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

Jia, Y.

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.

References

Brand, E., Leon, C., Nesbitt, M., Guo, P., Huang, R., Chen, H., Liang, L., Zhao, Z., 2017. Economic botany collections: a source of material evidence for exploring historical changes in Chinese medicinal materials. Journal of Ethnopharmacology 200, 209-227.

Chen, Z.M., Huang, S.B., 2005. Materia Medica Literature. Dongfang University Press, Nanjing.

Cui, X., Li, S., Wang, L., Zhang, J., Ma, A., 1992. Textual research of change of seed of Malva Crispa and seed of Abutilon theophrasti. China Journal of Traditional Chinese Medicine and Pharmacy (1), 19-21.

Guo, P., Brand, E., Zhao, Z., 2015. Chinese medicinal processing: a characteristic aspect of the ethnopharmacology of Traditional Chinese Medicine. ethnopharmacology, 303-316.

Jia, W., Gao, W., Yan, Y., Wang, J., Xu, Z., Zheng, W., Xiao, P., 2004. The rediscovery of ancient Chinese herbal formulas. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 18(8), 681-686.

Qiu, J., 2007. Traditional medicine: a culture in the balance. Nature 448(7150), 126-129.

Sun, M., Wang, S., Jing, Y., Li, L., He, M., Jia, Y., van Wijk, E., Wang, Y., Wang, Z., Wang, M., 2019. Application of delayed luminescence measurements for the identification of herbal materials: a step toward rapid quality control. Chinese Medicine 14(1), 1-13.

Wang, M., Franz, G., 2015. The role of the European Pharmacopoeia (Ph Eur) in quality control of traditional Chinese herbal medicine in European member states. World Journal of Traditional Chinese Medicine 1(1), 5-15.

Wu, G., 1997. Flora of China. Beijing Science Press, Beijing.

Zhao, G., Dai, S., Chen, R., 2006. Dictionary of Chinese materia medica (Zhong Yao Da Ci Dian), 2 ed. Shanghai Scientific & Technical Publishers, Shanghai

Zhao, Z., 2016. Illustrated Identification of Chinese Materia Medica in Hong Kong. Hong Kong Baptist University, Hong Kong.

Zhao, Z., Liang, Z., Chan, K., Lu, G., Lee, E.L.M., Chen, H., Li, L., 2010. A unique issue in the standardization of Chinese materia medica: processing. Planta Medica 76(17), 1975-1986.

Zhao, Z., Yuen, J.P., Wu, J., Yu, T., Huang, W., 2006. A systematic study on confused species of Chinese materia medica in the Hong Kong market. Annals-Academy of Medicine Singapore 35(11), 764.

Zhao, Z., Zhao, K., Brand, E., 2015. Identification of ancient Chinese medicinal specimens preserved at Natural History Museum in London. China Journal of Chinese Materia Medica 40(24), 4923-4927.

Zhonghua Bencao Edit Committee, 1999. Zhonghua Bencao. Shanghai Scientific & Technical Publishers, Shanghai.