The botany and macroscopy of chinese materia medica: sources, substitutes and sustainability

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THE BOTANY AND MACROSCOPY OF CHINESE *MATERIA MEDICA:* SOURCES, SUBSTITUTES AND SUSTAINABILITY

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ABSTRACT

Interest in Traditional Chinese Medicine (TCM) is global. The burgeoning international trade in its crude and processed plant ingredients (Chinese *materia medica* - CMM) reflects demand across all sectors of healthcare, yet the identification of source plants and CMM has been overlooked for many years leading to problems in safety, quality, efficacy and sustainable sourcing. The *Guide* (*Chinese medicinal plants, herbal drugs and substitutes: an identification guide*, Leon & Lin, Kew Publishing, 2017), which forms the core of this dissertation by publication, presents a fresh approach to the identification of 226 internationally traded CMM (officially recognised in the *Chinese Pharmacopoeia, CP2015*) along with their 302 official source plants.

Identification criteria are developed using macroscopy, and are based on authentic reference specimens created as a result of extensive fieldwork in China. Inclusion of 99 comparative descriptions of unofficial substitute plants and drugs (including adulterants and counterfeits), with their counterparts for official species, enable key distinguishing characters to be highlighted and thereby strengthen the rigour of identifications made. The approach demonstrates that macroscopy can be used to reliably identify and differentiate over 70% of official (CP2015) CMM from common substitutes and that macroscopy is a fast and cost-effective authentication method with many applications.

The research highlights the essential role of herbarium-vouchered reference drugs in CMM authentication as opposed to the use of market-obtained drugs whose botanical identity is inherently uncertain. The research's taxonomic review of all official species in the *Guide* demonstrates a significant disparity (16%) between the taxonomy adopted in the CP2015 and current plant taxonomic opinion, while a review of species conservation rankings and causal effects found that the wild populations of 23% of official species native to China (63 of 270 official species in the *Guide*) have become threatened as a direct result of over-harvesting for medicinal use. In addition, the research reveals the underlying causes of CMM substitution are dominated by clinician preference, followed by supply problems arising from over-harvesting of official species with unregulated markets trading in inferior or inappropriate look-alike items, together with issues of confused identification and nomenclature. Direct consequences of the inadvertent use of CMM substitutes include misleading clinical and research outcomes, serious adverse reactions and, in some cases, fatalities. Reliable identification of CMM therefore remains paramount for high quality research as well as safe and efficacious clinical practice. While for some CMM (ca. 30% of CMM in the *Guide*) robust identification requires analytical methods (e.g. chemical- and DNA-based ones), the research concludes that macroscopy continues to be a powerful tool for reliable and cost-effective identification of CMM in international trade.

Keywords: morphology, authentication, China, botany, taxonomy, conservation, medicine

CONTENTS

ACCOMPANYING MATERIAL

Copy of: *Chinese medicinal plants, herbal drugs and substitutes: an identification guide*, by C.J. Leon & L.Y. Lin, Kew Publishing, 2017.

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Full acknowledgements are set out in the published *Guide* (pp viii-ix).

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AUTHOR'S DECLARATION

I declare that all the material contained in this commentary is my own work. All the wording of the accompanying published book (hereafter referred to as the *Guide*) is mine; certain research was carried out by my co-author Professor Lin Yu-Lin, as specified in his letter given below.

CHINESE ACADEMY OF MEDICAL SCIENCES
PEKING UNION MEDICAL COLLEGE
IMPLAD
INSTITUTE OF MEDICINAL PLANT DEVELOPMENT

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FOR TRADITIONAL MEDICINE

To whom it may concern.

CO-AUTHORSHIP STATEMENT

With reference to the book entitled '*Chinese Medicinal Plants, Herbal Drugs and Substitutes; an identification guide*' authored by Christine Leon and myself and published by the Royal Botanic Gardens Kew and delivered as part of Christine's submission of '*PhD by Published Work*' at the University of Westminster, I can confirm that this publication was undertaken primarily by her as novel research.

My role in this publication is as follows: I managed the logistical aspects of most of our joint 14 field expeditions in China (1998-2013) that underpin the creation of the reference drugs illustrated in this book and helped with their identification and photography.

Christine has decided on the scope and design of the book, the content of each account and researched and written the text in full. I have reviewed the text, provided guidance on specifics and contributed minor editorial changes in its final stages.

Dated: ...29th Nov., 2016

Yours sincerely

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DEFINITIONS

The *Guide* refers to my published book '*Chinese medicinal plants, herbal drugs and substitutes: an identification guide'* Leon & Lin, Kew Publishing, 2017.

Traditional Chinese Medicine (TCM), dating back over 2,500 years, is widely practised in China today as a government-recognised healthcare system spanning herbal medicine, acupuncture, massage, exercise and dietary therapy. This term used here and in the *Guide* refers to its herbal component only.

Chinese materia medica (CMM)/drug: a commercial trade item of one or more plant parts derived from one, occasionally more, species (see *Pharmacopoeia species* below) and prepared in line with traditional TCM methods (see *Guide*, p. 9). Each CMM *t*akes the form of a crude (usually simply dried) or processed drug (i.e. heat-treated with or without adjuvants). Crude CMM are seldom seen outside China (or other source countries) because processing is designed (*inter alia*) to prolong shelf-life and usually requires specialist skills best performed in-country. Large CMM (crude and processed) are sliced or broken into smaller pieces called *Yin Pian* (decocting pieces) to facilitate release of active principles once in decoction. For CMM requiring no processing or slicing (e.g. Ling Xiao Hua, *Guide,* p.579) the CMM is traded in one form only so there is no difference between the crude drug and its decocting pieces. See also Table 1.

Pharmacopoeia species/official species: a plant species recognised by the 2015 edition of the Chinese Pharmacopoeia (CP2015) as the source of a CMM.

Unofficial substitute: a plant species or CMM used accidentally or intentionally as a substitute, contaminant or adulterant **not** included in the CP2015. This includes certain CMM and their source plants that, although widely used in TCM today, are currently excluded from the CP2015 for a variety of reasons, plus other accidental or intentional plant substitutes, contaminants and counterfeits (the latter derived from plant or other materials).

Identification versus *Authentication*: *identification* refers to the process of identifying a plant or trade items which may or may not already be named, whereas *authentication* is the process of confirming the identity of an already named (scientific or other) plant or trade item. The process of authentication is therefore a subset of identification and the two terms are used interchangeably according to context. For example, the choice of '*an identification guide*' in the *Guide*'s title reflects its use for named as well as unnamed plant species, CMM and other trade items.

ABBREVIATIONS

CMM	Chinese *materia medica*
CP	Chinese pharmacopoeia
IUCN	International Union for Conservation of Nature
RBG Kew	Royal Botanic Gardens, Kew
TCM	Traditional Chinese Medicine

1. INTRODUCTION

The resurgence of plant-based medicines, nutraceuticals and cosmeceuticals in the West has yet to be matched by the development of robust herbal quality-assurance (QA) systems. This is especially true of QA systems for herbal Chinese *materia medica* (CMM) which represent the bulk of ingredients used in Traditional Chinese Medicine (TCM), a therapy practised today in over 180 countries (Xinhua, 2016). The rapidly growing global market in CMM, estimated in 2012 to be worth US$83.1 billion (WHO, 2013), provides the raw ingredients not only for the expanding TCM industry but also the booming natural products sectors too. As supply chains struggle to keep pace with spiralling demand, this largely unregulated global market is vulnerable to rogue practices that has led to concerns about the quality and safety of CMM traded notably their correct identity, purity and appropriate processing (Shaw, 2010; Chan *et al.*, 2007; Zhang *et al*., 2012; Zhao *et al*., 2010). Lack of CMM reference herbs and limited dialogue between the disciplines of TCM and botany worldwide has resulted in poor botanical identification protocols across TCM and hampered the design of robust QA systems (Bauer & Franz, 2010).

CMM are characterised by i) their high diversity of trade forms, often the result of different processing methods (Pao Zhi) such as stir-frying, steaming or carbonising); ii) their complex trade nomenclature, often reflecting morphological appearance, geographical provenance and/or processing methods and iii) their frequent sourcing often from more than one plant species (Wu *et al.,* 2007; Zhao *et al*., 2006b, 2007, 2010). The Chinese Pharmacopoeia (2015 edition, hereafter ‘CP2015’) provides official specifications of these and other pharmaceutical characters for 506 herbal CMM and as such represents the Chinese government standard for these entities. The *Guide* documents 226 of these CMM. Note that the CP2015 has yet to develop specifications for all CMM in current use. The use of CMM in China can also be split into those destined for inclusion in TCM manufactured products as opposed to those prescribed as loose CMM for use in decoctions (the more traditional form of CMM administration). The information presented in the *Guide* is equally relevant to both, and also to those sectors using CMM outside the context of TCM.

Other features of CMM relevant to the present research are i) the origin of the source species (ca. 80% wild-harvested; the remainder cultivated on small or large-scale medicinal plant farms) and ii) their supply chains (typically long, with numerous middle-men and, in the main, poorly regulated) (Booker *et al*., 2012; Huang, 2011; Zhang *et al*., 2010).

The above factors and inherent complexity of CMM have shaped the design of my research and notably the scope and selection of the CMM documented and the substitutes, adulterants, contaminants and counterfeits with which they have been compared (see *Guide*, pp.1-9).

1.1 Why is botanical identification of CMM important?

Identification of source plants underpins not only their use in medicine but also other sectors such as conservation and livelihoods. Botanical clarity underpins:

- Efficacy: use of the incorrect species undermines the integrity of plant-based medicines.
- Safety: well-documented cases of adverse reactions owing to plant-based medicines could have been prevented with better understanding of the identity of the source plants (Shaw, 2010).
- Conservation: development of conservation plans, including medicinal crop production, is reliant upon the correct choice of plant species.
- Livelihoods: a broad range of stakeholders ranging from local communities to industry benefit from production of plant-based medicines accurately sourced.

1.2 Research questions

The over-arching aim of my research is to bring botanical clarity to the morphological identification of the official (CP2015) source plants officially used in TCM, and their commercially-traded CMM. Four main research questions underpin the work:

1. To what extent can macroscopic characters reliably differentiate official CMM from their common unofficial substitutes?
2. What is the taxonomic alignment of the current *Chinese Pharmacopoeia* (*CP2015*) with current taxonomic opinion, and how has this affected my circumscription of CMM?
3. What are the drivers underlying the occurrence of unofficial CMM substitutes in international trade?
4. To what extent does medicinal harvesting impact the conservation status of source plants?

2. CONTEXT

2.1 An interdisciplinary approach

The literature consulted spans the disciplines of TCM (specifically drug identification, sourcing, processing and trade nomenclature); plant taxonomy and nomenclature; herbal medicine safety, regulation and pharmacovigilance, and species conservation. My access to literature in Chinese has been limited due to the language barrier, but has been circumvented in part by use of journal translation databases (e.g. the China National Knowledge Infrastructure database (*CNKI*)) and in part by working with my Chinese co-author Lin Yu-Lin.

Cornerstone texts include the *Chinese Pharmacopoeia* (2010 English edition and 2015 Chinese edition) with pharmaceutical specifications for 506 official CMM; *Modern Chinese Materia Medica* (Xiao *et al.,* 2001-02); *Guangdong Pharmacopoeia* (Lin, 1990-96); *Chinese Herbal Medicine: Materia Medica*

(Bensky *et al.*, 2004) and *Pharmacology and Applications of Chinese Materia Medica* (Chang & But, 1987).

Key taxonomic and nomenclatural resources accessible on-line include the *Flora of China* (1994–2013) with over 31,000 plant taxa, and *Medicinal Plant Names Services* which provides access to ca. 300,000 scientific and non-scientific plant names.

2.2 CMM identification literature

CMM scientific publications since the 1980s have largely focused on the application of chemical analytical methods to pharmacological activity, and chemical markers for quality control and identification (Razmovski-Naumovski *et al*., 2010; Li *et al*., 2008; Kite *et al.*, 2003). The vast phytochemical literature that followed includes monographic works such as Wagner *et al.* (2011-15) *Chromatographic fingerprint analysis of herbal medicines* and Wang *et al.* (2013) *Monographs for Quality Evaluation of Chinese Crude Drugs*. Although specific to CMM, the application of these identification methods has proven limited since few marker compounds are species specific, and many are destroyed during CMM processing (Xie & Leung, 2009).

Given that TCM is an actively evolving medical system, temporal changes in CMM drug definitions have inevitably arisen between editions of the *Chinese Pharmacopoeia* over its 57 year history (Hao & Jiang, 2015). Prior to the *CP1997* edition, for example, 'Wu Wei Zi', was officially sourced either from *Schisandra chinensis* or *S. sphenanthera* but subsequent editions define the latter as a separate drug called 'Nan Wu Wei Zi' (*Guide*, pp. 686-7, 742-5). An awareness of these evolving definitions is essential when interpreting the wider literature. Thankfully there has been a trend towards one drug – one species in recent *CP* editions but despite this, the market place presents a different reality (see 'Wang Bu Liu Xing' in section 4.3.3., *Guide,* pp.732-735).

2.3 Safety

The effects on patient safety of the use of an unofficial substitute are often difficult to evaluate because CMM are typically used as multi-ingredient formulae of 5-15 herbs. Each formulation is prepared according to TCM principles with each ingredient performing a specific function when combined with others. Their substitution can disrupt a formula's delicate balance rendering it, at best, ineffective and at worst, harmful. For example, the potential toxicity of many CMM on their own is modulated when decocted with others. The pharmacokinetic interactions of these formulae is therefore complex and presents a huge challenge to their toxicological investigation (Shaw, 2010).

The most well-known series of adverse reactions occurred in Belgium in the 1990s with 112 patients diagnosed with acute renal failure over a 5 year period. The causative plant was proven to be *Aristolochia fangchi* (see 'Fang Ji – Stephaniae Tetrandrae Radix', *Guide*, page 124-9) owing to its content of aristolochic acids which are well documented to be both nephrotoxic and carcinogenic. The cause of the substitution was thought to be due to confusing trade names, coupled with the use of the plant outside its TCM context (Wu *et al.,* 2007).

Although the *Guide* includes safety information, where available, on a CMM-by-CMM basis, a detailed analysis of the implications of inaccurate species sourcing, poor processing or intentional substitution along the supply chain is beyond the scope of this thesis. The *Aristolochia* case series (above) illustrates the time and level of expertise required to thoroughly investigate cases of adverse reaction (Shaw, 2010).

2.4 Novelty of my work

With my research designed to bring botanical rigour to the CMM trade in Europe, several features, especially in combination, set my *Guide Chinese medicinal plants, herbal drugs and substitutes: an identification guide* apart from other texts:

- exhaustive use of *fully validated CMM* (i.e. cross-referenced to herbarium vouchers as opposed to market samples of unknown provenance);
- taxonomic and nomenclatural alignment of plant species with current world taxonomies;
- semi-technical plant descriptions written from scratch for audiences with minimal botanical training;
- wild *versus* cultivated source information;
- CMM substitutes selected from first-hand knowledge of field and markets in China and the UK focusing on substitutes known to occur *in international trade*;
- in-depth *comparative* descriptions and photographs of Chinese Pharmacopoeia CMM (2010; 2015) and their substitutes plus their equivalents for source plants;
- an *interdisciplinary* approach integrating information sets across many disciplines with, for CMM substitutes, a substitution comment giving a rationale for the likely cause of substitution;
- safety summaries;
- conservation and protected species status.

3. SCOPE AND METHODOLOGY

3.1 Coverage

Estimates of numbers of medicinal plant species native to China have ranged from ca. 5,100 (Xiao, 1991) to over 8,000 (Hamilton, 2004; Huang, 2011) and, most recently, to 10,000-11,250 (Pei & Huai, 2015). The 506 CMM listed in the *CP2015* represent the mainstream herbal drugs used specifically in TCM (as opposed to those used by China's ethnic minorities and others in *ad-hoc* folk medicines).

Criteria for selection of 226 CMM are covered in the *Guide*'s *Introduction* (p. 2) and represent 45% of *CP2015* CMM. Where trade substitutes have been detected, comparative descriptions are provided, including their source plants. See the *Guide* (pp. 5-11) for an overview of the supporting information provided for each CMM account.

3.2 Reference materials for official CMM and their unofficial substitutes[1]

Underpinning the whole *Guide*, and illustrated throughout, is a set of ca. 1,300 vouchered CMM reference drugs. These have resulted from my field collecting programme of 14 field expeditions across 21 provinces of China between 1998-2014 (see *Introduction* and *Expedition Map*, *Guide,* pp. 2-3). Representing crude and processed drugs and their decocting counterparts they are complemented by an equivalent set of materials for substitutes.

The important role of these reference materials in ensuring plant and CMM identification rigour throughout the research cannot be overestimated. These collections have been regularly consulted to help resolve adverse reactions implicating TCM herbs, notably as part of a joint Kew-Guy's Hospital *Traditional Medicines Surveillance Programme* (Perharic *et al.*, 1995; Shaw *et al.,* 1997) and for the *WHO Adverse Drug Monitoring Centre* (Farah *et al.*, 2000, 2006). They have also been used to provide physical reference materials for chemical and DNA-based authentication research undertaken by Kew and the Institute of Medicinal Plant Development (IMPLAD) (Chen *et al.,* 2010, 2014; Kite *et al.*, 2002, 2003, 2009).

3.3 Substitutes

The causes underlying the occurrence of each substitute have been investigated on a case-by-case basis using both the literature and first-hand field experience of CMM along their supply chains (mostly in mainland China, Hong Kong, Taiwan and the UK). Conclusions are summarised in a species-specific *Substitution Comment* alongside each substitute in the *Guide* (e.g. Ban Lan Gen, *Guide,* p. 48). This approach aims to inform future directions in herbal research, regulation and practice.

[1] see definition of 'unofficial substitute' p. vii

3.4 Choice of CMM identification technique

Despite macroscopy persisting as the main quality-control tool of CMM today (Zhao *et al*., 2011) comparative macroscopic research has been neglected in recent years (Leon, pers. obs. 2010-present), due largely to limited availability of reliable reference drugs and substitutes. Overcoming this limitation has been possible by ready access to my purpose-made reference materials (section 3.2). Although chemical and DNA-based techniques were originally considered as additional identification techniques for inclusion in the *Guide*, the expense needed in time, materials and their comprehensive application would have severely limited the number of species included making the *Guide* less representative of the scope of the substitution problem currently facing the international CMM market.

3.5 Botanical taxonomy and nomenclature

The TCM and associated Chinese literature abounds with much ambiguous scientific taxonomy and nomenclature. I have invested much effort, therefore, in its alignment (not a routine task) with current global plant taxonomic opinion notably using the *Flora of China (FoC)*, the *World Checklist of Selected Plant Families (WCSPF)* and the *Medicinal Plant Names Services (MPNS; Guide,* p. 6). For resolution of occasional but especially challenging names I have drawn on the expertise of specialist taxonomists at the RBG Kew.

3.6 CMM nomenclature

CMM nomenclature is notorious for its complexity and an understanding of it is vital to bridge the botanical/TCM divide (see Table 1). Perhaps most fundamental is that a single CMM is frequently sourced (officially, cf. CP2015) from more than one plant species. Latin pharmacopoeia names (e.g. Scrophulariae Radix) are frequently confused with Latin botanical names.

Chinese characters are used either in their simple or traditional forms; the latter are routinely used in Taiwan and other S.E. Asian countries where TCM is practised. Mainland China predominantly uses simplified characters.

3.7 Limitations

The prescriptive design of the *Guide* sometimes limited space, especially for *Substitution Comments* which frequently had to be condensed, while compromises also had to be made on the size and choice of CMM photographs and their close-ups. See also section 3.4.

4. RESEARCH QUESTIONS

4.1 To what extent can macroscopic characters reliably differentiate official CMM from their common unofficial substitutes?

4.1.1 Introduction & literature review

The macroscopic approach to CMM identification has been a feature of Chinese herbal texts (Ben Cao) dating as far back as 168 BCE (Zhao and Chen, 2014). Modern literature from the 1950s onwards has seen microscopy and, subsequently, chemical and DNA methods come to the fore. Modern analytical chemical methods (e.g. HPLC[1], LC-MS-MS[2] and GC-MS[3]) have a role to play in finger-printing and detecting reliable marker compounds but cost, turn-around times and scarcity of interpretation expertise are limitations. The robustness of DNA barcodes require careful interpretation (Hollingsworth *et al*., 2011) although, for the first time, have been included in the current edition of the Chinese Pharmacopeia (CP2015). The advent of whole genome sequencing and other omic techniques may deliver authentication solutions in time but their interpretation and application are still at an early stage (Buriani *et al.,* 2012).

In the meantime, CMM macroscopic identification texts have continued to hold their own with some 100 illustrated texts published during this same period (1950s onwards). This is the specialist field most closely aligned with my own. Predominantly written in Chinese, these texts tend to be

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[1] HPLC: high performance liquid chromatography
[2] LC-MS: liquid chromatography–mass spectrometry
[3] GC-MS: gas chromatography–mass spectrometry

significantly narrower in their information coverage for individual CMM, comparative descriptions of common substitutes is usually absent and, most significantly, verification of the identity of the source plants is totally lacking. The 7-volume Taiwanese text '*Good quality Chinese materia medica'* (Zhang, 2008) demonstrates the widest coverage of CMM types but, despite its wealth of high quality CMM photographs, is inaccessible to non-Chinese readers with captions entirely in Chinese and Latin botanical names deeply hidden in other cross-referenced volumes. Its closest rival for breadth of CMM is the *lllustrated dictionary of Chinese herbal medicines* (NICPBP, 1997-2002), valuable for its inclusion of substitutes but the CMM illustrated often resemble aged museum materials atypical of those likely to be encountered in today's markets. Only Ho *et al.* (2006), also from Taiwan, attempt a comparative approach, targeting a small number of CMM (60); its simple design serves as a quick reference for market traders and, as such, complements the above texts but once again the complete lack of evidence about the identity of the source plants undermines its scientific relevance.

Among the scarce English texts in this field (ca. 12 in total) most authoritative are the *American Herbal Pharmacopeia* monographs (with in-depth analytical, quality control and therapeutic information but sadly limited to only eight CMM; cited in the *Guide* under Upton) and Zhao & Chen's (2014) *Chinese Medicinal Identification* spanning 429 CMM. While the latter text includes twice as many CMM as in the *Guide*, the recurring issue of lack of evidence of source plant identity undermines its scientific integrity. Other limitations are Zhao & Chen's minimalist approach to information content, omitting botanical descriptions, wild/cultivated provenance, conservation status of source plants (and their substitutes), drug substitute comparisons and safety, and only passing references to processing types are made; neither is there any attempt to bring botanical clarity to the taxonomy and nomenclature of the source plants. Finally the style of CMM decocting pieces (Yin Pian) illustrated are more typical of those popular on the Hong Kong market rather than those found in international trade and are, therefore, less helpful as identification aids to these wider audiences.

4.1.2 Results

The major focus of the *Guide* is discrimination of unofficial substitutes, of which 99 are described in detail. For the reasons explained in sections 2.3 and 3.3 their detection is vital. The *Guide* demonstrates that 72% of these unofficial substitutes can be reliably detected macroscopically from their official counterparts. Examples include the detection of florets of 'Hong Hua' (*Carthamus tinctorius*) from its high-value official CMM 'Xi Hong Hua' (style and stigma of *Crocus sativus*, *Guide,* pp. 596-9), and the detection of 'Jia Ma Chi Xian' (aerial parts of *Bacopa monnieri*) from official 'Ma Chi Xian' (aerial parts of *Portulaca oleracea*, *Guide,* pp. 368-71). An additional 11% of unofficial substitutes can be detected in their crude form only. For example, the crude drug of 'He Shou Wu' (*Fallopia multiflora*) can be distinguished from that of its unofficial substitute sourced from *F. aubertii* (*Guide,* pp. 156-7), however when processed with black soya bean juice, the two are indistinguishable (pp. 158-9).

The remaining 17% of unofficial substitutes cannot be differentiated from their official CMM in either crude or processed forms. An example of a CMM requiring 'validation' with other methods is 'Chuan Mu Tong' (Clematidis Armandii Caulis, *Guide,* pp. 428-33) where reliable differentiation of the pharmacopoeia species *Clematis armandii* and *C. montan*a from the unofficial substitute (stem of *Aristolochia manshuriensis*) is imperative for legal and safety reasons. This substitute is banned in most countries owing to its cumulative nephrotoxicity (Debelle *et al.*, 2008).

4.1.3 Discussion

The question arises as to whether the relatively high proportion of substitutes that can be differentiated macroscopically is representative of the wider CMM market. There are insufficient data to argue that this pattern is representative of all CMM, but conscious bias in favour of more easily separated CMM can be ruled out. Several criteria were used for inclusion of CMM in the *Guide* (p. 2) but did not include likelihood that macroscopic identification would prove to be robust; this was only evaluated after macroscopic characterisation was carried out.

Even when macroscopic differentiation is considered ‘reliable’ it is nevertheless an end-user’s decision as to whether or not further validation using other methods is required based on context (e.g. the dispensing of a CMM by a TCM clinic for a patient’s prescription, the preparation of a quality control dossier for a formal application for Traditional Herbal Registration, or seizure by a customs officer of an international trade consignment potentially in breach of CITES).

Results indicate that the degree of processing of CMM is a major factor in determining whether macroscopy is a robust identification method. Species determination is therefore best performed on CMM prior to processing when identification characters are not yet obscured.

4.1.4 Conclusions

Despite the advent of laboratory-based methods, the macroscopic method continues to be a powerful identification tool for many CMM. The power of macroscopy is validated in the *Guide* through its comparative approach, based on consistent character-by-character differentiation. This approach assessed the robustness of macroscopy on a drug-by-drug basis and, where appropriate, recommends the use of other methods.

4.2. What is the taxonomic alignment of the current Chinese *Pharmacopoeia* (CP2015) with current taxonomic opinion, and how has this affected my circumscription of CMM?

4.2.1 Introduction & literature review

In the absence of a single, comprehensive and up-to-date global taxonomy for plants, the *Guide* has aimed to reflect current plant taxonomic opinion by mapping Latin botanical names to those accepted in *FoC*, *WCSPF* and *MPNS*. The taxonomic rationale for choice of Latin botanical names in the Chinese Pharmacopoeia is less precise; the main taxonomic sources are cited as the 'Flora of China *[FoC]* and Higher Plants of China etc.' but the preface of 2015 edition states that 'Latin names have [been] subsequently regulated and revised'. Such taxonomic ambiguity, perpetuated between all editions of the CP, has not only been a cause of confusion to the TCM community as whole, but has often required considerable research during production of the *Guide* and invariably resulted in some taxonomic mis-alignment between the CP2015 and the *Guide*.

4.2.2 Results

84% of Latin botanical names in the CP2015 have been adopted as accepted names in the *Guide* because they reflect current taxonomic consensus. The remainder have been treated as synonyms, or otherwise noted. All discrepancies are given under *Taxonomic/nomenclatural notes* for each species in the *Guide*. These have occurred at family, genus and species levels.

4.2.3 Discussion

Unlike many CMM specialists, my workplace at RBG Kew has provided me with an awareness of the development of a global plant taxonomy and the importance of mapping Latin botanical names through resources such as the MPNS. In an effort, to align the CP2015 Latin scientific names with this global aim, I have made three main types of taxonomic adjustment:

- Change in genus or species delimitation: this includes 'lumping' of taxa as one, or changes in generic circumscription. An example of the former is 'Xi Xian Cao – Siegesbeckiae Herba' (*Guide*, pp. 396-9) with the three CP2015 taxa reduced to one (*Sigesbeckia orientalis*) with a concomitant change in its genus spelling from *Siegesbeckia* to *Sigesbeckia.* On this occasion, a taxonomic view in the *Flora of Japan* was followed in preference to that of *FoC* or *MPNS* for reasons explained in the text. An example of change in genus is illustrated by the drug ‘Wu Jia Pi’, *Acanthapanax gracilistylus*, now regarded as *Eleutherococcus nodiflorus* (*Guide*, p. 526).

- Re-identification of source taxa: in three cases, use of my reference collections of herbarium-vouchered CMM resulted in the re-identification of source plants. For example, the identity of the source plant of the important drug ‘Shan Yao’ was found to be *Dioscorea polystachya* rather than the CP2015’s *D. opposita*（*Guide*， p. 268). Re-examination of material widely called *Cistanche tubulosa*, one of the parasitic source species of ‘Rou Cong Rong – Cistanches Herba’, has resulted in what appears to be an undescribed species and which, owing to its host-specificity to the genus *Tamarix*, my co-author and I have provisionally named *Cistanche* ‘Tamarisk’ (*Guide*, p. 470). I acknowledge here the taxonomic advice of Michael Gilbert (Missouri Botanical Garden).
- Ambiguous definition of type subspecies. For example, for ‘Hou Po’ (*Guide*, p. 508), the CP2015 omits the type varietal name ‘var. *officinalis’* for *Magnolia officinalis*. In this and other cases it is unclear whether the CP2015 refers to all infra-specific taxa or just the type variety. Where ambiguity remains this has been noted in the *Guide*’s ‘taxonomic/nomenclatural notes’ for each CMM.

Nomenclatural errors in CP2015, e.g. in spelling and author names, were very frequent and often took considerable time to resolve.

As argued for macroscopic research (see 4.1.3), the taxonomic findings just described are likely to be representative of wider CMM. No conscious effort was made to select taxonomically problematic CMM in the *Guide*.

4.2.4 Conclusion

Results of the taxonomic approach adopted throughout (see section 3.5) demonstrate an alignment of over 80% between Latin botanical names used in the *Guide* and *CP2015*. In the remaining cases where names are ambiguous, work carried out on the *Guide* demonstrates that resolution of these names requires specialist taxonomic expertise. The implication for CMM herbal quality control is that both industry and regulators require cross-sector collaboration with taxonomic institutes.

4.3. What are the drivers underlying the occurrence of unofficial CMM substitutes in international trade?

4.3.1. Introduction & literature review

The accidental or intentional occurrence of unofficial herbal substitutes (which includes clinical substitutes, adulterants, contaminants and counterfeits) is well-known among experienced TCM scholars, traders and practitioners but is poorly understood in the West. This is because i) the vastness and complexity of the global CMM trade makes these substitutes difficult to investigate systematically; ii) patterns of substitution change over time and space and iii) although their detection is often straightforward their identification is not. Furthermore, Understanding the current drivers of CMM substitution can help pre-empt their detection and management. Section 3.3 summarises the approach used here for their investigation.

The seminal book *Chinese herbal medicine materia medica* (Bensky *et al.*, 2004) is the first English text to list scientific names of 'alternate species', 'local variants' and 'adulterants' according to historical TCM texts. The review paper by Zhao *et al.* (2006a) presents one of, if not the only attempt in English to classify the origin of CMM substitutions, in this case, on the Hong Kong market. The only identification study specific to CMM traded in the UK is the recent work on fruits and seeds by van der Valk *et al*. (2017) which provides detailed discussions on the substitutes encountered in market sampling of 20 CMM.

4.3.2. Results

The 226 CMM described in the *Guide* represent 45% of those in the *CP2015*. Of these 226, 85 (38%) are reported to experience regular substitution (based on first-hand knowledge) when traded in international markets. A brief analysis of causal factors presented in the *Guide* (under 'Substitution Comment') is shown in Table 2.

4.3.3. Discussion

Examples of each of these causes of substitution are analysed below:

i) Clinical similarity/interchangeable use

This refers to the intentional use of a drug that has similar clinical properties to the official drug and which is used either out of clinical preference, or because of its easy availability, or for a combination of all three. Such local substitutions are typical in China and hark back to an earlier era when China's vast distances meant there was a greater reliance on locally available herbs. For example 'Ban Lan Gen' (Isatidis Radix) is sourced in northern China from *Isatis tinctoria*, but in southern China is from *Strobilanthes cusia* (*Guide*, p. 48).

A case of international substitution is 'Mu Xiang' (Aucklandiae Radix, *Guide,* pp. 210-9): the original source was the root of the Chinese native *Inula helenium*; this has been replaced *by Aucklandia costus* imported from the Indian Himalayas, which is considered to have superior clinical properties.

Clinical substitutions such as this represent by far the largest cause of substitution.

ii) Supply problems

Declining herbal resources are a product of many factors including booming world trade, new medical needs and climate change. The over-harvesting of 'Shan Dou Gen' (Sophorae Radix, *Guide,* pp. 260-3) sourced from the root of *Sophora tonkinensis* to treat China's rising incidence of throat cancer has led to its near extinction in the wild. In the absence of its successful cultivation the market has moved to an inferior substitute 'Bei Dou Gen' (Menispermi Rhizoma, *Guide*, p. 60, root of *Mensipermum dauricum*) another TCM herb in its own right.

iii) Mis-identification at point of harvest

Wild harvested species may be prone to mis-identification with morphologically similar species (often close relatives) which grow in close proximity. An example is the inadvertent substitution of 'Ma Chi Xian' (Portulacae Herba, *Guide,* pp. 368-71) with the totally unrelated but similar-looking (especially when not in flower) *Bacopa monnieri* (*Guide,* pp. 370-1). In contrast, species sourced from cultivated sites are by their nature predictable because of planned planting and management regimes. This is illustrated in CMM sampled from selected TCM outlets in the UK (van der Valk *et al.*, 2017): 95% of samples derived from cultivated plants (n = 103) were sourced from an official species; this contrasts with 78% from wild plants (n = 64).

iv) Confused Chinese trade nomenclature

With some 10,000-11,250 medicinal plant species in China, shared vernacular names are inevitable. For example, the vernacular trade name '王不留行 Wang Bu Liu Xing' (*Guide,* pp. 732) is used for at least two CMM derived from completely different species. The *CP2015* uses this name to refer to the seed of *Vaccaria hispanica* (Caryophyllaceae, Vaccariae Semen, *Guide*, p. 732) while in south China the identical name is widely used for the CMM derived from the fruit of *Ficus pumila* (Moraceae). Fortunately these two CMM are macroscopically very distinct, as are their therapeutic properties. Regional substitutions of this kind permeate CMM trade in China but owing to the much smaller numbers of CMM traded internationally, examples of such potential confusion are rare.

v) Cheaper morphological look-alikes for high-value drugs

Economic incentives for the use of cheap substitutes has a long history in herbal medicine. The market for American ginseng (*Panax quinquefolius*), for example, is regularly adulterated with cheap morphologically similar substitutes such as 'Dang Shen' (roots of *Codonopsis pilosula* in the Campanulaceae, *Guide,* pp. 102-5), popularly known as 'poor man's ginseng'.

4.3.4. Conclusions

The selection of CMM in the *Guide* focused on patterns of substitution in international trade hence the *incidence* of substitutions encountered in the *Guide* is not representative of the wider TCM trade. In contrast, the *drivers* of substitution is likely to be representative of the wider trade.

Researching substitution patterns and their causes presented one of the most challenging aspects of preparing the *Guide*, requiring a detailed understanding of individual species (such as wild versus cultivated sourcing and conservation status) as well as supply and demand issues of their commercially traded CMM. Factoring these research results into herbal quality assurance systems has considerable potential to improve their cost-effectiveness as well as ensure they are fit-for-purpose. Herbal substitution research of this kind, however, is acutely under-studied and requires urgent multidisciplinary support (van der Valk *et al.,* 2017).

4.4. TO WHAT EXTENT DOES MEDICINAL HARVESTING IMPACT THE CONSERVATION STATUS OF SOURCE PLANTS?

4.4.1 Introduction & literature review

Since the 1960s, China's flora has been subjected to the onslaught of China's extensive economic development boom with its highly damaging environmental fall-out such as large-scale deforestation, road construction, urbanisation, intensive agriculture not to mention globalisation of its TCM industry leading to spiralling demand for its medicinal resources (Huang, 2011). With ca. 80% of TCM plant species wild-sourced (Zhang *et al*., 2010) they are especially vulnerable to all of these pressures.

China's nationwide survey of TCM natural resources from 1983-1994 (Xu *et al.*, 2013) provides a backdrop for conservation. Assessing the conservation status of medicinal plants species, however, in a country the size of China and with a flora of over 31,000 species is a challenge; figures are at best provisional. The international Red-Listing programme (managed by IUCN) is slow to validate recommendations for species to be listed, such that a species that is absent from this global list is not necessarily out of danger. This is where national red-listing initiatives come into their own as interim indicators of threat. For example, Fu (1992) drew attention to some 25 threatened medicinal plant species in China's first plant red data book; 21 of these are described in the *Guide*. A flurry of much lengthier red lists swiftly followed, the most recent and comprehensive of which lists ca. 3,000 plant taxa (MECPAS, 2013) and served as one of the main sources of conservation assessment adopted throughout the *Guide*.

4.4.2. Results

Of the 302 official source species described in the *Guide*, 270 are native to China. Table 3 shows the breakdown of native species nationally threatened and the subset directly affected by medicinal over-harvesting. Two species are 'Extinct in the Wild': *Panax notoginseng* and *Prunus persica* but the cause of their extinction is unclear. 61 species are directly threatened by over-harvesting although this is not the sole threat to these species.

4.4.3. Discussion

To illustrate various conservation scenarios I can divide the 73 medicinal plant taxa that are nationally threatened into 3 main groups; these are not mutually exclusive:

1. Genera 'safe' in medicinal cultivation (*Eucommia*, *Dendrobium, Gastrodia, Glehnia*, *Paeonia*, *Phellodendron*). A review of China's *National Plant Conservation Strategy* states that of the approximately 600 mainstream TCM plants 200 have been brought into 'sustainable cultivation' (Huang, 2011). Their long-term security is in doubt if the genepools of their wild populations are not adequately conserved. Valuable traits required for future breeding programmes include disease resistance and adaption to climate change.

Loss of germplasm variability will also limit the application of bioprospecting that benefits from traditional knowledge of medicinal plant use (Saslis-Lagoudakisa *et al.,* 2012). Examples of threatened TCM species which may provide leads (along with their close phylogenetic relatives) for global disease conditions, notably cognitive disorders, include *Coptis chinensis* and *Magnolia officinalis* (source of 'Hou Po – Magnoliae Officinalis Cortex', *Guide,* pp. 508-11) (Howes & Houghton, 2003).

2. Those economically extinct (i.e. no longer economically viable for harvest due to their scarcity) and yet to be brought into commercial cultivation, such as *Sophora tonkinensis* (*Guide*, p.260). It is these species that are under greatest threat of extinction. Conservation work on some of these is underway (see below) but it is difficult to assess progress on other species because of the size of the country and number of species involved.

Detecting unofficial substitutes of wild-harvested species can provide early warning of supply problems for that species, suggesting its populations are threatened by over-harvesting. Identification of such substitutes, as described throughout the *Guide*, can inform conservation agendas. For example, the two official source species of 'Zi Cao' (*Arnebia euchroma* and *A. guttata;* see Arnebiae Radix, *Guide,* pp.336-9) are both critically endangered due to over-harvesting, and *ad-hoc* trade studies demonstrate the regular occurrence of substitutes.

3. Species whose wild populations have been the focus of recovery programmes (e.g. *Cistanche deserticola*, *Fritillaria cirrhosa*). *F. cirrhosa* (*Guide,* pp.78-85) has been the focus of a long-term and large-scale 'natural fostering' initiative to enable sustainable harvesting, however indiscriminate harvesting of the species in other parts of its range continues in order to meet demand.

It is not clear whether the proportion of threatened CMM source species in the *Guide* is representative of CMM source species as a whole. This is because one of the criteria for the selection of CMM included in the *Guide* was CMM prone to substitution and, as discussed above, some substitutions arise because of supply issues due to depleted wild populations.

4.4.4. Conclusions

Of the 302 official source species in the *Guide* 25% are declining nationally and fall into one of the IUCN threatened categories or are classified as Near Threatened. This problem has been recognised through national surveys (as cited above) and although a variety of conservation measures are in place for some of these species, there is an acute need for an in depth strategic programme for their conservation and sustainable sourcing (Chen et al., 2016; Huang, 2011).

5. CONCLUSIONS AND FUTURE DIRECTIONS

This research demonstrates that the macroscopic approach can reliably identify crude and processed drugs of many TCM species. Macroscopy provides a fast and cost-effective method both to authenticate a drug's identity and to discriminate it from common unofficial substitutes. Where macroscopy is considered insufficiently robust for the drugs included in the *Guide*, laboratory-based methods are recommended but their availability in contexts such as markets and dispensaries is limited by practical considerations.

The routine use of verified drug reference materials is becoming increasingly widely recognised as essential by the many disciplines reliant on accurate herbal drug identity. The creation of these reference resources is however hugely time and labour-intensive and accordingly very few such resources exist; a recent Sino-American collaboration provides a recent example (Eisenberg *et al.,* 2011). The reference collections underpinning the *Guide* demonstrate how international collaborations can deliver such resources. Where traceability to source plants is possible, their identification provides the ultimate proof of a drug's identity, hence the emphasis placed on living plants as well as drugs throughout the *Guide*.

The disconnect between the TCM community and its botanical counterpart hinders transfer of taxonomic knowledge, and its impact is visible in the use of ambiguous and outdated names in, for example, the *Chinese Pharmacopoeia*. Inaccuracies tend to be perpetuated throughout the herbal literature due to lack of good practice. Solutions include improved dialogue between these communities and standardised nomenclatures that link TCM names to accepted Latin botanical names. The work involved in the *Guide* illustrates that this knowledge transfer cannot be automated, but relies upon time-consuming interactions between relevant specialists.

Highlighted throughout are those TCM drugs most likely to be substituted in international trade. The occurrence of substitutes is an expression of clinical preference, confused identifications and nomenclatures, dispensary availability, unscrupulous trading as well as early warning of declining wild populations. These factors underline the importance of plant and herbal drug identification and which in turn impact efficacy, safety and sustainable supply.

The *Guide*, and the approach it takes, aims to encourage a more considered approach to plant and drug identification. It is not enough to apply identification criteria in isolation; other factors such as likelihood of substitution must be taken into account. Ultimately this approach will lead to improvements in clinical practice, better framed herbal medicine and conservation regulations, and scientific robustness in natural product research.

Table 1: Types of Chinese *materia medica* (CMM) name

CMM name type	**Example 1 (CMM officially sourced from 1 species & 1 processed trade type)**	**Example 2 (CMM officially sourced from 3 species & 3 processed trade types)**
Latin Pharmacopoeia name (usually Latinised genus plus plant part)	Scrophulariae Radix (or Radix Scrophulariae)	Coptidis Rhizoma (or Rhizoma Coptidis)
Chinese name in simplified characters	玄参	黄连 (酒黄连; 姜黄连; 萸黄连)
Chinese name in traditional characters	玄參	黃連 (酒黃連; 薑黃連; 萸黃連)
Pin Yin name(s)	Xuan Shen	Huang Lian (Jiu Huang Liang - wine processed; Jian Huang Liang - ginger-processed); Yu Huang Liang - processed with *Tetradium ruticarpum* fruits)
Wade Giles name	Hsuan-Shen	Huang-Lien
English vernacular name(s)	figwort root	golden thread
Latin scientific name of source species &plant part	*Scrophularia ningpoensis* Hemsl. - root	*Coptis chinensis* Franch.; *C. deltoidea* C. Y. Cheng & P. K. Hsiao; *C. teeta* Wall. - root

Table 2: Causes of substitution

	No. species substitutions
clinical similarity/interchangeable use	48
supply problems	18
mis-identification at point of harvest	15
confused Chinese trade nomenclature	2
cheaper morphological look-alikes for high-value drugs	2
Total	85

Table 3: CP2015 threatened plant species in the *Guide* (n=270) according to IUCN categories.

	threatened by any cause	threatened by medicinal over-harvesting
Extinct in the wild (EW)	2	2
Threatened & declining *(Critically Endangered (CR); Endangered (EN); Vulnerable (VU); Near Threatened (NT)*	73	61

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