DL in herbal materials are also reflected by their chemical profiling (Sun et al., 2018; Sun et al., 2019a) as well as therapeutic activities (Sun et al., 2017). The ability of DL to rapidly distinguish between herbal material with different growth conditions, processing states, taxonomic identity or therapeutic properties, all of which are linked to differences in chemical compositions in the materials, suggest that DL is a promising technology for further evaluation of the quality of herbal material (Sun et al., 2017; Sun et al., 2018).

In this work, we have tested whether DL can also be used to detect changes in herbal medicine over time. We performed DL analysis on historic TCM collections of the species *Glycyrrhiza glabra* L., *Glycyrrhiza inflata* Batalin, *Glycyrrhiza uralensis* Fisch., *Curcuma aromatica* Salisb., *Zingiber officinale* Roscoe, *Alpinia officinarum* Hance and *Acorus calamus* L. and contemporary materials of their corresponding species. The results obtained from our DL measurements show that DL properties indicate differences between aged and contemporary herbal materials, and that DL may be further used to verify the storage time of herbal materials. Therefore, DL can provide new insights into the quality and safety of herbal medicines.

Materials and Methods

1. Herbal materials

Historic herbal material was sampled from the collections of Chinese medicine that are housed in the Economic Botany collection of Naturalis Biodiversity Center (Leiden, the Netherlands), which were obtained in the 1950s in Indonesia and from collections of the Utrecht University Museum, stored in the Wachendorfzaal of Utrecht Botanical Gardens (Utrecht, the Netherlands). Due to the small amount of herbal material stored per species, only a limited amount of samples could be taken from the museum collections for this study. Contemporary herbal materials were obtained from the Institute of Chinese *Materia Medica*, the Beijing Institute of Chinese Medicine, National Institutes for Food and Drug Control and

TongRenTang Co., Ltd., all located in Beijing, China. All samples were verified for the correct taxonomic identification by Dr. Mei Wang and Dr. Yuhua Shi and later deposited at the European Center for Chinese Medicine and Natural Compounds of Leiden University (Leiden, the Netherlands).

2. Sample preparation and DL Measurement

Herbal materials were milled by a grinder (model QE-100, Yili Company, Zhejiang Province, China) and passed through a sieve to obtain 150 μm particles. The powdered herbal material was kept in light-proof boxes containing some 3-5 mm silica gel (BoomBV, Meppel, the Netherlands) at room temperature for 16 h before the DL measurements (Sun et al., 2016b).

DL assays were performed according to the published protocol (Sun et al., 2016b). The instrument used in our measurements was development by Meluna Research (Geldermalsen, the Netherlands) and included a photomultiplier tube (PMT) (type 9558QB; Electron Tubes Enterprises Ltd., Ruislip, UK), vertically positioned on a dark sample chamber kept at 22 °C. The PMT contained a cathode end (51 mm diameter) with sensitivity at 300-800 nm. The PMT was cooled to −25 °C in order to reduce the dark count rate to 10 counts per second. A fast preamplifier (model 9301, ORTEC, Oak Ridge, TN) was used to amplify the photon emission signal. Data were extracted by a computer with a model 6602 counting card (National Instruments, Austin, TX). For each sample, 1 g powder was taken and put into a petri dish (diameter: 35mm), then exposed to light for 10 s using a model 284-2812 white halogen excitation source (Philips, Germany). The DLs of these samples were successively measured three times. The data obtained from the three measurements were used to analyze the DL properties of each sample. The DL decay signature was obtained by recording the number of photon counts in consecutive 0.05-s periods for a total of 60 s, yielding a total of 1200 data points.

3. Statistical analysis of DL properties.

In order to calculate the DL properties of the samples, all the photon counts measured during the 60 s of each decay curve were used according to the following hyperbolic function (Sun et al., 2018):

$$I_{(t)} = \frac{I_0}{(1 + \frac{t}{Tau})^{Beta}}$$

$$T = (e^{\frac{1}{Beta}} - 1) \times Tau$$

This hyperbolic function is a general formula for fitting the DL decay curve of samples. The four parameters (I0, Beta, Tau and T) obtained by this hyperbolic function can well express the characteristics of the DL decay curve (Pang et al., 2016; Sun et al., 2018). I0 is the initial intensity of the DL curve, Beta is an index factor associated with the rate of DL decay, and Tau and T represent the DL characteristics and decay time, respectively. The parameters of the repeated measurements (at least three times) were averaged and used to represent the DL properties of each sample. Principal components analysis (PCA) scores were used to indicate the level of discrimination between DL properties by tools provided in the MetaboAnalyst software package (http://www.metaboanalyst.ca). A two-tailed, unpaired Student's t test and One-way analysis of variance (ANOVA) with least significant difference (LSD) post hoc analysis (SPSS version 23.0) were used to compare the DL properties between herbal samples; differences were considered significant at $p < 0.05$.

Results

In order to assess the applicability of DL techniques in detecting differences between aged and contemporary herbal material, five different types of herbal products, each with historical and corresponding recent materials were used in this research. The samples measured in this study are shown in Table 5.1. The four parameters of the DL decay curves were calculated by a hyperbolic function, which was used to fit the observed decay curves. The differences in four separate parameters were visualized by the PCA, which allowed us to achieve a focused view of the variance in the four properties. The correlation of each parameters to the different samples was illustrated in a PCA biplot.

Alpinia officinarum and *Acorus calamus* were firstly analyzed. For these two species we had only samples from two different points in time: historical samples from around 1900 and modern samples from 2017. The DL decay curves of *A. officinarum* (Figure 5.2A), clearly show differences between samples from 1900 and 2017. The four parameters of the DL decay curve that were compared all differed significantly between the recent and aged samples (Figure 5.2B). Figure 5.2C displays the PCA results in the form of a score plot, in which the *A. officinarum* samples were clustered into two age groups. The PCA biplot (Figure 5.2D) reveals that parameters I0, Beta, Tau and T are responsible for distinguishing between the two groups.

Table 5.1 Sample information.

Pharmaceutical Name	Sample ID	Scientific Name	Sample Source	Sampling Time
Glycyrrhizae Radix et Rhizoma	G.g_1900	*Glycyrrhiza glabra* L.	Utrecht Botanic Gardens	1900
	G.g_1929	*Glycyrrhiza glabra* L.	Naturalis Biodiversity Center	1929
	G.g_2018	*Glycyrrhiza glabra* L.	Institute of Chinese *Materia Medica*	2018
	G.i_2018	*Glycyrrhiza inflata* Batalin	Institute of Chinese *Materia Medica*	2018
	G.u_2018	*Glycyrrhiza uralensis* Fisch.	Institute of Chinese *Materia Medica*	2018
Curcumae Radix	C.a_1900	*Curcuma aromatica* Salisb.	Utrecht Botanic Gardens	1900
	C.a_1957	*Curcuma aromatica* Salisb.	Naturalis Biodiversity Center	1957
	C.a_2018	*Curcuma aromatica* Salisb.	National Institutes for Food and Drug Control	2018
Zingiberis Rhizoma	Z.o_1900	*Zingiber officinale* Roscoe	Utrecht Botanic Gardens	1900
	Z.o_1952	*Zingiber officinale* Roscoe	Naturalis Biodiversity Center	1952
	Z.o_2017	*Zingiber officinale* Roscoe	TongRenTang Co., Ltd.	2017
Alpiniae Officinarum Rhizoma	A.o_1900	*Alpinia officinarum* Hance	Utrecht Botanic Gardens	1900
	A.o_2017	*Alpinia officinarum* Hance	TongRenTang Co., Ltd.	2017
Acori Tatarinowii Rhizoma	A.c_1900	*Acorus calamus* L.	Utrecht Botanic Gardens	1900
	A.c_2017	*Acorus calamus* L.	TongRenTang Co., Ltd.	2017

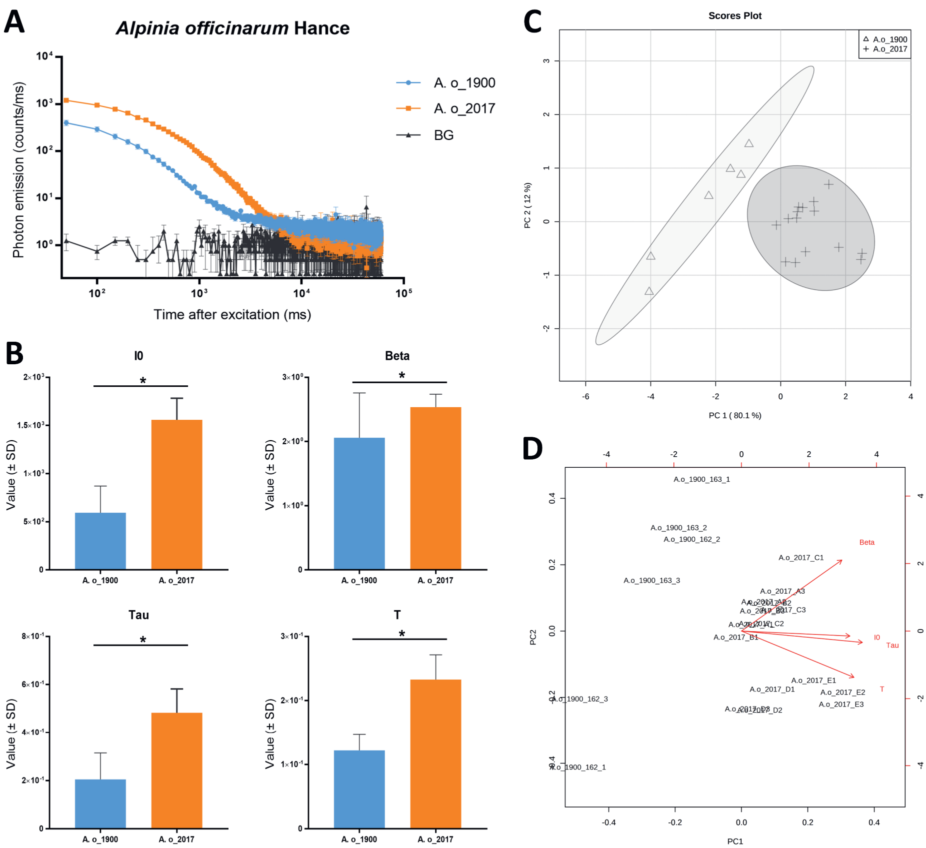

Figure 5.2 DL analysis of *Alpinia officinarum* Hance samples. A) DL decay curves comparison among *Alpinia officinarum* Hance samples. BG = background. B) Comparison of DL properties among the *Alpinia officinarum* Hance samples. I0 is the initial intensity of the DL curve, Beta is an index factor associated with the rate of DL decay, and Tau and T represent the DL characteristics and decay time, respectively. *, $p < 0.05$. C) PCA score plots of the DL properties obtained from *Alpinia officinarum* Hance samples. D) PCA biplot indicating how each parameter influences the similarity of DL decay curves.

The DL decay curve of *Acorus calamus* (Figure 5.3A) also shows that samples of different ages have different curves. The DL parameters analysis proved that the initial intensity (I0), curve rate (Beta), DL curve characteristics (Tau) and decay time (T) are significantly different between these two samples (Figure 5.3B). The PCA score plot shows that samples of different age clustered into separate groups (Figure 5.3C). The PCA biplot indicates that all four parameters contribute to separate samples of different ages (Figure 5.3D). The results of our DL analysis of *A. officinarum* and *A. calamus* show that DL technology is capable of discriminating between historic and recently collected herbal materials. All four parameters exhibited significant differences and the PCA clustered samples of unequal ages into different groups. However, as the tested materials were collected in time periods 117 years apart, we wondered whether specimens with less extreme age differences would also differ in their DL properties.

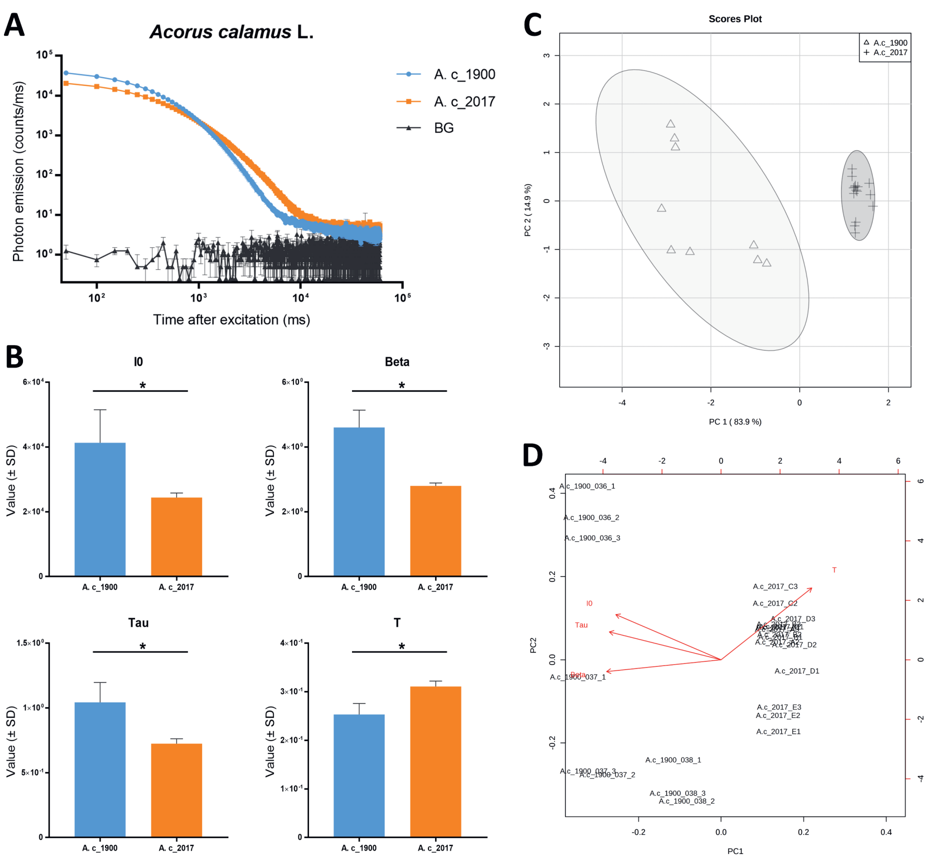

Figure 5.3 DL analysis of *Acorus calamus* L. samples. A) DL decay curves comparison among *Acorus calamus* L. samples. BG = background. B) DL properties comparison among *Acorus calamus* L. samples. I0 is the initial intensity of the DL curve, Beta is an index factor associated with the rate of DL decay, and Tau and T represent the DL characteristics and decay time, respectively. *, $p < 0.05$. C) PCA score plots of the DL properties obtained from *Acorus calamus* L. samples. D) PCA biplot shown how strongly each parameter influence the similarity of DL decay curves.

To answer this question, we used samples of *Curcuma aromatica* and *Zingiber officinale*, which were approximately stored for 60 and 120 years, and compared them to contemporary samples of corresponding species. We subjected the samples to DL analysis to verify whether this technology was able to distinguish three different storage times that were not so far apart. The DL analysis results of *C. aromatica* are presented in Figure 5.4. Samples from 1957 and 2018 had similar DL decay curves, while the curve of the sample from 1900 was quite distinctive (Figure 5.4A). To compare the four parameters of the DL decay curves, a one-way ANOVA test was used. Results revealed that for four parameters, the sample from 1900 was significantly different from other two more recent samples, while the samples from 1957 and 2018 did not significantly differ except for parameter T (Figure 5.4B). The PCA results (Figure 5.4C) show that all tested samples were divided into three clusters based on storage time and that the sample from 1900 clustered far from the other two groups. The PCA biplot indicates that parameter I0 and T were heavily responsible for identifying the clusters (Figure 5.4D). Together these results suggest that DL technology is able to distinguish samples of *C. aromatica* of 120 years old from 60-year-old samples, but not between 60-year-old and contemporary samples.

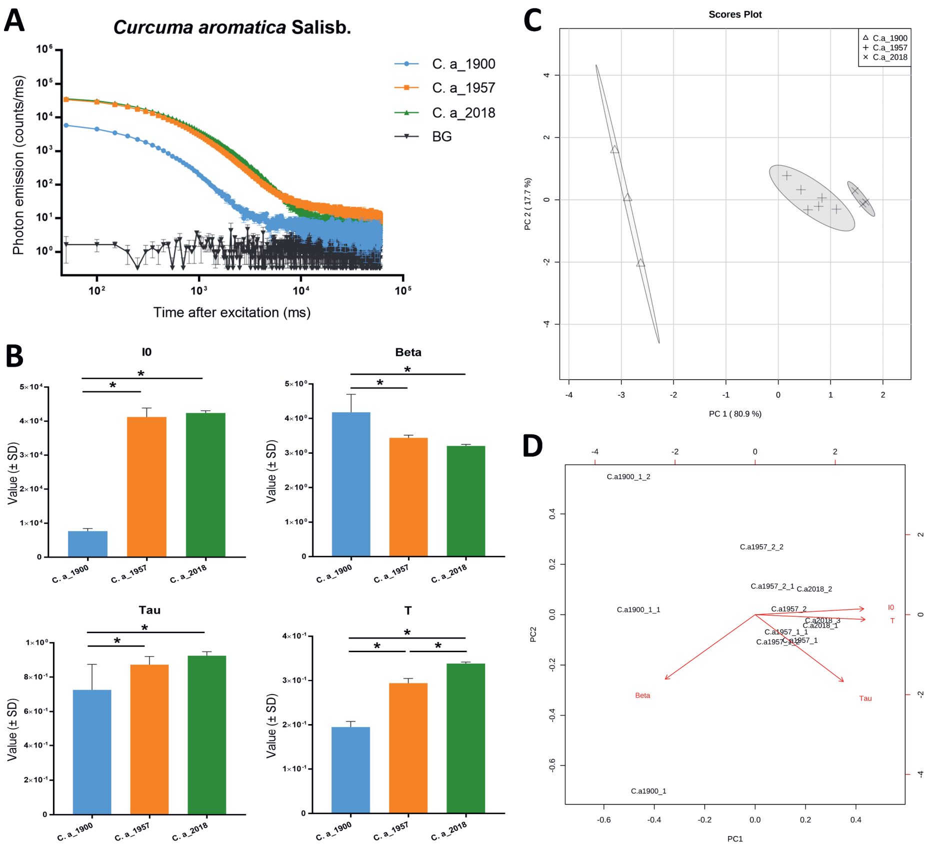

Figure 5.4 DL analysis of *Curcuma aromatica* Salisb. samples**.** A) DL decay curves comparison among *Curcuma aromatica* Salisb. samples. BG = background. B) DL properties comparison among *Curcuma aromatica* Salisb. samples. I0 is the initial intensity of the DL curve, Beta is an index factor associated with the rate of DL decay, and Tau and T represent the DL characteristics and decay time, respectively. *, $p < 0.05$. C) PCA score plots of the DL properties obtained from *Curcuma aromatica* Salisb. samples. D) PCA biplot shown how strongly each parameter influence the similarity of DL decay curves.

The DL decay curves for *Zingiber officinale* are shown in Figure 5.5, The sample from 2017 was strikingly different than the other two (Figure 5.5A). The parameters of the DL decay curves suggest that only parameters Beta and T differ significantly between the samples (Figure 5.5B). The PCA results illustrate that samples from 2017 formed a quite distinct cluster, and that the samples from 1900 and 1952 formed two relatively close clusters (Figure 5.5C). The PCA biplot demonstrates that the parameters Beta and T were responsible for dividing the samples from each other. These results indicate that DL technology is able to distinguish ginger roots of 120 and 60 years old from relevant contemporary samples, but not between samples of 120 and 60 years old.

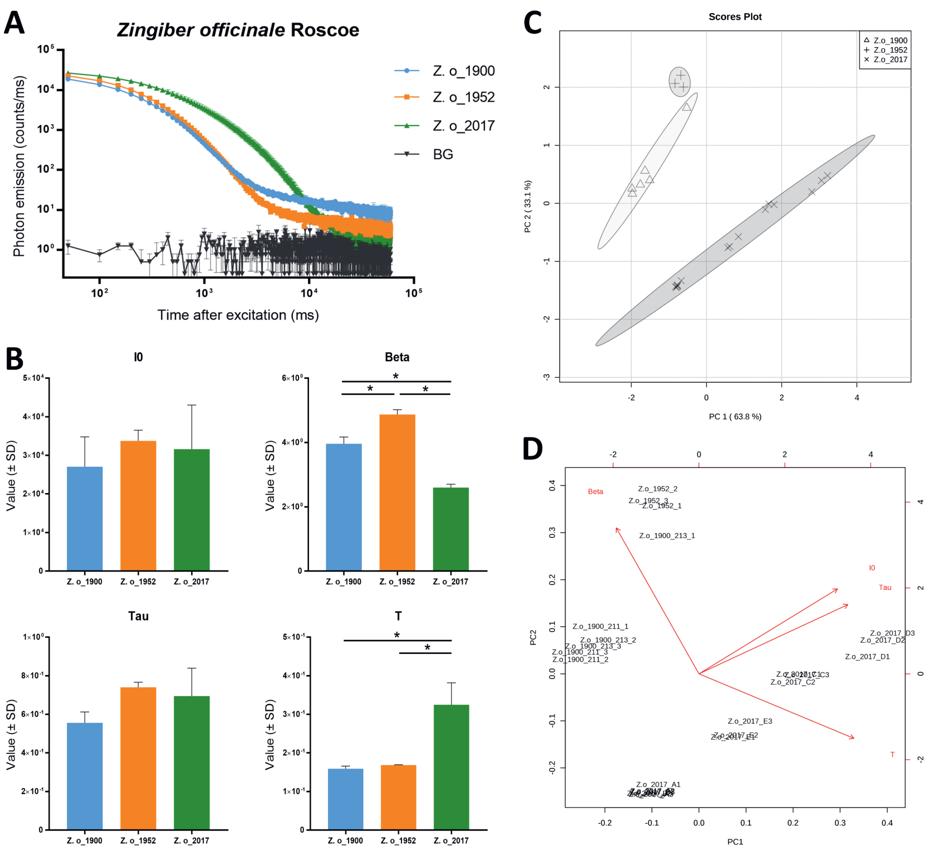

Figure 5.5 DL analysis of *Zingiber officinale* Roscoe samples. A) DL decay curves of *Zingiber officinale* Roscoe samples of different ages. BG = background. B) DL properties of the three different *Zingiber officinale* Roscoe samples. I0 is the initial intensity of the DL curve, Beta is an index factor associated with the rate of DL decay, and Tau and T represent the DL characteristics and decay time, respectively. *, $p < 0.05$. C) PCA score plot of the DL properties obtained from *Zingiber officinale* Roscoe samples. D) PCA biplot showing how each parameter influences the similarity of DL decay curves.

For *Curcuma aromatica*, DL analysis showed no significant differences between samples from 1957 and 2018, but both of them significantly differed from the one from 1900. We speculate that 60 years of storage time does not change its DL properties, but 120 years is long enough to do so. Conversely, the DL results of *Zingiber officinale* had no significant differences between samples from 1900 and 1952, but both of them significantly differed from the one from 2017.

Apparently, the DL properties of ginger roots change after 60 years of storage time, but after that they remain stable. The opposite is true for curcuma roots, which apparently start to change in DL properties after ca. 50 years. These findings suggest clearly that time-dependent changes in DL properties of herbal products occur, but that these changes are also species-dependent. Further research with more samples of multiple storage times and more species is needed to verify our speculation.

Apart from changes in DL values over time, we were also interested in the performance of DL technology in distinguishing closely related taxonomic species. Therefore, we compared contemporary and historic samples of Glycyrrhizae Radix et Rhizoma, known as liquorice root, and widely used as medicine, food supplement and flavoring agent. The botanical identity of our historical samples of Glycyrrhizae Radix et Rhizoma was *Glycyrrhiza glabra* L. However, according to the 2015 edition of the Chinese Pharmacopoeia, three different, botanically related species (*G. glabra*, *G. inflata* Batalin and *G. uralensis* Fisch.) can be used as Glycyrrhizae Radix et Rhizoma (Chinese Pharmacopoeia Commission, 2015). Therefore, in our study, two differently aged samples of Glycyrrhizae Radix et Rhizoma (*G. glabra*) and several contemporary samples of Glycyrrhizae Radix et Rhizoma of three different species were used for DL analysis. With samples collected at three distinct points in time and three different species, we continued to verify the capability of DL technology to distinguish among samples of different age and among closely related species.

Figure 5.6 presents the results obtained from the DL analysis of the various samples of liquorice roots. The DL decay curves of G.g_1900 and G.i_2018 are clearly different from the other samples (Figure 5.6A), which are all above the background level. Four parameters of the DL decay curves were compared between all samples using a one-way ANOVA test (Figure 5.6B). For parameter I0, sample G.g_1900 and G.i_2018 are significantly different from the others. For parameter Beta, sample G.g_1929 differs significantly from the other samples. The Tau parameter of sample G.g_1900 is significantly different as well as between the G.g_1929 and G.i_2018. The T parameter of sample G.g_1900 is significantly different from the other samples. The PCA score plot shows that the Glycyrrhizae Radix et Rhizoma samples are divided into three groups: samples collected in 1900, 1929 and 2018. Interestingly, despite the different species and batches, samples collected in 2018 are clustered into one group. The PCA biplot reveals that parameters I0, Tau and T are mainly responsible for distinguishing group 1900 from the other two groups. Parameter Beta is responsible for distinguishing between group 1929 and group 2018 (Figure 5.6D).

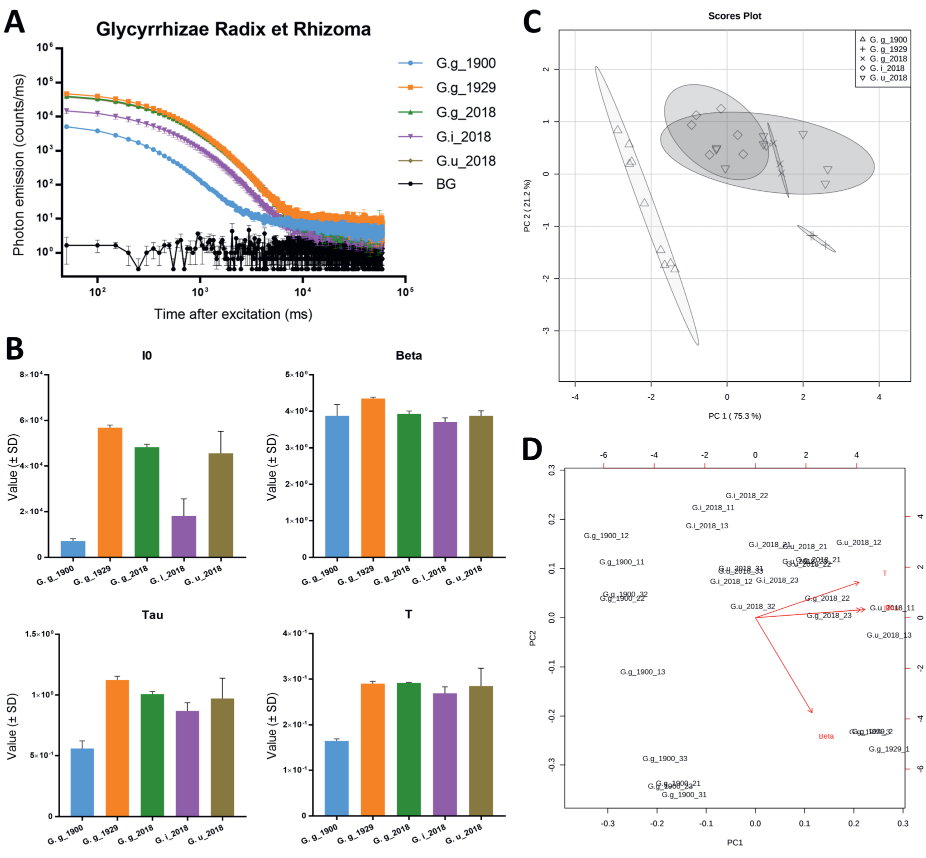

Figure 5.6 DL analysis of Glycyrrhizae Radix et Rhizoma samples. A) DL decay curves comparison among Glycyrrhizae Radix et Rhizoma samples. BG = background. B) DL properties comparison among Glycyrrhizae Radix et Rhizoma samples. I0 is the initial intensity of the DL curve. All five samples' I0 parameter were significantly different ($p < 0.05$) from each other, except G.g_2018 - G.g_1929 group and G.g_2018 - G.u_2018 group. Beta is an index factor associated with the rate of DL decay. The Beta parameter of G.g_1929 was significantly different ($p < 0.05$) from the other four samples. Tau represent the DL characteristics. The Tau parameter of G.g_1900 and G.g_1929 - G.i_2018 group and G.g_1929 - G.u_2018 group were significantly different ($p < 0.05$). T describes the DL decay time. T parameter of G.g_1900 was significantly different ($p < 0.05$) from the other four samples. C) PCA clustering of DL properties obtained from Glycyrrhizae Radix et Rhizoma samples. D) PCA biplot showing how each parameter influences the similarity of DL decay curves.

Our PCA data illustrate that different aged samples of the same species clustered into different groups, while distinctive species with same collection time showed no significant differences in DL values. Four parameters showed no significant differences, except I0 in sample G.i_2018. PCA clusters were mostly overlapping. Taken together, these results suggest that the DL technique is capable of discriminating samples of different ages of

Glycyrrhizae Radix et Rhizoma (at least for *G. glabra*), but not able to discriminate between closely-related species with same collection time.

Glycyrrhizae Radix et Rhizoma is one of the most frequently used herbal products in traditional Chinese medicine. On account of similar active ingredients (glycyrrhizic acid and liquiritin) and clinical effect, the three different species *G. glabra*, *G. inflata* and *G. uralensis* are grouped under the same pharmacological term (Chinese Pharmacopoeia Commission, 2015). Moreover, genetic studies show that the gene sequences of these three species are highly similar (Kondo et al., 2007). This may be the reason that the DL values of recent samples of these three species are not significantly different. But when taking storage time into account, we do not know whether age has the same impact on DL properties for the three different species. As we only had access to historic samples of *G. glabra*, and not for the other species, we do not know whether DL can distinguish different species of Glycyrrhiza in historic collections.

Discussion

Investigation of ancient Chinese herbal materials will help us not only to understand the origin and historical use of Chinese herbal medicine, but also to clarify the confusion on botanical identity, nomenclature and changes in species and plant parts over time. Studying historical samples with DL technology gives us new insight into the possible changes in chemical properties of herbal materials over time. Especially when there is a limited amount of herbal material available for testing, DL technique gives us support and solution from an analytic point of view. As DL has already applied to identify different processing methods (Sun et al., 2018) and determination of authenticity (Sun et al., 2019b), the novelty of the present study is the analysis of aged herbal materials, which provides unique opportunities to understand the effect of long-term storage on herbal materials.

In this research, we found that DL can provide sensitive measurements that reflect differences between historic and contemporary herbal materials. DL properties can be affected by changes of molecular conformations and interactions such as forming of hydrogen bonds and carbon-to-nitrogen ratio, resulting in the radiant transfer of energy from one excited molecule to another, causing a change in the material's DL kinetics. Recently, Grasso et al. (2019) reported significantly different DL kinetics of intensities and decay time intervals between amylose and cellulose, which share the same glucose-based repeat units, but have differently molecular structures, and the different DL properties of these two compounds may be related to the soliton mechanism (Brizhik et al., 2000; Brizhik et al., 2001). Amylose and cellulose are polysaccharides, which occur widely in herbal material as bioactive components, such as liquorice roots (*Glycyrrhiza* spp.) (Li et al., 2013). With increasing storage time, the polysaccharide content in plants may change, causing a change of molecular structure (Zhang, 2016). Large time intervals may cause significant changes in the chemical composition of polysaccharides. This may be the reason that DL distinguished historic and modern samples of Glycyrrhizae Radix et Rhizoma, but not the three botanically different *Glycyrrhiza* samples collected in similar periods.

The bioactive components in the other medicinal species used in this research are mainly volatile oils (Chinese Pharmacopoeia Commission, 2015). The volatile oil content of herbal material also changes during the storage time (Wu et al., 2015), which may be the reason why the DL characteristics of our long-term stored samples were so different from recently harvested samples. Future studies should focus on the chemical differences between historical and contemporary herbal material to investigate whether DL could characterize the chemical changes caused by storage time.

Storage time is an important factor in the stability of plant products and thus the quality of herbal medicine. Storage usually modifies the composition of herbal medicines, directly affecting safety and therapeutic value (Wu et al., 2015; Zhang, 2016). Most methods used to study composition changes caused by storage time are HPLC or GC-MS (Martinazzo et al., 2009), but these require expensive analytical tools and sample loss is inevitable. Compared to chromatographic methods, DL is a direct, rapid approach, which is quite affordable and does not imply sample loss. Moreover, DL can provide a comprehensive perspective for the sample's overall features, rather than only measuring the amount of certain components (Sun et al., 2017). Therefore, DL maybe a suitable technology to detect changes in herbal material influenced by storage time. In addition, due to distinctiveness and limited amounts of ancient herbal materials, DL is suitable to study the differences between ancient and contemporary herbal material of the same species. Because of DL's sample loss-free nature, it is suitable as the first analytic method, so it can be decided afterwards if it is necessary to employ further destructive methods such as DNA analysis (Han et al., 2016) and chemical profiling studies. Our study has shown that DL has the potential as a practical approach to verify the applicability of herbal material for clinical use. However, we need to establish a significant database for this purpose. In general, herbal material that has been stored for decades or centuries is no longer suitable for clinical use, but may provide valuable information to understand (changes in) properties of the material. To examine this possibility, using herbal materials with different storage time (e.g., from 1 to 5 years) and combining DL, chemical study and bioactivity analysis will provide a better understanding of changes in herbal material over time.

Conclusion

In this study, we used historical Chinese herbal medicine as research object to verify whether Delayed Luminescence was a suitable technology to analyze the differences between aged herbal material and corresponding contemporary herbal material. Our findings suggest that DL is a promising approach tool to study historical herbal material, as it is able to identify different properties among samples with different storage time. Our study also showed that patterns of properties changes are likely to be plant species dependent. Our study contributes to the lack in scientific data on the effects of storage time on herbal material. More research should focus on expanding the number of herbal species for DL analysis, data accumulation and mining to better understand DL technology's potential on assessment of quality related aspects of herbal material.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Y Jia, M Wang and T van Andel designed the study. Y Jia E. Wijk and R van Wijk conducted the statistical analyses and prepared figures. Y Jia and M Sun performed DL measurements. Y Shi and Z Zhu carried identification of herbal samples. Y Jia and M Wang drafted the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

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Chapter Six

General Discussion and Conclusion

Discussion

Historical Chinese *materia medica* collections in the Netherlands revisited

Historical Chinese *materia medica* collections preserved in the Netherlands, though largely unstudied for decades or even a century, possess significant research value. Many CMM were in use prior to the introduction of modern taxonomy in China, and traditional Chinese drug names often represent "medicinal plant complexes" that include more than one species (Brand et al., 2017). The confusion extends beyond shared common names and includes regional variation in botanical identity, the parts of plants used, and medical applications. The study of historical collections would clarify the nomenclature confusion, biological sources, medicinal parts and medical applications through comparison with modern CMM. The current state of knowledge regarding the historical prevalence of accepted species and adulterants in Chinese herbal medicine remains incomplete (Chen and Huang, 2005). This thesis examined the historical collections to determine the prevalent CMM practice spanning over three centuries by identifying common CMM items among different collections from various periods. These new findings offered new perspectives on understanding the history, dynamic changes in CMM. It also dmonistrated that there is a strong continuity in CMM but also with time-dependent changes in CMM. Furthermore, it is of utmost significance that all of these new findings are based on historical physical specimens, thereby bridging the long-standing gap between specimen research and literary studies.

Our thorough investigation of historical CMM collections and specimens has reintroduced some of them to the public view. A historical CMM collection preserved in Utrecht University Museum, the Westhoff collection was assumed to have been acquired by the Dutch ophthalmologist Dr. C.H.A. Westhoff in Indonesia around 1870 (**Chapter 2**). Out of 395 examined specimens, nearly 80% consisted of plant material and related substances, while 18% comprised animal and mineral substances. Regarding the medicines derived from plants, the dominant families were Fabaceae (5% of the specimens), Asteraceae (4 %) and Lamiaceae (4 %), with roots/rhizomes and fruits/seeds accounting for 49% of the utilized parts. Nearly 25% of CMM had undergone processing. These processing methods involved more than just simple preparations, such as cleaning and cutting. They also included elaborate methods like stir-frying, sometimes with adjuvants.

A private collection of historical CMM, the Catlender collection in Leiden, dated back to the 1980s (**Chapter 4**). Among the 297 specimens, 83% were plant-based materials, while 12% were derived from animals and minerals. Concerning the medicinal plants, Fabaceae (7% of the specimens) and Asteraceae (6%) still dominated as the most frequently occurring families. Similar to the Westhoff collection, the most frequently used parts were roots/rhizomes and fruits/seeds (together 56%).

In addition to these two complete collections, Naturalis Biodiversity Center and the Utrecht University Botanic Gardens housed a much larger number of historical botanical specimens collected from Southeast Asia. Among these numerous specimens, we included the well-known CMM species *Glycyrrhiza glabra* L., *Curcuma aromatica* Salisb., *Zingiber officinale* Roscoe, *Alpinia officinarum* Hance, and *Acorus calamus* L. in our study (**Chapter 5**).

Comparing historical and modern Chinese *materia medica* collections

In our comparison of these historical collections with more recent Chinese *materia medica* collections from Europe and China, as well as the recent Chinese Pharmacopeia (2015), we see mostly continuity in biological ingredients, medicinal parts, preparations and uses over time. However, we also see some differences in species, plant parts used, processing methods and medical applications.

The differences in CMM species have diverse underlying causes

1. Regional substitution: We observed that Eriocaulon sexangulare L. was used as Eriocauli Flos in the Westhoff collection, whereas it should have been *E. buergerianum* Körn. according to the Chinese Pharmacopoeia (**Chapter 2**). This substitution frequently occurs in southeast China (Wu, 1997; Zhonghua Bencao Edit Committee, 1999) and is also widely accepted in the currently marketed material in Hong Kong (Zhao, 2016). Furthermore, this substitution in the Westhoff collection was also noted in the historical Sloane and Hooper collections in the UK (Brand et al., 2017; Zhao et al., 2015).

2. Shortage of natural resources and economic substitution: The genuine source of Borneol, *Dryobalanops aromatica* C.F.Gaertn., was found in the Westhoff collection. However, since 2000, *Cinnamomum camphora* (L.) J.Presl has replaced D. aromatica to meet the growing demand. A similar case was discovered by Brand et al. (2017) in the Hooper collection, where Dendrobium plicatile Lindl. was found to have been used as Dendrobii Caulis for economic purposes.

3. Nomenclature confusion: Dong kui zi (Malvae Semen, 冬葵子) is commonly referred to as the seed of *Malva verticillata* L., but in the Westhoff collection we encountered the seeds of *Abutilon theophrasti* Medik. This confusion was previously documented by Cui et al. (1992), who attributed it to errors in professional CMM books published in the mid-20th century. Our recent discovery confirms that this confusion happened much earlier, dating back as far as c. 1870 (**Chapter 2**). Unfortunately, the nomenclature confusion of CMM still exists in the modern market, and it is not limited to just a few isolated cases (Zhao, Z. et al., 2006).

4. Adulteration: Substituting genuine Chinese *materia medica* by unknown substances was not uncommon. Instances of this have been discovered in the cases of Lygodii Spora (海金沙) and Aristolochiae Fructus (马兜铃) in the Westhoff collection

(**Chapter 2**), as well as Fritillariae Bulbus in the Hooper collection (Brand et al., 2017). However, adulterating with other unknown substances, visually similar to genuine CMM, and thereby transforming what should be a single substance into a mixture, has only been observed in the Westhoff collection. For example, the fruits of *Leonurus japonicus* Houtt (*chong wei zi* 茺蔚子) and the seeds of *Astragalus complanatus* Bunge (*sha yuan zi* 沙苑子) are both mixed with unidentified substances (**Chapter 2**).

The emergence of new medicinal parts or replacements of plant parts also reflects changes in the use of Chinese *materia medica*. Comparing four historical CMM collections with a modern trade list of CMM provided us with direct physical evidence of the changes in medicinal plant parts. For example, the fruit of *Citrus* × *aurantium* L. consistently appeared as a medicinal part in all five of these different collections. However, the flowers of *Citrus* × *aurantium* L., as a medicinal part, were only found in the Hooper collection. Additionally, the seeds and fruit peel of *Citrus* × *aurantium* L. were only listed as independent medicinal parts in more modern collections (Catlender collection and Zhong Hua trade list). This trend of variation in medicinal parts could also be observed in specimens from different historical periods, including *Nelumbo nucifera* Gaertn., *Reynoutria multiflora* (Thunb.) Moldenke, and *Dimocarpus longan* Lour. (**Chapter 3**)

With regard to differences in processing methods over time, Chinese *materia medica* specimens in historical collections also serve as evidence of changing trends in medicine preparation. Within the Westhoff collection (**Chapter 2**), there are 21 specimens that were stir-fried with wine. However, nine of these 21 CMM are no longer processed in this manner today. One of these nine is the root of *Phytolacca acinosa* Roxb. (*jiu shang lu*, 酒商陆), whose processing method changed in the late 19th century, substituting vinegar for wine as the adjuvant. Modern research has demonstrated that using vinegar can reduce the medicine's toxicity (Zhonghua Bencao Edit Committee, 1999). As for the remaining eight specimens, there are no historical or current records of them being processed using wine. Another example is the sclerotium of *Polyporus umbellatus* (Pers.) Fires (*xian zhu ling*, 鹹猪苓) in the Westhoff collection, which was stir-fried with salt water. None of the contemporary CMM monographs (Zhao, G. et al., 2006; Zhonghua Bencao Edit Committee, 1999) include this processing method. Such changes in processing methods could be unofficial or regional preparation methods or improvements with no apparent or undocumented benefits, eventually forgotten over time.

Processing methods influence the constituents, pharmacological effectiveness and thus the clinical applications of CMMs. Processing is often applied to CMMs to reduce side effects, enhance or modify therapeutic effects, or facilitate transportation and storage (Guo et al., 2015; Wang and Franz, 2015). As the methods of processing used in modern times often differ from the methods applied in ancient times (Zhao et al., 2010), historical samples can potentially clarify which processing methods were applied in earlier eras (Brand et al., 2017). Although, some changes in processing methods were identified in the Westhoff collection, the research on the Sloane and Hooper collection (Brand et al., 2017; Zhao et al., 2015) did not provide complete information regarding whether the specimens had undergone processing. Meanwhile, the CMM from the Catlender collection (1980s) and Zhong Hua trade list have almost not been processed, except for simple cleaning and cutting. The specimens in the Catlender collection were likely acquired from wholesalers, and the specimens in the Zhong Hua trade list were definitely used in the wholesale market. Therefore, for the study of dynamic changes in the processing methods of CMM, the evidence for physical material is still limited. To obtain a more comprehensive understanding of the "evolution" of processing methods of CMM, future investigations should include more historical specimens and contemporary samples in retail CMM pharmacies.

The research questions addressed the change in CMM applications over time. To what extent can historical collections be used to compare illnesses or symptoms in the past with those mentioned today?

The Westhoff collection catalogue provides insights into the historical use of Chinese *materia medica* (**Chapter 3**). Fever (9% of the catalogue entries), skin diseases (7%), strengthening (7%) and wounds (7%) were the most frequently mentioned medical indications and/or symptoms around 1870. Out of the 436 Chinese *materia medica* entries documented in the Westhoff catalogue, only 73 (17%) of them did not align with any descriptions found in the modern CMM monographs for the respective drugs. This also includes entries that were misunderstood or mistranslated due to abstract concepts in traditional Chinese medicine, such as "*qi*" and "*wind*" were misunderstood as flatulence (**Chapter 3**). Considering that the knowledge in the catalogue may have come from a traditional Chinese medicine practitioner or a Chinese medicine merchant, the fact that there were so few discrepancies could indirectly indicate a high level of credibility for the information contained in this catalogue. In addition, the information in the Westhoff catalogue revealed social and cultural aspects of CMM in the Chinese migrant community in late 19th-century Indonesia, where ginseng (*Panax ginseng* C.A.Mey.) was very popular and cockscomb (*Celosia cristata* L.) was not only used as medicine but also served as a garden ornamental by affluent Chinese immigrants in Java, a practice with a history of several hundred years in China (**Chapter 3**).

Regarding the continuity of Chinese *materia medica*, comparing the historical specimens together to modern traded CMM provided solid physical evidence that many aspects remained the same over centuries. The composition of botanical families and medicinal parts in these four historical collections and the currently traded CMM list shows a remarkable continuity over a 300-year time span. Fabaceae represents 5.3% to 7.2% of the specimens, with Asteraceae (4.1% to 5.7%) being the second most common family among these five collections. The use of roots and/or rhizomes, fruits and/or seeds as medicinal plant parts accounts for approximately 50% of all specimens across these five collections. A total of 14 plant species were consistently found in all studied collections, whereas 47 species were shared by all collections except the oldest and least complete, the Sloane collection. Although our conclusion is that the main body of Chinese *materia medica* has hardly changed in terms of plant taxa over the past three centuries, having only 14 or 47 common species among these collections appeared inconsistent with this conclusion. One significant reason for this inconsistency was the considerable number of specimens that had not been identified at the species level in several of these collections. Specifically, the Sloane collection had 22 incompletely identified specimens, the Westhoff collection had 104, the Hooper collection had 84, the Catlender collection had 60, and the Zhong Hua trade list had 76. It is important to note that the majority of these unidentified specimens were not entirely unrecognizable; rather, their identification difficulties arose from their diverse sources in the plant kingdom. Based on the specimens themselves and their vernacular names, we could only identify them to the genus level. Among these specimens lacking species-level identification were some common CMM items, such as liquorice root (found in five collections) and rhubarb root (present in all excluding the Sloane collection). Unfortunately, the Hooper collection lacked vernacular names for its specimens. If such names had been available, we could have identified more common CMM by comparing vernacular names across these five collections.

Finally, research on historical CMM specimens can tell us whether the properties of these medicinal substances remain similar, degrade or increase over time. A selection of historical CMM specimens from the 1900s to the 1920s, the 1950s, and a few recent samples were analyzed using delayed luminescence (DL). The results showed that DL properties were significantly different between historical and contemporary CMM for all five species selected for our research, across all tested time periods, spanning roughly 50 years and/or 100 years. Additionally, historical specimens provided validation for the use of DL technique for Chinese *materia medica* quality control. Our study confirmed that the patterns of DL property seem to depend on the plant species (Sun et al., 2019). These findings suggest that the DL technique could be a promising tool for quickly authenticating genuine CMM samples from counterfeit ones, determining their storage time, and developing a method for assessing the quality of Chinese *materia medica* with regard to storage time (**Chapter 5**).

Historical CMM collections abroad

In the recent past, several important studies based on historical CMM collections in the United Kingdom were published: the Sloane collection in the Natural History Museum in London (Zhao et al., 2015) and the Hooper collection in the Royal Botanic Gardens Kew (Brand et al., 2017). These results provide valuable references for conducting research on historical CMM collections, illustrating the substantial potential of the historical collections in elucidating changes in botanical identity, medicinal parts, and processing methods of CMM. They have also served as an inspiration for our research.

Unfortunately, the two studies on historical CMM collections in the U.K. did not present all the original label names of the specimens, nor did they present their corresponding catalogue information in a complete manner. They selectively provided content about label names in a few case studies (Brand et al., 2017; Zhao et al., 2015). On the contrary, the specimens in the Dutch Westhoff collection not only include vernacular names (the label names) but also have a comprehensive catalogue documenting their biological and medicinal information. This information was very helpful in understanding the social and cultural aspects of traditional Chinese medicine in a specific time and space.

Research limitations and future perspectives

Traditional Chinese medicine often employs plant mixtures instead of single-species preparations (Jia et al., 2004; Qiu, 2007). In the Westhoff collection, there are eight pre-made medicines composed of various substances mixed together and stored in the form of powders or pills. The catalogue does not provide specific information about the components of these medicines, and their identities cannot be determined solely based on their vernacular names. As a result, these medicines remain unidentified to this day. These unidentifiable mixtures may also exist in other historic collections of Chinese *materia medica*. If future research can identify the specific ingredients of these pre-made medicines using methods like chemical analysis or DNA barcoding, this will offer us greater insights into historic Chinese medicinal mixtures and expand the knowledge of CMM preparation methods beyond decoctions.

Over centuries of use, advances in cultivation have been necessary to supply many CMM that cannot be sustained solely by harvesting from wild populations. As wild and cultivated materials often differ in their macroscopic and pharmacological features, in some cases it is possible to ascertain information about the wild versus cultivated origin of CMMs by examining specimens organoleptically (Brand et al., 2017). Unfortunately, the specimens within the historical CMM collections we studied, specifically the Westhoff and Catlender collections, were mostly cut and sliced, which limited their ability to provide such important information. Hopefully, future studies of other historical collections could provide us with insights into the timeline surrounding the transition of CMM from wild to cultivated sources.

Delayed luminescence has been verified through the examination of historical CMM specimens, suggesting that this technique holds promise as an efficient tool for determining the storage time of the specimens. However, the samples used in our research (**Chapter 5**) do not adequately reflect well-spaced points in time, as they only encompass materials from two or three distinct time periods. Furthermore, the storage durations for these samples all exceed 50 years, and in some cases, even a century, making them less applicable to practical scenarios. Generally, incorporating medicinal materials that have been stored for over a century into a prescription would not be considered feasible. Therefore, future research should focus on more samples from different time points, with storage times limited to a few years, to make the research results more relevant for practical applications in CMM safety and control.

This study aimed to draw attention to the value of historical collections and their importance in pharmacognosy. Numerous quality and safety issues in today's Chinese herbal market have historical origins, having evolved gradually over centuries of use. Physical specimens from pre-modern collections provide an exceptional foundation for assessing these historical changes.

Conclusion

In this Ph.D. thesis, the research on the dynamic changes of Chinese *materia medica* over time was grounded in the examination of physical specimens. By comparing each historical specimen with the corresponding modern standards of CMM, changes have been discovered that occurred in various categories, affecting not only the biological origins, medicinal parts, and processing methods but also the vernacular names of drugs and their medical applications. Analyzing the specimens within four historical collections and a list of currently traded CMM from a holistic perspective provided new insights into the dynamic changes of Chinese *materia medica*. The botanical families and medicinal parts in these four historical collections show a remarkable similarity over a 300-year time span. The research results demonstrated a continuity is using the CMM. Fabaceae and Asteraceae are still the most represented families in modern CMM, while underground plant parts and fruits and/or seeds still account for approximately 50% of all specimens traded today.

This research will raise awareness of the significance and importance of studying historical Chinese *materia medica* and traditional *materia medica* from other ethnicities and cultures. We hope to inspire other scholars to explore more research in Chinese *materia medica* from the perspective of physical specimens, combined with corresponding catalogues, rather than relying solely on historical literature. Furthermore, we aspire to see more forgotten historical collections of medicinal specimens reappear in private property or museum depots, providing additional physical material for future research.

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Summary

Traditional Chinese medicine (TCM) is an ancient medical practice with a history spanning several thousand years, and it continues to be widely practiced in and outside of China today. Chinese *materia medica* (CMM) reflects the medicinal ingredients integral to TCM, and their use is guided by the principles of TCM theory. Over several thousand years of application and development, Chinese *materia medica* has not remained unchanged but has continually evolved. The evolution of CMM involves both continuity and dynamic change. The continuity of CMM is reflected by the preservation and inheritance of CMM ingredients and application methods that have proven effective through long-term research and practical validation over thousands of years. The dynamic change in CMM involves replacing established plants and animal species with different parts or species of CMM that have demonstrated superior therapeutic effects after research. It also involves abandoning and excluding CMM species with poor or adverse effects. Moreover, the names of CMM can be changed in time due to regional and changes of dynasties. Additionally, changes may occur due to the scarcity of natural resources for specific drugs or the pursuit of economically viable alternatives. These factors collectively drive the dynamic change of Chinese *materia medica*.

In the thousands of years of history of traditional Chinese medicine, the biological identity of CMM could only be determined through their vernacular names or simple descriptions of morphological characteristics. The current binomial nomenclature was not introduced in China until the early 20th century. Therefore, studying the evolution of Chinese *materia medica* by examining physical specimens in historic collections helps us accurately identify the plants and animals with expected therapeutic effects. This clarifies the confusion caused by (historic) vernacular names, ensuring the safe use of Chinese *materia medica.* This ensures that the development of new drugs based on information on traditional CMM from written sources stays on the right track. Artemisinin, discovered in *Artemisia annua* L., serves as a good example whose discovery begins with the clarification of the botanical identity of the medicinal plant, relying on the vernacular name documented in ancient literature.

Currently, much of the research on the evolution of Chinese *materia medica* (CMM) relies on comparing written texts: historical monographs and documents. While numerous issues related to CMM evolution have been successfully addressed through textual research, some uncertainties persist in confirming the evolution process and biological identity of specific CMM due to a lack of historical records or incomplete textual documentation. However, examining historical CMM specimens can compensate for the limitations of textual research from a physical specimen perspective. Furthermore, research on specimens and textual research complement each other, offering more comprehensive support for the study of CMM evolution.

In addition to studying the evolution of Chinese *materia medica*, historical specimens, because they have undergone long-term preservation, can also be used as important research

material for other fields of study. For example, historical specimens can be utilized to verify whether the delayed luminescence (DL) technique can serve as an effective method for measuring the dynamic changes of CMM or discriminating the storage time of CMM.

Due to the colonial connections between the Netherlands and (South-) East Asia since the 17th century, and the keen interest of Dutch scholars and the public in exotic plants from the East, numerous plant specimens from these regions are preserved in Dutch museums or private collections. Consequently, historical Chinese *materia medica* specimens are likewise included in these collections. The historical CMM specimens preserved in the Netherlands, which have not undergone a thorough study, can offer valuable physical evidence for researching the evolution of Chinese *materia medica*. This thesis focuses on the historical CMM specimens preserved in the Netherlands. Through comparison with CMM literature records and modern CMM samples, the evolution of CMM is investigated. Additionally, several historical specimens were subjected to delayed luminescence (DL) to verify the feasibility of this technology in discriminating the storage time of Chinese *materia medica*.

In **Chapter 2**, we conducted a comprehensive study of a historical Chinese *materia medica* collection, the Westhoff collection, spanning approximately 140 years and consisting of around 400 specimens. Through identifying aspects such as taxonomic identity, medicinal parts, processing methods, and comparing them with corresponding literature and modern samples, we successfully uncovered evidence of dynamic changes in Chinese *materia medica*. These findings not only substantiate certain conclusions from textual research; some of them also reveal new evidence of dynamic changes in Chinese *materia medica*. Those historical specimens that did not change also demonstrated the continuity in the evolution of Chinese *materia medica* from a physical perspective.

In **Chapter 3**, an examination was conducted on a handwritten catalogue corresponding to the Westhoff collection. Apart from information like vernacular names and the medicinal parts, this catalogue presented the medical indications for symptoms or illnesses related to each Chinese *materia medica* specimen. This provided an unique opportunity to explore the evolution of CMM from a medical usage perspective. Our findings reveal that 78% of medicinal indications in the catalogue align with current reported Chinese *materia medica* indications. Additionally, the catalogue indicates the most frequently mentioned illnesses or symptoms that were treated at that time. The catalogue also sheds light on important aspects of Chinese *materia medica* circa 1870, including popular herbal medicines, their geographical origins, and the social aspects of traditional Chinese medicine.

Chapter 4 presents a comparative study of four historical collections of Chinese *materia medica* and includes a list of contemporary CMM available in both the Chinese and the EU market. The objective is to explore the evolution of Chinese medicinal materials by examining physical specimens. Specimens in these five collections, spanning over 300 years, illustrate that the core of CMM has experienced minimal changes in terms of medicinal plant taxa and plant parts used throughout this extensive period. Furthermore, the persistent presence of shared CMM among collections of various ages confirms the continuity in the use of CMM. Dynamic changes in CMM are primarily related to the conservation of endangered species, the safe usage of CMM, and the exploration of new pharmacological applications for well-known species. Overall, the examination of historical CMM specimens reveals significant continuity and subtle changes in Chinese *materia medica* spanning 300 years.

Chapter 5 validates the delayed luminescence (DL) technique by employing historical CMM specimens from the 1900s to the 1920s, the 1950s, and recent samples. This technique measures the decaying ultra-weak luminescence displayed by materials after exposure to light and has previously proven successful in detecting variations in CMM arising from different growth conditions and processing methods. This chapter examines whether DL can discriminate differences attributed to storage time. The results showed that the DL technique can distinguish CMM based on age, but DL values of CMM depend on the particular species. The findings imply that DL technology could serve as a method for detecting storage time, but additional research and validation of this approach are still necessary.

The historical CMM specimens are the focus of this thesis, contributing to the comprehension of the historical, continuous, and dynamic changes in traditional Chinese medicine and Chinese *materia medica*. They offer an additional perspective to conclusions derived from textual records or present new viewpoints that may differ from literary data. Simultaneously, the advantages and characteristics of historical specimens, not found in textual records, further elucidate the significant value of historical CMM specimens. Unfortunately, in comparison to research on literary sources, the study of historical specimens remains inadequate. This is, of course, attributed to unavoidable objective factors, such as CMM's inability to be preserved and transmitted like written texts. Additionally, these medicinal substances are primarily intended for use by patients during their effective periods for treating diseases or maintaining health, rather than being stored in cabinets for extended periods as decorative items. Besides these objective factors, well-preserved ancient specimens may be overlooked and neglected by the public due to the limited understanding of their important research value and significance. For instance, collections such as the Westhoff Collection and Catlender Collection were hardly studied before this thesis. The aspiration is that this thesis will bring these historical specimens, which have been out of the public eye for many years, back into focus, enabling more researchers and the general public to comprehend the crucial research value and significance of historical specimens. Furthermore, this thesis aims to bring awareness to other ancient medicinal specimens scattered worldwide, unnoticed and unattended, offering a new and deeper understanding of the history and development of medicine, as well as humanity's history and development.

Samenvatting

Traditionele Chinese geneeskunde (TCM) is een oude medische praktijk met een geschiedenis van duizenden jaren, en vandaag de dag nog veelvuldig beoefend, zowel in China als daarbuiten. Chinese *materia medica* (CMM) weerspiegelt de medicinale ingrediënten die gebruikt worden voor TCM, geleid door de principes van de TCM-theorie. Gedurende duizenden jaren van toepassing en ontwikkeling is de Chinese *materia medica* niet onveranderd gebleven maar voortdurend geëvolueerd. De evolutie van CMM omvat zowel continuïteit als dynamische verandering. De continuïteit van CMM wordt weerspiegeld door het behoud en de overdracht van ingrediënten en toepassingsmethoden die effectief zijn gebleken door langdurig onderzoek en praktische validatie over duizenden jaren. De dynamische verandering in CMM omvat het vervangen van gevestigde onderdelen van planten- en diersoorten door andere soorten of andere onderdelen die na onderzoek betere therapeutische effecten hebben aangetoond. Het houdt ook in dat sommige ingrediënten met nadelige bijwerkingen of ongewenste effecten worden opgegeven en uitgesloten. Bovendien kunnen de Chinese namen van CMM in de loop der tijd veranderen als gevolg van regionale en politieke veranderingen. Veranderingen kunnen ook optreden door schaarste van natuurlijke populaties van specifieke medicijnen door overmatig oogsten en/of het streven naar economisch haalbare alternatieven. Deze factoren samen zijn de drijvende kracht van de dynamische verandering van Chinese *materia medica*.

In de duizenden jaren geschiedenis van de traditionele Chinese geneeskunst kon de biologische identiteit van ingrediënten alleen worden bepaald aan de hand van hun volksnamen of eenvoudige beschrijvingen van morfologische kenmerken in de geschreven literatuur. De huidige binominale nomenclatuur (geïntroduceerd door Linnaeus in de 18e eeuw) werd pas in China geïntroduceerd in het begin van de 20e eeuw. Het is aan de hand van historische Chinese literatuur dus niet altijd duidelijk over welke specifieke planten en dieren het gaat. Daarom helpt het bestuderen van fysieke exemplaren in historische CMM collecties ons bij het nauwkeurig identificeren van planten en dieren met verwachte therapeutische effecten en het traceren van de evolutie van Chinese *materia medica*. Dit schept duidelijkheid in de verwarring veroorzaakt door (historische) volksnamen en draagt bij aan het veilige gebruik van Chinese *materia medica*. Hiermee wordt ook gewaarborgd dat de ontwikkeling van nieuwe geneesmiddelen op basis van informatie over traditionele CMM uit geschreven bronnen op het juiste spoor blijft. Artemisinine, en stof met een effectieve werking tegen malaria, die onlangs werd ontdekt in de plant *Artemisia annua* L., dient als een goed voorbeeld waarvan de ontdekking begint met de verduidelijking van de botanische identiteit van de geneeskrachtige plant, gebaseerd op de volksnaam gedocumenteerd in oude Chinese literatuur.

Op dit moment is veel van het onderzoek naar de evolutie van Chinese *materia medica* (CMM) gebaseerd op het vergelijken van geschreven teksten: historische monografieën en documenten. Hoewel tal van kwesties met betrekking tot de evolutie van CMM met succes

zijn aangepakt via tekstueel onderzoek, blijven sommige onzekerheden bestaan bij het bevestigen van het evolutieproces en de biologische identiteit van specifieke ingrediënten vanwege een gebrek aan historische gegevens of onvolledige tekstuele documentatie. Het onderzoeken van historische CMM-collecties, demonstratiekasten of dozen met vele potjes met kleine hoeveelheden Chinese kruiden, kan de beperkingen van tekstueel onderzoek compenseren vanuit een fysiek exemplaarperspectief. Bovendien vullen het onderzoek naar exemplaren en tekstueel onderzoek elkaar aan, waardoor meer alomvattende ondersteuning wordt geboden voor de studie van de evolutie van CMM.

Naast het bestuderen van de evolutie van Chinese *materia medica* kunnen historische exemplaren, omdat ze langdurig zijn bewaard, ook dienen als belangrijk onderzoeksmateriaal voor andere vakgebieden. Historische collecties plantmateriaal kunnen worden gebruikt om te verifiëren of de techniek van delayed luminescence (DL) kan dienen als een effectieve methode voor het meten van de dynamische veranderingen van CMM of het onderscheiden van de opslagtijd van CMM. Door de tijd heen veranderen (mogelijk) de chemische eigenschappen van de medicijnen en daardoor de wijze waarop het materiaal licht doorlaat.

Vanwege de koloniale banden tussen Nederland en (Zuidoost-) Azië sinds de 17e eeuw, en de grote interesse van Nederlandse wetenschappers en verzamelaars in exotische planten uit het Verre Oosten, worden talrijke Chinese kruidencollecties bewaard in Nederlandse musea of in privécollecties. De historische CMM-collecties in Nederland, die voor dit proefschrift nog niet grondig waren bestudeerd, kunnen als waardevol fysieke bewijs dienen voor het onderzoeken van de evolutie van Chinese *materia medica*. Dit profeschrift richt zich op de enkele historische Chinese kruidencollecties in Nederland. Door ze te vergelijken met (historische en moderne) literatuur over TCM en moderne CMM (Chinese kruiden die op dit moment worden verhandeld in de EU) wordt de evolutie van CMM onderzocht. Daarnaast werden enkele historische exemplaren onderworpen aan de techniek van delayed luminescence (DL) om de haalbaarheid van deze technologie bij het onderscheiden van de opslagtijd van Chinese *materia medica* te verifiëren.

In **Hoofdstuk 2** hebben we een uitgebreide studie uitgevoerd naar een historische Chinese *materia medica*-collectie, de Westhoff-collectie, die ongeveer 140 jaar oud is en bestaat uit ongeveer 400 glazen potjes met verschillende Chinese kruiden. Door aspecten zoals de taxonomische identiteit, medicinale onderdelen, en de verwerkingsmethoden te identificeren en ze te vergelijken met bijbehorende literatuur en moderne Chinese geneeskruiden, hebben we bewijs gevonden van dynamische veranderingen in Chinese *materia medica*. Deze bevindingen bevestigen niet alleen bepaalde conclusies uit tekstueel onderzoek; sommige onthullen ook nieuw bewijs van dynamische veranderingen in traditionele Chinese geneeskunst. Die historische geneeskruiden die nog identiek zijn aan degenen die vandaag de dag nog in gebruik zijn, toonden ook de continuïteit van Chinese *materia medica* vanuit een fysiek perspectief.

In **Hoofdstuk 3** werd een onderzoek uitgevoerd naar een handgeschreven catalogus die overeenkomt met de Westhoff-collectie. Naast informatie zoals volksnamen en de medicinale delen, gaf deze catalogus de medische indicaties voor symptomen of ziekten gerelateerd aan elk Chinees *materia medica*-specimen weer. Dit bood een unieke kans om de evolutie van CMM te onderzoeken vanuit een medisch gebruikersperspectief. Onze bevindingen onthullen dat 78% van de medicinale indicaties in de historische catalogus overeenkomt met de huidige gerapporteerde indicaties voor Chinese *materia medica*. Bovendien geeft de catalogus de meest genoemde ziekten of symptomen aan die destijds werden behandeld. De catalogus werpt ook licht op belangrijke aspecten van Chinese *materia medica* rond 1870, waaronder de meeste populaire kruidengeneesmiddelen, hun geografische oorsprong en de sociale aspecten van traditionele Chinese geneeswijzen in het voormalig Nederlands Indië.

Hoofdstuk 4 presenteert een vergelijkende studie van vier historische collecties van Chinese *materia medica* en omvat een lijst van hedendaagse CMM die beschikbaar zijn op zowel de Chinese als de Europese markt. Het doel was om de evolutie van Chinese medicinale materialen te verkennen door fysieke exemplaren te onderzoeken. Exemplaren in deze vijf collecties, die samen meer dan 300 jaar beslaan, illustreren dat de kern van CMM minimale veranderingen heeft ondergaan wat betreft medicinale plantentaxa en gebruikte plantendelen gedurende deze periode. Bovendien bevestigt de aanhoudende aanwezigheid van overeenkomstige ingrediënten tussen de collecties van verschillende leeftijden de continuïteit in het gebruik van CMM. Veranderingen in CMM over de tijd zijn belangrijk voor wat betreft het overstappen op minder bedreigde, botanisch verwante soorten, het veilige gebruik van CMM en de verkenning van nieuwe farmacologische toepassingen voor bekende soorten. Over het algemeen tonen de onderzoeken van historische CMM-exemplaren aanzienlijke continuïteit en subtiele veranderingen in Chinese *materia medica* gedurende 300 jaar.

Hoofdstuk 5 valideert de techniek van delayed luminescence (DL) door historische CMM-exemplaren uit de jaren 1900 tot 1920, de jaren 1950 en kort geleden geoogste Chinese kruiden te gebruiken. Deze techniek meet de afnemende ultra-zwakke luminescentie die materialen vertonen na blootstelling aan licht en heeft eerder succesvol variaties in CMM gedetecteerd die voortkomen uit verschillende groeiomstandigheden en verwerkingsmethoden. Dit hoofdstuk onderzoekt of DL verschillen kan onderscheiden die aan de opslagtijd / ouderdom worden toegeschreven. De resultaten toonden aan dat de DL-techniek CMM kan onderscheiden op basis van ouderdom, maar de DL-waarden zijn afhankelijk van de specifieke soort. De bevindingen suggereren dat DL-technologie zou kunnen dienen als een methode voor het detecteren van ouderdom, maar aanvullend onderzoek en validatie van deze aanpak zijn nog steeds noodzakelijk.

De historische CMM-exemplaren staan centraal in dit proefschrift en dragen bij aan het begrip van de historische, continue en dynamische veranderingen in de traditionele Chinese geneeskunst en de Chinese *materia medica*. Ze bieden een aanvullend perspectief op conclusies afgeleid van tekstuele gegevens of presenteren nieuwe standpunten die kunnen verschillen van eerdere literatuurstudies. Tegelijkertijd belichten de voordelen en kenmerken van historische collectie-exemplaren, die niet te vinden zijn in tekstuele gegevens, de significante waarde van historische CMM-collecties. Helaas blijft, in vergelijking met onderzoek naar literaire bronnen, de studie van historische CMM collecties ontoereikend. Dit is uiteraard toe te schrijven aan het feit dat er vele malen minder complete CMM collecties bewaard zijn gebleven dan geschreven teksten. Bovendien zijn deze meeste medicinale kruiden primair bedoeld voor het gebruik door patiënten voor het behandelen van ziekten of het behouden van gezondheid, in plaats van dat ze voor langere tijd in kasten worden bewaard als decoratieve items. Het is waarschijnlijk wel zo dat goed bewaarde oude CMM ingrediënten in museumcollecties over het hoofd worden gezien en onzichtbaar voor het publiek vanwege het beperkte begrip van hun onderzoekswaarde en betekenis. CMM verzamelingen zoals de Westhoff-collectie en Catlender-collectie waren nauwelijks bestudeerd vóór dit proefschrift. De hoop is dat dit onderzoek deze historische exemplaren, die vele jaren uit het zicht zijn geweest, weer onder de aandacht brengt, zodat meer onderzoekers en het grote publiek de cruciale onderzoekswaarde en betekenis van historische exemplaren begrijpen. Bovendien beoogt dit proefschrift bewustwording te creëren over andere oude CMM collecties die wereldwijd in museums en privécollecties liggen, onopgemerkt en onbeheerd. Deze historische collecties bieden een nieuw en dieper begrip van de geschiedenis en ontwikkeling van traditionele Chinese geneeskunst, die zo belangrijk is in de geschiedenis en ontwikkeling van de mensheid.

Curriculum Vitae

Yusheng Jia was born on November 4th, 1990, in Nei Mongol, China. He obtained his bachelor's degree in Biology from Inner Mongolia Agricultural University in 2013 and participated in a research project on the expression of exogenous antifreeze genes in Arabidopsis for his undergraduate thesis. From 2013 to 2017 he studied at Shanghai Ocean University, obtaining his Master's degree in Biology. During his master's studies, he conducted research on the symbiotic relationship between lactic acid bacteria and yeast in kefir grains, which are cultures used in fermenting milk to produce kefir. In 2015, he joined a school visiting team, touring various universities in Belgium. Since then, he has nurtured the idea of studying in Europe.

In 2017, following Prof. Xumin Wang's recommendation, he connected with Dr. Mei Wang and Prof. Tinde van Andel. In 2018, he initiated his doctoral research at Naturalis Biodiversity Center and Leiden University in the Netherlands. His doctoral research primarily focuses on historical Chinese *materia medica* specimens preserved in the Netherlands. Using classic and novel tools, he investigates the continuity and dynamic changes in Chinese *materia medica*. Additionally, he validates the feasibility of the delayed luminescence technique for determining the storage time of Chinese *materia medica*. After completing his doctoral degree, he plans to return to China, reunite with his family, and contribute to his country's development.

List of Publications

Jia, Y., Wang, M., Lambers, P. H., & van Andel, T. (2024). The catalogue of the Westhoff collection of Chinese *materia medica* (c. 1870): Evidence of interaction between a Chinese medicine practitioner and the Dutch in Indonesia. *Journal of Ethnopharmacology*, 318, 116987.

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