Emergent quality issues in the supply of Chinese medicinal plants

中草藥供應中發生的品質問題

A mixed methods investigation
of their contemporary occurrence
and historical persistence

當代發生和歷史延續混合調查法

A

Thesis

by

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submitted for examination in partial fulfilment of the

Degree of Doctor of Philosophy

Awarded
1st June 2023

By

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VOLUME I of III

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2023

Abstract

English Abstract

Quality issues that emerged centuries ago in Chinese medicinal plants (CMP) were investigated to explore why they still persist in an era of advanced analytical testing and extensive legislation so that a solution to improve CMP quality could be proposed.

This is important for 85% of the world's population who rely on medicinal plants (MP) for primary healthcare considering the adverse events, including fatalities that arise from such quality issues. CMP are the most prevalent medicinal plants globally.

This investigation used mixed-methods, including 15 interviews with CMP expert key informants (KI), together with thematic analysis that identified the main CMP quality issues, why they persisted, and informed solutions. An unexplained case example, *Eleutherococcus nodiflorus* (EN), was analysed by collection of 106 samples of EN, its known toxic adulterant *Periploca sepium* (PS), and a related substitute, *Eleutherococcus senticosus* (ES), across mainland China, Taiwan and the UK. Authenticity of the samples was determined using High-performance thin-layer chromatography.

Misidentification, adulteration, substitution and toxicity were the main CMP quality issues identified. Adulteration was found widespread globally with 57.4% EN found authentic, and 24.6% adulterated with cardiotoxic PS, mostly at markets

and traditional pharmacies. The EN study further highlighted that the reason CMP quality issues persisted was due to the laboratory-bound nature of analytical methods and testing currently used that leave gaps in detection throughout much of the supply chain.

CMP quality could be more effectively tested with patented analytical technology (PAT) and simpler field-based testing including indicator strip tests. Education highlighting the long-term economic value and communal benefit of delivering better quality CMP to consumers was recommended in favour of the financial motivation for actions that lead to the persistence of well-known and recurrent CMP quality issues.

Chinese Abstract

摘要

本文通過研究幾世紀前出現的中草藥（以下簡稱 CMP）品質問題，探究在分析測試方法先進和立法完備的時代仍然存在這些問題的原因，從而提出提高中草藥品質的解決方案。

這樣的研究十分重要，因為全球 85%的人口基礎保健都有賴於草藥（以下簡稱 MP），而此類品質問題會導致包括死亡在內的不良事件。中草藥是全球使用最普遍的草藥。

該項研究採用混合法，與中草藥專業關鍵性人物（以下簡稱 KI）進行 15 次訪談並進行專題分析，確定主要的中草藥品質問題、問題持續存在的原因以及具備合理依據的解決方案。通過在中國大陸、臺灣和英國收集 106 份細柱五加（以下簡稱 EN）、已知有毒摻雜物杠柳（以下簡稱 PS）和相關替代品刺五加（以下簡稱 ES）樣本，對細柱五加（以下簡稱 EN）這一未經解釋的藥例進行分析。採用高效薄層色譜法測定樣本真偽。

研究發現主要的中草藥品質問題包括誤認、摻假、以次充好及毒性。摻假現象在全球範圍內普遍存在，57.4%的 EN 為真品，24.6%的 EN 摻有具有心臟毒性的 PS，主要見於市場和傳統藥店。EN 研究進一步強調，CMP 品質問題持續存在的原因是，現時使用的分析方法和檢測方法受實驗室限制，在全供應鏈大部分環節都存在檢測漏洞。

CMP的品質可以通過專利分析科技（以下簡稱PAT）和更簡單的現場測試（包括訓示條測試）進行更有效的測定。建議開展教育活動，強調向消費者提供更高品質CMP的長期經濟價值和共同利益，以取代導致眾所周知和反復出現的CMP品質問題持續存在的經濟動機。

Declaration of novelty

This research is the first mixed-methods investigation to substantively consider CMP quality issues collectively as a unified problem that has persisted historically to contemporary times from such a broad perspective. It contrasts the trend of previous researcher which focused mainly on individual quality issues and towards increasingly specialised investigations through the lens of (bio)chemical characterisation relying on analytical instrumentation orientated solutions.

It generated new insights around what are the key CMP quality issues of concern, why they recur, and informed a novel solution to CMP quality issues by interviewing senior experts in the field of CMP quality.

This research showed where quality issues occur in the global herbal supply chain by studying *Eleutherococcus nodiflorus* (EN), a CMP that embodies the most commonly reported CMP quality issues of misidentification, substitution, adulteration and toxicity. It demonstrated that the previously unexplained reason why these quality issues occur in the EN supply was most likely from intentional profit motivated human action, and not predominantly from error, as formerly suggested in the literature.

This thesis framed CMP quality issues collectively as a singular recurrent problem which illustrated those which recur in recent times are similar to those in previous centuries. Substantiating the necessity for an alternative solution to that currently in place. It showed current solutions to CMP quality issues and those

proposed by leading global organisations such as the European Medicines Agency, China National Products Administration, and the World Health Organization are based on increasingly sophisticated analytical instrumentation that further restrict herbal testing to laboratory environments where quality issues do not predominantly occur. A review of quality tests described in pharmacopeias mandated by legislation in the context of where testing is required in the supply chain showed that testing is not aligned with where the quality issues occur and the problems they are designed to detect. It found that CMP quality issues in many stages of the herbal supply chain remained obscured and, therefore, recur. It showed how the current situation fosters opportunities for those who wish to alter the quality of CMP for profit gain within the gaps where testing is not conducted, predominantly outside laboratory environments.

This thesis research informed an alternative solution to CMP quality issues and generated new insights into why they persist by consulting with key informants. It highlighted that CMP quality issues often arise from profit-motivated human behaviour, which is not the central focus solutions currently in place nor those proposed by the responsible global organisations for the future.

An alternative solution was proposed based on the principle of using simpler, less expensive in-field testing distributed along the supply chain where quality issues are more likely to occur. A reliable, permanent, and more transparent information-gathering system, such as Blockchain, is recommended to capture quality information in a non-erasable, more traceable system that is accessible globally.

CMP quality problems over a 32-year period were comprehensively reviewed and collated. A meta-analysis of why they recured as reported in the literature, and twenty consultations with senior experts in the field of CMP quality informed a solution.

Studying EN, a case example with multiple CMP QI quality issues, illustrated the abovementioned findings in-field, and in practice. It identified where and why adulteration of EN occurs in the global supply chain. It found that the previously unexplained reason why EN adulteration occurs is more likely intentional and profit-motivated. It detected one-quarter of the EN global supply tested was adulterated with a cardiotoxic substitute, *Periploca sepium*, and a concerningly low proportion, 57% were authentic.

A novel solution was proposed that is simpler, less expensive, more comprehensive, and potentially more effective than current testing. A demonstration of a pH strip test that differentiated EN from PS illustrated one such simple test.

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Dedication

To the most clever person I have ever known, Mary Burke, better known to me as Mam. My two sisters, Catherine and Rose, and my brother Thomas, uncle Pat, nephew John, were with us all at the start of this PhD journey. Although they may no longer be here in person, I know they have been guiding and helping me in spirit every step of the way. I dedicate this work to their memory.

Acknowledgements

To **Dr. Anthony Booker** and **Professor Michael Heinrich,** who have both mentored me and fostered my knowledge of Chinese herbal medicine across the globe geographically and the span of its long history. They have kindly indulged my ideas, challenged my thinking, and shown patience in what has been a busy four years of research. I find them both a source of inspiration and admiration in their hard work and knowledge, which they selflessly and positively share.

To **Dr. Alizon Draper,** who expanded my knowledge of research and how perspective shapes everything that we (think that we) see, know and form opinions upon. Her influence has been invaluable.

I am grateful to all those who have advised and advanced my knowledge during my research journey including:

Guy Wadddell

Mike Potter

Nikki Laurence

Volker Scheid

To all those who helped me in **China Medical University**, Taichung, Taiwan, and the **China Academy of Medical Sciences** in Beijing, China, in sourcing

and accessing information, documents and sourcing samples. Many have given their time and expertise in support of the pursuit of knowledge.

To my sponsors **Amy Tso at Herbprime** UK., Ltd and **Sun Ten**, Taiwan who have generously funded this research over many years without ever seeking anything in return but the advancement of herbal medicine knowledge. I thank you sincerely for your support in allowing me to take this research journey of a lifetime.

Finally, to all my **PhD colleagues**, for their company, especially all at the Michael Heinrich advanced research (tea-drinking?) group, for your fabulous humour and friendships that will last a lifetime. I have learned an immeasurable amount from listening to you speak about your research, your presentations and simply being in your company.

Thank you to Xixi Yang, Kim Fisher, and Shih-Hui Kuo for your friendship, love and support. You have taught me what selflessness and support really means. I can never thank you enough.

To Meowi my cat who kept me company while I wrote, my feet warm in winter, and occasionally tried to contribute to the writing with his own paws and by sitting on the keyboard. Despite his efforts, and to the best of my knowledge, I promise he has not made any significant contributions to the work and do declare all the contents of this thesis are those of the doctoral researcher.

Declaration

I declare that all the material contained in this PhD thesis is my own work and a true reflection of the research conducted.

Abbreviations and Terms

Abbreviations

ABC	American botanical council
BAPP	Botanical adulterants prevention program
BRM	Botanical reference material
CHM	Chinese herbal medicine
ChP	Chinese pharmacopoeia
CWJ	Ci wu jia, 刺五加, Chinese name for *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim
CMP	Chinese medicinal plant(s)
CNMPA	Chinese national medical products administration
CP	Chinese pinyin language term
EMA	European medicines agency
EN	*Eleutherococcus nodiflorus* (Dunn) S.Y.Hu
EP	European Pharmacopeia
ES	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim
GAP	Good agricultural practice guidelines
GCP	Good collection practice guidelines
GMP	Good manufacturing practice guidelines
GPTCM	Good practice in traditional Chinese medicine research in the post-genomic era group
GxP	Good practices guidelines including GAP, GCP, GMP.
HPTLC	High-performance thin layer chromatography

ISE	International society for ethnopharmacology
MP	Medicinal plants
PAT	Patented analytical technology
PS	*Periploca sepium* Bunge
Ph Int	International pharmacopeia
PRISMA	Preferred reporting Items for systematic reviews and meta-analyses
SATCM	Chinese state administration of TCM
TCM	Traditional Chinese medicine
THMPD	Directive on traditional herbal medicinal products (2004/24/EC)
TP	Taiwanese pharmacopeia
WJP	Wu jia pi, 五加皮, Chinese name for *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu
WHO	World Health Organization
XJP	Xiang jia pi, 香加皮, Chinese name for *Periploca sepium* Bunge

Thesis terms

Chinese medicinal plant(s), any plant listed in the Chinese Pharmacopeia 10th edition (CCP, 2019).

Chinese herbal medicine(s), Chinese medicinal plant(s) presented as a commercial product(s) or in a prescription intended for the purposes of health or well-being.

“Chinese medicinal plants”, “herbs”, and “Chinese herbal medicine”, are used alternately to indicate Chinese herbal plant material throughout this PhD thesis. In general, CMP are considered plants during cultivation and early stages of the supply chain, and more as CHM or medicines later in the supply when processed or defined as products; however, there is an overlap with these descriptions and are used interchangeably.

The term “recur” or “recurrence’ is intended to indicate a repeated occurrence of a quality issue within this Contemporary Era, which spans from approximately the post-World-War II period to the present.

The term “persistence” indicates a historical recurrence over a longer term than the Contemporary Era.

“Quality issue” is intended to broadly describe any altered herbal quality attribute of CMP that is fraudulent, has posed problematic to control, or is potentially

detrimental to consumer health or well-being, including but not restricted to those implicated in adverse health events.

Note on the term “Quality”: Care has been taken not to define “quality” at the outset or during the doctoral thesis, but instead show the development of its variable and transitional meaning form historical to present times, as will be described further.

Chapter One Introduction

1.1 Introduction

Medicinal plants are an important healing resource historically from which 80% of pharmaceutical drugs have been derived (Bauer and Brönstrup, 2014) and contemporarily as 85% of the world's population are estimated to rely on them as a primary mode of healthcare (Pešić and Stanković, 2015). There is an increasing global trend in plant medicine use, particularly in Europe since the 1990s (Ekor, 2014). However, the relatively rapid growth in herbal use has seen a corresponding rise in the number of quality problems observed and discovered through routine testing, academic investigations including reports of adverse events (Hoban et al., 2018; Coghlan et al., 2015a; Bensoussan, Myers and Carlton, 2000).

The last half-century saw an unprecedented rise in herbal usage and supply, with a rise of 49% in Europe and 42% in the USA, respectively, during the 1990s (Ernst, 1998; Eisenberg et al., 1998). China overtook USA in the year 2000 as the world's greatest medicinal crop grower when 2.6 million tonnes were produced, which placed Chinese medicinal plants (CMP) as the most prevalent medicinal plants globally (Xiang et al., 2022; NSBC, 2018; FAO, 2020, p.7). Currently, CMP maintains this prominence, a trend predicted to continue based on the recent reports on China's economic growth (Bekkers, Koopman and Rêgo, 2021).

However, along with the rapid proliferation of CMP also came increased reports of quality issues, such as misidentified medicinal plants, the substitution of one CMP for another, and adulteration with bulking agents to add value in addition to

synthetic drugs so that consumers could more easily perceive their medical effects. Even though recurrent quality issues were often of little consequence or, on occasion, rendered medicinal plants ineffective at treating minor health ailments, in many other cases, significant adverse events were reported, including fatalities (Posadzki, Watson and Ernst, 2013). As CMP usage becomes more prevalent, so does the potential for such issues to affect a significant proportion of the global population's well-being. This situation prompts consideration of why long-known and well-known quality issues persist in a time of advanced analytical tests that can detect such problems and which are mandated by legislation. Much effort has been expended internationally to assure herbal quality and protect consumers. Still, quality problems similar to those observed since the 1990s and recorded centuries before in China recur and persist into the 21st century (Ichim and de Boer, 2021; Jiang et al., 2020; Lau et al., 2003; Bensoussan et al., 2000).

1.2 Research aim

The aim of this research was to address these issues by investigating why similar and well-documented Chinese medicinal plant quality issues that emerged centuries ago still recur in this Contemporary Era of advanced analytical testing and extensive regulation so that a solution to the problem of their persistence may be proposed by; exploring the knowledge of key informants expert in the field of Chinese medicine, followed by collection and analysis of a Chinese medicinal plant, *Eleutherococcus nodiflorus* to investigate unexplained adulteration with cardiotoxic *Periploca sepium* and a related plant, *Eleutherococcus senticosus* in the global herbal supply.

1.3 Research objectives

The first of the three objectives was to explore the knowledge of key informants expert in the field of Chinese medicine, initially through a pilot questionnaire and then interview; followed by thematic analysis to identify what similar and well-documented Chinese medicinal plant quality issues occurred to generate insights into why they persisted, so that a solution to the problem of their persistence could be proposed.

The second of three objectives was to collect Chinese medicinal plant samples; *Eleutherococcus nodiflorus, Periploca sepium* and *Eleutherococcus senticosus* from the global supply chain across mainland China, Taiwan and the United Kingdom; then analyse the samples using high-performance thin-layer chromatography to determine their authenticity and examine why this unexplained adulteration recurs, so that solutions to the problem of its persistence may be proposed.

The third and final objective was to gather the findings to describe concisely:

- the identity of the main CMP quality issues that persisted;
- insights into why they persisted; and
- a proposed solution to the problem of their persistence.

1.4 Research strategy

This research lay in the field of Chinese herbal medicine situated within the more general field of life sciences. The research approach was exploratory in nature and used mixed methods to accomplish the objectives as set out in two studies described in Chapters Three and Four.

The research investigated why similar and well-documented Chinese medicinal plant quality issues that emerged centuries ago still recured in this Contemporary Era of advanced analytical testing and extensive regulation, so that a solution to the problem of their persistence could be proposed.

Two separate but related studies were conducted for this investigation.

The first study, called the “KI study”, explored the knowledge of key informants expert in the field of Chinese medicine. This was followed by the second “EN study” that examined a Chinese medicinal plant (CMP) called *Eleutherococcus nodiflorus* (EN) as a case study. EN was identified as a CMP with multiple unexplained problematic quality issues by three key informants during the KI Study. Although the KI study began before the EN study, they ran concurrently.

The aims, objectives, methodology, discussion, findings, and conclusion are described in detail for each study in their respective chapters. The ethical approval for consulting with key informants is described in Chapter Three.

The first KI study explored the knowledge of key informants expert in the field of

Chinese medicine with a pilot questionnaire and interview, then analysed the data thematically to identify what similar and well-documented Chinese medicinal plant quality issues occurred. The aim was to gain insights into why they recurred, and to inform a solution to the problem of their persistence. This study is described in Chapter Three.

The second EN study collected samples of *Eleutherococcus nodiflorus* and its known adulterants *Periploca sepium* and *Eleutherococcus senticosus* throughout the global supply chain across mainland China, Taiwan, and the United Kingdom. The authenticity of the samples was determined using high-performance thin-layer chromatography. It was anticipated that this data could inform why unexplained cases of EN adulteration recurred and, furthermore, inform a solution to its persistence. This study is described in Chapter Four.

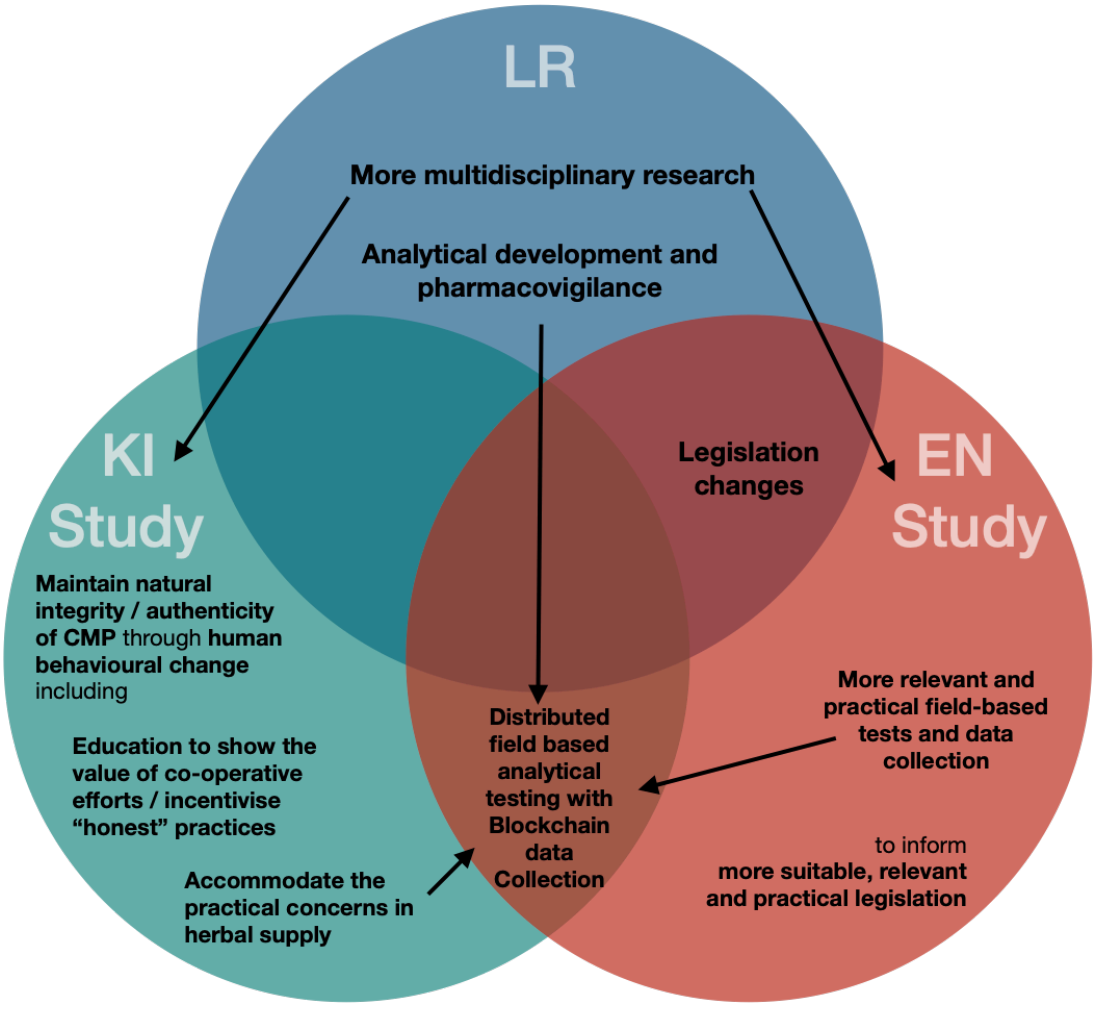
Similar to other multi-disciplinary research described in the literature review, Chapter Two, the findings of the two studies were brought together in mutual context to further explore how together they could inform the aim and objectives of the investigation in Chapter Five.

Chapter Five drew together the findings and examined insights from both the KI and EN studies in context of existing knowledge described in the literature and how they could collectively inform the main aim and objectives set out for this investigation. This clarified the identity of the main recurrent and problematic CMP quality issues, why they persisted, and a solution to the general problem of their persistence was proposed.

The background to the research and literature for this thesis is introduced in Chapters One and Two, to more clearly introduce and place the studies in context, before the findings were gathered, synthesised, and described in concise discussion within Chapter Five.

Figure 1.1 visually illustrates how the thesis research contributed to arriving at a proposed solution to CMP quality issues.

FIGURE 1.1 VISUAL ILLUSTRATION OF HOW EXISTING KNOWLEDGE IN THE LITERATURE-BASE (LR) AND THE TWO STUDIES (KI AND EN) CONTRIBUTED THE PROPOSED SOLUTION.



LR = Literature Review**, KI** = Key Informant study**, EN** = *Eleutherococcus nodiflorus* study case example

1.5 Background

Problematic quality issues such as misidentification, substitution and adulteration of Chinese medicinal plants (CMP) have been recorded for centuries (Zhao et al., 2014, p17). In more recent times, many of these were discovered during routine testing, while others were detected incidentally during academic investigations (Coghlan et al., 2015a; Hoban et al., 2018). Particularly during the review of adverse events reports, some included fatalities (Vanherweghem et al., 1993; Bensoussan et al., 2000). Although problems with CMP quality are sometimes apparent from organoleptic observation of the texture and aroma of herbs perhaps spoiled through microbial growth or extraneous material such as soil, other quality issues relating to chemical contamination are less apparent (Fu et al., 2002).

Detecting non-apparent CMP quality issues required considerable technological and legislative developments to facilitate current mandated testing (Liu et al., 2015). These developments shaped technological advancements and defined acceptable “quality” of CMP supplied to EU-UK consumers (Leong et al., 2020a). Increasingly capable technology enabled progressively better characterisation of physical and biochemical quality attributes (Shen and Shi, 2020).

Defining naturally variable material with more advanced testing technology presented further challenges as the biochemical complexity of CMP became evermore apparent with each new advancement. Including the paradox, in which on the one hand, much more is now known about the chemical composition of CMP, it can more easily be authenticated and its adulterants detected, yet on the

other hand, similar incidences of misidentification, substitution, and adulteration remain common occurrences across the EU-UK. Despite many years of concerted efforts by expert groups to prevent their recurrence, why they recur is still relatively less understood (Blumenthal et al., 2019; Xu and Bauer, 2012). This situation warrants further consideration, particularly as recently occurring quality problems are similar to those recorded in China many centuries ago. They persist in this contemporary era of advanced technology and legislation.

Incidences of CMP quality issues and associated adverse events prompted significant efforts to detect their occurrence. Theses principally involved adopting and refining testing technology, such as physical testing and analytical chromatography techniques previously used for pharmaceutical and environmental analysis (Ahmed and Ullah, 2020). These methods are currently collated and described in various international herbal pharmacopeias, including the Chinese Pharmacopeia (ChP), Taiwanese Pharmacopeia (TP), and European Pharmacopeia (EP). National and international legislation mandated the use of these pharmacopeial methods for official testing, recording and reporting purposes. In doing so, they defined the basic requirements for minimum "quality" CMP (CCP, 2019; THPC, 2019; COE, 2019).

In addition to physical and chemical testing, other minimum quality guidelines to direct how CMP should be handled within the various stages of the herbal supply chain were produced. These Good Practice guidelines (GxP) were originally developed in the United States and later adopted as a framework that guided the recording and creation of standard procedures for practices including cultivation,

harvesting, processing and manufacturing internationally (Zhang et al., 2021). GxP is enforced by the European Medicines Agency (EMA) in Europe, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and the Food and Drug Administration (FDA) in the USA. National organisations may declare compliance with GxP as signatories to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In adopting these guidelines, additional minimum standards for "acceptable quality" of CMP were set internationally (EMEA, 2022; MHRA, 2020; Fan et al., 2012)

Supplying herbal medicines to the European market is currently regulated by the Directive on Traditional Herbal Medicinal Products (2004/24/EC), abbreviated to THMPD, which mandates an "appropriate quality" standard for herbs that are "safe" and impart an effect in line with that expected with traditional usage. The directive additionally requires that herbal products are labelled accordingly (EU, 2004). Typically, evidence of at least 30 years of traditional use is required, except for cases where the same species has demonstrated safety and efficacy within the EU for 15 years, such as for *Ginkgo biloba* L., and *Hypericum perforatum* L. (HMPC, 2015; HMPC, 2018). However, their distribution to consumers is restricted under prescription by specific types of registered biomedical physicians such as general medicine practitioners, in relatively small doses by herbal practitioners, and in homoeopathic products (Bilia and do Céu Costa, 2021).

Implementing this directive has given legal force to the aforementioned accepted

minimum standards of quality, outlining which species of medicinal plants are allowed for general use and who can access medicinal plants in the EU region.

However, following efforts to collectively define and maintain minimum quality standards for CMP over the last half century, similar problematic quality issues have recured. Since the implementation of ChP in 1953, EP in 1969, GxP in 1978, and the THMPD in 2004, and considerable subsequent advancements in testing, misidentification, substitution and adulteration of CMP still recur. Furthermore, these issues were recorded centuries ago in classical Chinese medicinal texts, are well known, and current analytical methods have demonstrated capability to detect such quality problems. Testing with these methods is mandated by legislation. Yet, they still persist in this Contemporary Era.

Predominant solutions currently proposed for future improvements to medicinal plant quality by the European Medicines Agency (EMA), Chinese National Medical Products Administration (CNMPA) and the World Health Organization (WHO), are built upon on similar principles to those previously implemented. To develop and rely on more sensitive and sophisticated analytical testing, additional stringent regulation and further harmonisation of standards internationally are needed (EMA, 2019; Xu et al., 2021; WHO, 2013). However, if previous reliance on these principles has not stemmed the persistence of well-known and recurrent quality issues, should they be reconsidered?

A comprehensively recorded, researched, and reported case example of such an issue persisting is one which resulted in multiple fatalities. That of toxic

Aristolochia fangchi Y.C.Wu ex L.D.Chow and S.M.Hwang, Chinese pinyin (CP: Guang fang ji) used substituted in place of *Stephania tetrandra* S.Moore (CP: Han fang ji), which has been documented since the 1200s.

The sale of the herb *A. fangchi* was prohibited in China in 1268, and the family of any deceased citizens poisoned by it were entitled to legally pursue the prescribing physician (Chen in Fleischer, Su and Lin, 2017)). Seven centuries later in Europe, during which numerous analytical testing techniques and regulations had advanced significantly, numerous fatalities and 138 subsequent nephrotoxicity cases were reported from ingesting the same CMP contained in slimming pills (Vanherweghem et al., 1993). Similar poisonings soon emerged in the UK, France, Germany and Spain, and a further 156 cases throughout East Asia (Debelle, Vanherweghem and Nortier, 2008). Substitution of *A. fangchi* in place of *S. tetrandra* was attributed as the cause when it was administered in slimming pills at a Belgian clinic (Vanherweghem et al., 1993).

Though many herbal analysis and regulatory advances have been implemented in the form of pharmacopeial testing (COE, 2019), Good Practice guidelines for collection, agricultural, collection and manufacturing as GxP (Zhang et al., 2021), and multi-governmental European-wide legal controls (EU, 2004), this same issue recurs. Over seven centuries following known toxic adverse events in China from *A. fangchi* and two decades after fatalities in Belgium, poisoning from the same *Aconitum* medicinal plant is still reported (Hofmann et al., 2020b) and records of multiple adverse events still recur (Hu et al., 2020) notwithstanding the development of a high-performance liquid-chromatography (HPLC) and liquid-

chromatography coupled to mass spectrometry (LC–MS) advanced method specifically for testing *S. tetrandra* (Tankeu et al., 2016).

This case example of misidentification and substitution with a toxic CMP is one of the many recorded quality issues that persisted, which seem to be particularly problematic with medicinal plants from the Chinese herbal tradition. In a landmark publication that reviewed 26 previous systematic reviews on herbal medicine products, including both CMP and those form other traditions, widespread adulteration with dust, pollens, insects, rodents, parasites, microbes, fungi, mould, toxins, pesticides, toxic heavy metals, and prescription drugs were reported (Posadzki, Watson and Ernst, 2013; Hoban et al., 2018). Higher rates of adulteration incidents were observed in CMP. Ninety-four per cent of TCM were contaminated or adulterated, compared with 37% of Western herbs. A few cases, two of the 59 samples, found that the contents matched those expected. This was in agreement with Coghlan et al. (2015a), where an earlier study found 92% of samples containing 26 different types of CMP tested were either substituted or contaminated. A study specifically for adulteration with undeclared synthetic pharmaceutical drugs reported a relatively high rate, almost a quarter 24% of 2,609 samples surveyed in China contained undeclared pharmaceutical substances including anti-inflammatories, steroids, and analgesics (Huang, Wen and Hsiao, 1997).

Multiple problematic quality issues persisted notwithstanding significant improvements in herbal testing. This is evident in the increasingly complex and more hyphenated versions of analytical instrumentation that appear in advancing

research publications and modern pharmacopeias (Fitzgerald, Heinrich and Booker, 2019). More basic analytical techniques used historically have advanced, such as thin-layer chromatography into their newer and more recent iteration, high-performance thin-layer chromatography (HPTLC), alongside other sophisticated testing instrument combinations such as ultra high-performance liquid chromatography-mass spectrometry (COE, 2019). Herbal Pharmacopeia monographs direct the use of such analytical techniques for identifying and testing the purity and content of medicinal plants, so that misidentified, adulterated or substandard quality herbs can be detected (Shen, He and Shi, 2021). The number of herbal inclusions in the ChP has risen from 65 medicaments in the 1st edition in 1953, to 2,711 monographs in the current 11th edition (CCP, 2019). The EP contains 73 specific CMP monographs in the current 10th edition (Leong et al., 2020a). Yet, misidentification, adulteration and CMP quality issues continue to persist.

Regulatory controls and guidelines have advanced considerably together with analytical testing over the last few decades. Various GxP “Good”, “Agricultural”, “Collection” and “Manufacturing” practice guidelines, often abbreviated to GAP, GCP and GMP respectively, have been issued internationally. Within Europe (EU-GACP) in 2002, China (China-GAP) in 2003, by the World Health Organization (WHO-GACP) in 2004 and in America (American-GACP) in 2017 (Zhang et al., 2021). Additionally, Australia’s Therapeutic Goods Act has controlled Chinese herbs since 1989. Comparatively, the EU has mandated the licencing of herbal products since 2011 under the THMPD, adopted in the UK in the form of a Traditional Herbal Registration (THR) scheme since 2005 (Heinrich

et al, 2015). CMP quality testing in the USA comes under the remit of the Public Health Service Act, updated in 2015 (Fleischer et al., 2017). However, as noted above and as described further in this research, multiple CMP quality issues still persist.

Future strategies on the quality of herbal medicine have been proposed by the WHO (WHO, 2013), the Chinese National Medical Products Administration (Xu et al., 2021) and the European Medicines Agency (EMA, 2019). However, even though these future proposals usefully build upon previous approaches, as outlined later, significantly innovative analytical or regulatory strategies to deal with the persistence of CMP issues are not apparent.

The Chinese strategy follows their long-standing goal towards “modernisation” of traditional Chinese medicine (Qiu, 2007) and in alignment with the Chinese National Medical Products Administration (NMPA) recently joining the International Council for Harmonisation (ICH) in 2017, adopting their principles to develop the Chinese Pharmacopeia towards, “...adherence to the principles of scientificity” (Xu et al., 2021). These further place analytical testing and its tighter validation requirements central to maintaining herbal quality compliance (EMA, 2021a)

Within the European Union, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) compiles information on herbal substances for market use, whereas the European Pharmacopeia forms the legislative basis for herbal quality and testing requirements (EMA, 2021b). The

EMA published its “European medicines agencies network strategy to 2025”. As herbal medicines constitute a minority share of the monographs, its report would not be expected to highlight herbs specifically. Instead, it outlines intentions for increasing access to biomedical drugs, digital information, the topic of antibiotic resistance and supply chain security, and other concerns arising from the COVID-19 pandemic (EMA, 2019). Therefore, the above-mentioned THMPD directive and EP remains in effect as the regulatory footing for the foreseeable future to guide CMP use and quality. It is supported by a traditional a Chinese Medicine European Pharmacopeia working group set up in 2008 in collaboration with the Chinese State Administration of TCM (SATCM) to advise on adoption of the Chinese pharmacopeia monographs to the pharmacopeia (Franz and Wang, 2015). The current EP 2019 contains 73 substances classified as TCM, and a further 32 are in process for future inclusion, although some monographs with a tradition of Chinese use, such as *G. Biloba* and *H. perforatum* as previously mentioned, are also considered European (Heinrich, Kum and Yao, 2022; Leung et al., 2020). Comparatively, there are 2,711 herbal TCM monographs in the current 2020 versions of the ChP, many of which are used routinely by Chinese medicine practitioners throughout Europe (CCP, 2019).

Overall, these strategies are based on previous approaches that rely on increasingly more capable analytical testing used within an international GxP framework. Questioning the common basis of these three proposed future strategies requires “taking a step back”, to reconsider the problem from a broader perspective.

First, to inquire, what are the main CMP issues that emerged historically that still persist? Secondly, why do they persist in the context of many apparent testing and regulation developments?

Finally, could such investigation inform other approaches, rather than continuing along a similar path of further iterating current testing and regulatory countermeasures?

Such questions formed the focus of investigating the persistence of long-known and detectable CMP quality issues, as presented in this thesis.

This investigation aimed to clarify the identity of the main persistent CMP quality issues, the reasons for their persistence, and propose alternative approaches to that may improve the current situation of recurrent problematic CMP quality issues. The findings that will be presented were built upon the existing peer reviewed published knowledge-base, new knowledge derived from collecting the opinions of experts in the field of CHM quality, and through the detailed analysis of an unexplained adulterated CMP case example: *Eleutherococcus nodiflorus* with a cardiotoxic adulterant, *Periploca sepium*.

1.6 Emergence of quality issues

The quality of medicinal plants was evaluated in the past organoleptically by observing their colour, shape, texture, or aroma (Zhao, Liang and Ping, 2011). Changes in these quality attributes indicated when plants were ripe, whether they were subjected to non-optimal growth conditions, pest attack, or microbial spoilage. Those that wilted and had an abnormal appearance, texture or odour were left behind in favour of better-quality ones. It seemed reliable once the collector was familiar with the identity of the plants in the area, and how their physical form changed throughout the seasons. However, the organoleptic approach became less reliable as the developing herbal trade brought varieties of similar herbs grown under different climatic conditions and unfamiliar herbal species. Medicinal plants were more likely mistaken for others and spoilage could occur in-transit. As the scale of supply increased the sources and handling conditions of herbs were often obscured from the practitioners prescribing and patients consuming them. They relied on others to assess the quality, select, collect, store and transport the medicinal plants. While increased efficacy of scale in supply allowed for more widespread availability, the reduction in transparency also fostered opportunities to sacrifice quality in favour of profit (Bian, 2014).

Xie and Wang found that 76 kinds of Chinese medicine quality issues had already emerged before the fall of the Qing dynasty in 1911 and the succeeding republican period, comprising 11 kinds of counterfeits and 68 varieties of adulteration. Fraudulent practices to improve the appearance of Chinese medicines were predominantly recorded during the Northern and Southern dynasties**,** 420–589 CE, intended to conceal spoilage by mildew, moths and other

insects. Counterfeiting that included basic substitution of medicinals were recorded more often in the Tang dynasty, 618–907 CE, which became progressively more skilled and subtle in later periods during the dynasties of Ming, 1368 to 1644 CE, and Qing, 1616 to 1911 (Xie and Wang, 2013). Xie and Wang chronologically mapped the emergence of quality issues and the number of different types of adulteration as they were first recorded (*Table 1.1*).

TABLE 1.1 SUMMARY OF NUMBER OF RECORDED EMERGENT CHINESE HERBAL QUALITY PROBLEMS FROM THE YEAR CE 1061 TO 1901

Number of noted quality issues	Classical herbal reference	Year (CE)
Eight	*Bencao Tujing* (本草圖經)	1061
Three	*Ben Cao Yan Yi* (本草衍義)	1116
Twenty-seven	*Bencao Mengquan* (本草蒙)	1565
Eleven	*Bencao Gangmu* (本草綱目)	1578
Fifteen	*Bencao Yuanshi* (本草原始)	1612
Twelve	*Pao Zhi Da Fa* (炮炙大法)	1662
Nine	*Ben Cao Chong Yuan* (本草崇原)	1674
Eight	*Ben Jing Feng Yuan* (本經逢原)	1695
Ten	*Ben Cao Qiu Zhen* (本草求真)	1769
One-hundred-and-ten	*Wei Yao Tiao Bian* (偽藥條辨)	1901

In summary, earlier accounts were of relatively more simple modifications to medicinals intended to increase their value, described as:

- Adding earth, stones and salt to bulk weight sale value.
- Soaking *Asarum heterotropoides* F.Schmidt (CP: Xi xin, 細辛) in water to straighten it into a more valuable form.
- Steaming honey to enhance the aroma and sweetness.
- Sprinkling wine on angelica roots, *Angelica sinensis* (Oliv.) Diels (CP: Dang gui, 當歸) to freshen its appearance.

Later accounts describe more innovative techniques, particularly with producing fake lookalike medicinals by moulding and colouring flour, mixing water and glue with wood, and processing animal hides. More expensive varieties were most commonly targeted, including *Ophiocordyceps sinensis* (CP: Dong chong xia cao, 冬蟲夏草), *Poria cocos* (Schwein.) F.A.Wolf (CP: Fu ling, 茯苓), processed *Reynoutria multiflora* (Thunb.) Moldenke (CP: He shou wu, 何首烏) and donkey hide gelatine, *Equus asinus L.* (CP: E jiao, 阿膠). A progressive sequence of Classical Chinese herbal medicine texts recorded these from primary sources and their re-collations spanning c. 200 BCE to the present.

The primary approach to detecting counterfeit, substitute and adulterated medicinals in the pre-20th century was by comparing illustrations and descriptions in reference texts used in context with mentored knowledge and accumulated personal experience. Numerous reference works appeared to authenticate CMP

and transmit CHM expertise and knowledge. The historical corpus of Chinese medicinal materials texts currently stands estimated at an excess of 800 works and 100,000 articles which have been extensively catalogued (Lu, 1999), reviewed (Goldschmidt, 2008), (Unschuld, 1986; Pan et al., 2014) and discussed in detail, (Goldschmidt, 2022; Lo and Man; Unschuld, 2010; Zhang and Unschuld, 2008).

A blend of antecedent knowledge and contemporary concepts of herbal quality are manifest in current herbal pharmacopeias wherein ancient descriptions of flavours and herbal characters sit side-by-side detailed descriptions of chemical characterisations. The contents of pharmacopeias are collated, reviewed and agreed by committees of experts who possessing knowledge derived from both traditional and contemporary sources (Franz and Wang, 2015). These pharmacopeias serve as references for authenticating the identity of medicinal plants, many of which also include preparation methods and instructions for use. Pharmacopeias used in mainland China (ChP), Taiwan (TP), and Europe (EP) contain descriptions of extensive methods for testing for adulteration and the expected minimum content of active ingredients. If pharmacopeial tests are conducted under precisely controlled and documented conditions in authorised facilities by certified staff, the results have legal standing (CCP, 2019; THPC, 2019; COE, 2019). The WHO currently lists 60 pharmacopeias that include 57 national, three regional and subregional, and one that is registered as an international pharmacopeia (WHO, 2022). The Chinese pharmacopeia commission produces the highest publication output rate compared with that of the other national pharmacopoeia commissions globally (Tyagi, 2022, p357).

Although this amassed information is a significant step towards collecting and centralising the medicinal plant knowledge-base, much more still remains. Of the more than 28,000 known and recorded medicinal plant species, less than 16% are described in such regulatory publications (Willis, 2017, p24).

Online resources from both regulatory agencies and others have become important points of reference. Following the advent of the World Wide Web in this Contemporary Era, online sources enabled access to both the contents of pharmacopeias and additional content previously unavailable in manuscript formats, such as high-resolution photographs and videos of commonly confused species and their substitutes (MOHW, 2021; CMRO, 2023). Online resources will likely play an increasingly prominent role as alternatives to more traditional printed media. The United States Pharmacopeia (USP) has declared online-only issues of future supplements and editions (Piervincenzi, 2020). Online sources that describe problematic quality issues are potentially more extensive and dynamic than traditional written records. Many of which are now listed in electronic databases frequently updated by large-scale herbal markets in China, such as that provided Kangmei.

The Kangmei CMP market in Bozhou, China, has been a herbal trading site for centuries, and since formally establishing in 1997 it has become the world's largest Chinese medicine market. It provides online information relating to the supply, quality and agreed set prices of CMP across the six major markets located in Bozhou, Anguo, Chengdu, Yulin, Lianqiao and Puning. It publishes online daily bulletins relating to CMP supply and quality issues of the of more than

2,500 various types of Chinese medicines sold to 30,000 customers daily (Wenshu, 2015). It collated eight common adulteration types over the last 28 years identified at the site with examples (in Chinese) (Kangmei, 2022b). Further details are provided in *Table 1.2*

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
1. Weight addition	Substances added to increase weight and therefore sale value.	*Lonicerae Flos*, Jin yin hua, 金銀花, *Chrysanthemi Flos,* Ju hua,菊花 and *Carthami Flos,* Hong hua, 紅花 soaked in water with yellow, red or white soybean flower. *Tetrapanacis Medulla*, Tongcao, 通草 soaked in sulphate, salt and sugar then dried. Barium or aluminium sulphates.
	Water, Talcum powder, gypsum powder, cement, sediment, inorganic salts.	Talcum powder with *Angelicae Dahuricae Radix* Bai zhi, 白芷 and *Trichosanthis Radix,* Tian hua fen,天花粉, *Paeoniae Radix Alba*, Bai shao, 白芍.
2. Substitution with visually similar herbs	Looks similar or enhanced fragrance for forgery.	American ginseng, *Panax Quinquefolium* Radix, Xi yang shen, 西洋參 substituted by *Angelicae Dahuricae Radix* Bai zhi, 白芷 and other ginseng fake products.

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
2. Substitution with visually similar herbs		*Xanthii Fructus*, Cang er zi, 蒼耳子 with Dong bei region equivalent. *Tetrapanacis Medulla,* Tongcao, 通草 with *Aeschynomene indica*, He meng, he meng 合萌 or *Trevesia palmata,* Ci tong cao, 刺通草. *Coicis Semen*, Yi yi ren, 薏苡仁 with *Phyllanthus niruri* , Cao zhu zi, 草珠子 Sandalwood *Santali Albi Lignum*, Tan xiang, 檀香 with cypress wood, *Cupressus funebris*, Bian baimu, 扁柏木 mixed with other wood pieces and sprayed with sandalwood scent. Genuine *Pinelliae Rhizoma* , Zhen zhu ban xia, 珍珠半夏, for *Rhizoma Typhonii Flagelliformis*, Shui ban xia, 水半夏.
	Cinnamon: "Impersonated" with fragrance.	*Cinnamomi Cortex* , Rou gui 肉桂 with *Cinnamomum burmannii* , Yin xiang, 阴香 species. *Dioscoreae Rhizoma* , Shan yao , 山藥 with *Dioscorea alata*, Shen shu, Purple yam, 参薯.
	Sichuan materials replaced by Zhejiang or Anhui equivalents.	*Fritillariae Cirrhosae Bulbus*, Chuan bei mu, 川貝母 substituted with smaller ones from Zhejiang or Anhui regions.

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
3. Dyes	Dye Fraud Dyeing inferior quality: Dye poor-quality slices to improve the appearance and increase the price. Impersonation: Slices of some plants of similar shape but different colours dyed to forge authentic slices, and use other substances to process and counterfeit medicinal materials. Staining doping is divided into three scenarios: dyeing forgery, dyeing doping, and dyeing with inferior materials.	Three types of dyeing dye fraud where one herb is coloured to fraudulently pass as another. Dye doping, where dyed materials are blended with authentic herbs. Dye used make herbs look new and therefore increase value. **Type 1 Dying fraud** Red iron oxide paint used to dye roots of other plants dyed with to look like *Salviae Miltiorrhizae Radix*, Dan shen, 丹參. Black iron oxide paint to other plant materials such as *Ipomoea batatas* sweet potatoes, to look like He shou wu, *Polygoni Multiflori Radix*, 何首烏. Process *Paeoniae Radix Alba*, Bai shao, 白芍, to look like *Aconiti Radix Preparata*, Zhi chuan wu, 製川烏 and *Aconiti Kusnezoffi Radix,* Cao wu, 草烏. **Type 2 Dye doping** Building materials such as lime or concrete powder dyed with industrial Orange II and

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
3. Dyes	Doping; safflowers are mixed with building materials dyed red with golden orange II; safflowers are mixed with calcium carbonate powder dyed yellow with goldamine O; artificial yellow dye is mixed with calcium carbonate and silicate powder dyed with several dyes such as goldamine O and golden orange II.	Auramine O dyes to bulk *Carthami Flos* , Hong hua, 紅花. **Type 3 Dye used herbs to look like new** Various yellow dyes added to decocted *Coptidis Rhizoma,* Huang lian, 黃连. Auramine O added to previously used *Corydalis Rhizoma,* Yan hu suo, 延胡索, to look like new. Used *Dan shen*, 丹參, *Salviae Miltiorrhizae* dyed to look like new, particularly that from the more valuable Shan dong dan shen (山東丹參)
4. Modification of authentic material to add value	Decocted pieces reused: Recycle extracted Chinese medicinal herbs, cut them into slices, dry then sell again. Forgery: Make fake He shou wu by pressing flour into irregular pieces and mixing into Poria.	**Flavours and aromas added to used herbs, sold as new** *Phellodendri Cortex*, Huang bo, 黃柏. *Schisandrae Fructus*, Wu wei zi, 五味子. *Notoginseng Radix*, San qi, 三七. *Forsythiae Fructus,* Lian qiao, 連翹. *Ginseng Radix,* Ren shen, 人參、and *Panacis Quinquefolii Radix*, Xi yang shen, 西洋參.

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
4. Modification of authentic material to add value	Use plastic to imitate the appearance of pangolin through plastic moulds.	**Some herbs with natural volatile aromas are sprayed with aromatic oils to smell more realistic. Such as;** *Illicium Verum*, Da hui xiang, 大茴香. *Aquilariae Lignum Resinatu,* Chen xiang, 沉香. *Ginseng Radix,* Ren shen, 人參. *Aucklandiae Radix*, Mu xiang, 木香/ *Carthami Flos*, Hong hua, 紅花. *Salviae Miltiorrhizae*, Dan shen, 丹參 and *Atractylodis Macrocephalae Rhizoma*, Bai zhu, 白朮. *Paeoniae Radix Alba,* Bai shao, 白芍. **Adulteration – full substitution** More expensive and scarce herbs in particular are forged from other material such as: *Solanum tuberosum L.* (Solanaceae), white potato chips, Ma ling shu 馬鈴薯 for *Gastrodia Rhizome*, Tian ma, 天麻.

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
4. Modification of authentic material to add value		*Poriae Cutis*, Fu ling pi, 茯苓皮 pressed with flower to make *Polygoni Multiflori Radix*, He shou wu, 何首烏.
5. Modification with non-authentic material to add value	"Beautify"	*Polygoni Multiflori Radix*, He shou wu, 何首烏 is attached to the surface of black vinyl plastic.
6. Counterfeit with poorer quality	Volatile medicinal materials are agitated, immersed in oil, or steamed. Sandalwood that has been mottled or its fragrance reduced is soaked or steamed in oil, and the jujube kernels are stir-fried in oil and presented as sour jujube kernels.	Out of date or poorer quality materials Soaked or steam infused *Santali Albi Lignum,* Tan xiang, 檀香. Old or non-sour dates stir fried in oil to taste like *Zizyphi Spinosae Semen,* Suan zao ren, 酸棗仁.

TABLE 1.2 CHINESE MEDICINE QUALITY ISSUES RECORDED OVER 28 YEARS AT KANGMEI INTERNATIONAL MARKET IN BOZHOU, CHINA

Type of adulteration	Details	Examples observed at Kangmei Bozhou market
7. Substitution with non-medicinal plant parts	The non-medicinal part of the same medicinal material is impersonated as a medicinal part, or the non-medicinal part has not been removed. For example, dogwood is mixed with stalk cores, honeysuckle with too many leaves and young branches, and mulberry leaves contain too many young branches.	*Corni Fructus*, Shan zhu yu, 山茱萸 mixed with stalks. *Lonicerae Flos*, Jin yin hua, 金銀花 with many leaves. *Mori Folium*, Sang ye, 桑葉 with young branches.
8.Composition adulteration	Submit ingredients to counterfeit qualitative tests, or add other ingredients to increase weight. For example, berberis juice is soaked in yellow bark trees and filled with yellow cypresses.	Ingredients added to pass qualitative testing, the juice of *Berberidis Radix Succus*, xiao bo zhi, 小檗汁 is added to *Phellodendri Cortex*, Huang bo, 黃柏 to pass berberine content quality testing.

Adapted from Kangmei market online resources: at https://www.kmzyw.com.cn/baike/20191227/1577436958000.4456.html

The information supplied by CMP markets is an important resource for identifying commonly observed quality problems, however it is largely restricted to quality issues that can be visually discerned at the marketplace, or detected by relatively simple methods. There are additional non-apparent adulterants arising from contamination including microbial toxins, aflatoxin, those from heavy metals, pesticides and the undeclared synthetic pharmaceutical drugs. Successive improvements in testing methods have shown that these are significant and common (Qin et al., 2020; Chen et al., 2020; Luo et al., 2021).

1.7 Emergence of methods to detect quality issues

A long lineage of classical Chinese herbal texts attest to efforts throughout history to correctly authenticate and detect CMP adulteration. The oldest still in existence, the “Formulas for 52 diseases”, (CP: Wu shi er bing fang, 五十二病方), was found in 1973 within the Ma wang dui (馬王堆) tomb 3, in Hunan, China, dating to 168 BCE. It is the earliest manuscript known to identify CMP by visual comparison with drawings and their respective tastes. It was the first in a lineage of successive reference texts spanning to the present day and foremost reference for CMP quality, the Chinese Pharmacopeia (Harper, 1998; CCP, 2019). Chinese medicine historians claim that the origin of the “Divine Farmer’s Classic of Materia Medica” (CP: Shen nong ben cao jing, 神農本草經), re-compiled in the Ming dynasty, c.1400 CE, was much earlier in the late Eastern Han dynasty c. 200 BCE (Zhao and Liang, 2017, p1; Unschuld, 1986, p17). It details the authentication of 365 medicinals by appearance, taste, harvesting, and processing methods. It records the first technical augmentation of organoleptic

assessment by burning Chinese medicinals in a flame to identify cinnabar (CP: Dan sha, 丹砂) through “testing with fire”, and observe its transformation into mercury. A revised version of this classic reference, by Tao Hong-Jing in the Liang dynasty c. 490 CE, listed common mistakes found in earlier records, that identified “poor quality and easily misidentified Chinese medicinals”, published under the title, “Collection of commentaries on the Classic of Materia Medica” (CP: Ben cao jing ji zhu, 本草經集注). Entries for each substance were systematically categorised by name, taste, properties and medical applications. Alternative names, harvesting details, processing methods, production areas and macroscopic descriptions were also included (Zhao et al., 2014, p17; Harper, 1998).

Detection methods relying on differences in physical and chemical properties of medicinal plants had been discovered and used in conjunction with organoleptic examination. Commonly principles used relative density, solubility, and visible characteristics when burned in a flame to verify the authenticity of a medicinal plant, as shown in *Table 1.3* (Zhao et al., 2014).

TABLE 1.3 ORGANOLEPTIC METHODS FOR DIFFERENTIATING AUTHENTIC FROM NON-AUTHENTIC CHINESE MEDICINAL PLANTS

Authentic plant and test	Non-authentic plant and test
The roots of *Sparganium stoloniferum* (Graebn.) Buch.-Ham. ex Juz. Chinese pinyin (CP: Jing san leng, 京三棱), sink after soaking in water.	Similar looking substitute *Bolboschoenus yagara* (Ohwi) Y.C.Yang & M.Zhan, (CP: Pao san leng, 泡三棱) floats.
Expensive saffron*, Crocus sativus* L., (CP: Fan hong hua, 番紅花), dissolves with a vertical thread of yellow colour	Cheaper substitute safflower, *Carthamus tinctorius* L., (CP: Hong hua, 紅花), dissolves into a diffuse cloud of yellow in water.
The resin of *Boswellia carteri* Birdw., (CP: Ru xiang 乳香) when placed in flame releases a light characteristic odour and melts slowly	In contrast to its cheaper substitute *Liquidambar formosana* Hance, (CP: Feng xiang zhi, 楓香脂) that discharges a strong fragrance and melts quickly.

Such traditional methods are still used to check for adulteration at markets. Buyers dip their hands into herbal containers and rub hands to sense any apparent friction, and therefore presence of additives. If the friction is lower than expected it could indicate powder adulterants such as talcum to increase weight or modify for a fresher appearance. If the friction is higher it can suggest possible addition of building materials such as sand, cement or concrete to bulk weight. Buyers verify their impressions by slowly turning their hands in sunlight to check for greasy, glistening or sparkling coating. This type of test is commonly conducted for the roots of *Angelica sinensis* (Oliv.) Diels (CP: Bai zhi, 白芷) and *Trichosanthes kirilowii* Maxim., (CP: Tian hua fen, 天花粉), and *Paeonia lactiflora*

Pall. (CP: Bai shao, 芍藥) (Kangmei, 2022b). However, detection of adulterants using such traditional means of examination are easily circumvented by those skilled in adulteration. Materials added together that both increase and decrease friction simultaneously also obscure the abnormal appearance of additives in daylight. However, the limitations of traditional methods and the need for more sensitive detection methods is well established (Wang et al, 2015)

Each human sense that could assess CMP quality has been augmented or replaced with modern means of detection. Observation of colour in medicinal plants is now more commonly conducted using advanced optical detectors that measure how specific wavelengths of light within prepared solutions change over a number of minutes as the phytochemicals separate along the distance of a chromatography column, rather than observing how plants' colours degrade over the seasons. Changes in shape and texture of herbal materials are now measured using optical microscopes to compare the forms of crystals and cell structures within the plants. Infrared frequency spectrophotometers are used to determine small changes in how light interacts with the surface and within the herbs. The aromatic and chemically volatile components in herbs sensed previously by smell are now analysed by drawing a sample into a stream of gas that is then electrically charged in flame photometers. These detection principles are manifest in the technology used for the most common types of medicinal plant chromatography methods such as thin-layer (TLC), high-performance liquid (HPLC), gas chromatography (GC), and spectrophotometric techniques (Fitzgerald, Heinrich and Booker, 2020). These are described in the ChP, TP, EP and other pharmacopeias as the current standard references for authenticating

and determining the quality of medicinal plants. The emergence of similar detection principles as direct successors of traditional organoleptic sensing are apparent in current research, most notably the; “electronic-”, “-eye”, “-nose” and “-tongue”, for authenticating and assessing the quality of CMP, are referred to further here by a new term, “electroleptic” techniques (*Table 1.4*).

TABLE 1.4 "ELECTROLEPTIC" BASIS OF MODERN INSTRUMENTAL ANALYSIS WITH EXAMPLES

Electroleptic basis	Analytical test
Eye	Imaging technology and recognition software algorithms for the CMP*, Fritillariae Cirrhosae Bulbus* and *Corni Fructus*, the pulp of the ripe fruit of *Cornus officinalis* Sieb. et Zucc., can accurately discriminated their different morphological characteristics with more than 97% accuracy (Liu et al., 2020).
Nose	Differentiates which of 8 regions *Aucklandiae Radix* is grown (Li, Luo and Sun, 2021) Fine quality attributes of tea can be similarly discriminated (Kaushal et al., 2022) Discriminates if *Magnoliae officinalis cortex* has been processed with raw or ginger juice methods (Zhang et al., 2022), Predicts reliably which method has been used to dry *Zingiber officinale* Roscoe (Yu et al., 2022).
Tongue	Predicts how palpable herbal prescriptions taste for patients consuming single or mixed herbal formula decoctions (Wu et al., 2022). Evaluates the relative bitterness and sweetness of alkaloids and glycoside content. Naturally and synthetically derived additives can be indicated by the "tongue" such as; berberine hydrochloride (alkaloid), geniposide (terpenoid), and arbutin (glycosides) as mother liquor, sophoridine (alkaloid), gentiopicroside (terpenoid), and puerarin (glycoside) (Li et al., 2019).
Combinations of "nose", "eye" and "tongue" in analytical arrays	Differentiates ten individual constituents and quantifies eight compounds in samples of the Xiao chai hu tang CHM formula in 31 minutes (Xue et al., 2021) Characterises CMP preparations previously considered difficult to analyse, such as *Gardeniae fructus Praeparatus* (Zheng et al., 2022).

Although technologies based on electroleptic sensor-type concepts have been successfully demonstrated in research and limited production environments with promise for the future, routine testing and characterisation of CMP quality has been predominantly conducted using analytical methods described in the current pharmacopeias (Shen et al., 2021; Ahmed and Ullah, 2020).

Knowledge of medicinal herb quality and associated problems has advanced together in lock-step with capabilities of test methods used to discern finer quality attributes and detect their adulterants. Herbal analysis technology has developed significantly over the last century, and herbal quality testing required by legislation is at its most extensive. However, similar and well-known quality issues that emerged historically still recur across the herbal supply chain (Choudhary, et al., 2022; Han, Elliott and van Ruth, 2022).

Although advanced testing capability exists, analysis is generally conducted in relatively controlled environments such as laboratories. This presents practical challenges for reliably analysing CMP, as most are still collected from the wild under conditions which are not readily controllable (Zhang et al., 2010; Qin et al., 2022). Assessing herbal quality historically and organoleptically at small scales was most likely easier than later when more a distinct division between collection and usage emerged. Smaller and mainly local antecedent supply chains have recently expanded to global proportions. Their multiple handling stages, transport, storage and general complexity fostered additional problematic quality issues (Cunningham and Long, 2019). The emergence of the supply chain has therefore influenced the quality of CMP and current persistent issues.

1.8 Emergence of the Chinese medicinal plant supply chain

Chinese herbal medicine supply chains likely began well before documented history. Records of the legends referring to shamanic or "nature-worshipping" pre-13th century BCE, when Chinese writing first appeared are based on archaeological finds of medical characters written on the bones of animals including turtle shells (Xu et al., 2014). Details of herbal supply routes first emerged when local farmers offered tithes of ginseng and rhubarb to the feudal rulers of various states prior the unification of China during the Qin dynasty, 2nd century BCE. As nine specific areas were considered superior for particular CHM, the rulers required specific quantities of medicine from each area. These were general supply arrangements that included furs, weapons, pottery and other objects of value, together with herbal medicine. Bian's PhD thesis specialising in the history of the interactions between the state, commerce and Chinese medicine further outlines that herbal medicine routes within China developed rapidly during Mongol Yuan rule (CE 1279 to 1368), when a considerable network of long-distance roads and a relay of goods through official outposts was constructed. The Chinese "Grand Canal", already linking the northern capital in Beijing, was extended to the southern area of the Yangxi region, a route that previously presented difficulty as natural waterways generally flowed from West to East. This facilitated the development of the North-South goods and herbal supply chains (Bian, 2014, p154).

Knowledge of how ancient Chinese herbal trade routes formed also derived from the other regions it suppled. Exchanges between China and Persia have a deep-rooted history, the earliest traces date to the Warring States and Qin Dynasties,

post-550 BCE (Stanley-Baker, 2022). The ancient East Asian spice and herbal medicine trade routes that existed during post-Mongol rule were the embryonic trade route of those existing currently, more recently termed “silk routes”. A term created by the German geographer Ferdinand von Richthofen in the late 1800s, that span from eastern China across to modern-day Europe (Shi et al., 2022, p2). Evidence of Persian trade is observed in Li Shizhen’s “Compendium of Materia Medica” from the late 1500s, who was particular in recording the origins of herbal material. The 1,892 Chinese Materia Medica collated included 46 from Persian sources. Twenty are still listed in the current ChP, including the highly valued Saffron or *Crocus sativus* L., (CP: Fan hong hua, 番紅花). Natural indigo, *Persicaria tinctoria* (Aiton) Spach, or *Isatis tinctoria* subsp. *tinctoria* (CP: Qing dai, 青黛), and many medicinal resins such as Myrrh, *Commiphora myrrha* (T.Nees) Engl, and Frankincense, *Boswellia sacra* Flück (CP: Ru xiang, 乳香) (CCP, 2019), (Shi et al., 2022).

The silk routes developed as “short-cuts” and are blueprints for China’s “belt and road” initiative, claimed to strengthen international trade routes, of which CMP is considered an important cultural and economic component (Hinsley et al., 2020). Herbal medicinal exports amounted to over US$ 4 billion annually by 2019 (Xiang et al., 2022, p2).

The herbal supply chains now well-established and identifiable in this Contemporary Era emerged during the transition from Imperial rule to the current People’s Republic of China political status, together with a desire by the new Chinese government to trade with Europe. As discussed further in the next

section, it was during this period that the pharmacopeias recorded early forms of analytical tests which characterised CMP quality and detected misidentified, substituted and adulterated medicinal plant material. This process influenced and later defined what is currently considered acceptable standard CMP quality.

1.9 Emergence of pharmacopeia defined quality

1.9.1 Emergence of the pharmacopeias

Following the forced abdication of the last Emperor in 1912 and the formation of the Republic of China (ROC), many years of instability and infighting ensued, resulting in warlord factions grappling for power and civil war (Lary, 2015). Herbal medicine played an important role as a primary resource for healing the many wounded fighters and civilians caught up in the turmoil and subsequent Japanese invasion. The Chinese Pharmacopeia provided an essential reference for controlling the quality of herb supplies at a time when many local herbal farmers had lost their land to warlords. The doctors who then practised in more Western style hospitals could not be certain of the quality of the herbal materials to which they had access and needed a reliable reference for traditional Chinese herbal medicines side-by-side with modern pharmaceutical drugs (Fitzgerald, Heinrich and Booker, 2020). The first Chinese Pharmacopeia published in Shanghai during 1930 contained 670 drugs. It comprised a blend of occupier influences and testament to their (British, American, Japanese, and German) difficulty arriving at a consensus for drug quality standards (Read, 1930).

The Americans published a Chinese version of the United States Pharmacopeia in 1926, which contributed many of the Western drugs to this new Chinese pharmacopeia, such as adrenalin and insulin used by the recently trained Western-styled pharmacists in China, who also needed to control vaccines for smallpox, diphtheria and tetanus. The German-Japanese analytical methods were then the most advanced at the time and contributed to about one-quarter of the Chinese pharmacopeia. The British influence was seen in the monographs of syrups of opioids and glucose and tinctures of cannabis (Read, 1930). Together, the new Chinese pharmacopeia became a synthesis of the best global standards and analytical methods the international community had to offer at that time. Once the People's Republic of China was established in 1949, the new government launched its national version, also confusingly titled the "first Chinese Pharmacopeia", on which it was based, as were the successive eleven versions over the following 70 years to the present day (CCP, 2019).

After World War II, the World Health Organization was established in a spirit of post-war global harmonisation (WHO, 1958). This included a role in international heath legislation and publishing the International Pharmacopeia (Ph Int) in 1951, containing 344 monographs and 84 quality tests. The first European Pharmacopeia soon followed in 1967, much inspired by the already well-established British and the United States Pharmacopeias (Commission, 1953). Similarly, these pharmacopeias have published successive editions to the present day that include progressively advanced CHM testing methods and quality criteria (COE, 2019; USP, 2020).

The contemporary proliferation of CHM to Europe and the United States was

accelerated following the publicity of the American presidential visit to China in 1971 by Nixon, after which global attention turned to Chinese medicine (Li, 2014). This interest coincided with the interim Chinese leader Deng Xiaoping's intentions to "open-up" China to the west in 1978 as part of significant economic reform. This catalysed a foreign demand and consequent supply of CMP abroad. By the mid-1980s, 25 Chinese medicine colleges were established in China, and more than two million Chinese medicine hospital beds were in place, a multiple thirty-times that of when the PRC formed in 1949 (Jingfeng, 1988). The 1980s saw the previous historically tight government grip on everyday Chinese people released as local communes were abandoned. This trend from communality towards individualisation extended to a "household responsibility" system where the government allowed and expected an agricultural food (including herbs) output quota for each household, paving the way for the commodification of CMP for the first time at such a large scale, and their commercial export to the European market and beyond (Ash, 1988).

Former government restrictions on land use were relaxed, allowing individuals to grow and sell herbal produce. Shifting the concept of herbs to a more "value-based" commodity led to an expanding trade with the West. This created a supply-and-demand dynamic, a value chain and an associated herbal manufacturing industry to support it. Western-style pharmacopeias guided and specified herbal quality attributes that increasingly replaced the traditional local practitioner wild-foraging, self-cultivating and self-assessment methods. This trend facilitated the expansion of herbal markets to an international scale. In 1985 the first dual Chinese and English language ChP edition was issued that would later strongly influence herbal monographs in the European Pharmacopeia,

which remains the central reference for CHM quality assessment (ChP, 1985). These sources were developed from tests used in Western pharmaceutical research and a manufacturing environment that guided the types of analysis and standards (Ahmed and Ullah, 2020). This included the standards currently used for CHM in clinical trials, the basis on which clinical data is generated, what is considered a standard and safety in the proceeding decades (Guo et al., 2022; Ping and Zuguang, 2009).

As herbs took on a more economic-based and value-based identity, classifying and grading herbs became important in determining market price. These established test methods allowed for the determination of subtle variations of quality in greater detail, influencing how herbs were graded, priced and regulated globally (Gediya et al., 2011; Aburjai and Natsheh, 2003).

Greater value CMP defined as higher grades, created further economic motivation for the adulteration. This required legislation to monitor and improve how CMP was handled and tested throughout the supply chain. A framework of practices in response to adulteration had already been developed in the USA, the GxP guidelines, were subsequently adopted internationally.

1.9.2 Emergence of "Good Practices"

"Good" guidelines intended to protect consumers by improving the safety, efficacy and quality of medicine in production processes are referred to collectively as GxP. "Good", "Agricultural", "Collection" and "Manufacturing" practice guidelines, commonly abbreviated to GAP, GCP and GMP, respectively. GxP were initially developed to "build" rather than test quality though employing

“good” principles of medicine production (Arayne, Sultana and Zaman, 2008, p431). Adherence to a combination of pharmacopeia test specifications and compliance to well-defined GxP was considered a prime strategy to ensure bulk herbal material quality and consistency (Oluyemisi, Henry and Peter, 2012; EMA, 2022). GxP principles progressively developed into a sequence of process-like guides that directs where and which pharmacopeia testing is appropriate throughout a supply chain (WHO, 2007b).

GxP was initially developed in response to adulteration of food and pharmaceutical products in the early 1900s and later emerged in its current format during the 1970s. The first regulation, the Pure Food and Drug Act of 1906, arose as a result of public pressure on the American Congress reacting to the publication of a book detailing adulteration practices called “the jungle” in 1905. The 1906 act was updated in following a sequence of high-profile events, including the use of diethylene glycol in an “elixir” in 1933, phenobarbital adulteration in sulfathiazole tablets in 1941, and the emergence of teratogenic effects relating to prescribing Thalidomide in the 1960s. Tens of thousands adverse effects were recorded. These, together with many subsequent cases of adulteration, inspired the first American 21 CFR 210 rule of modern GMP in 1978 (Immel, 2001). This subsequently influenced The World Health Organization (WHO) who, informed by American legislation, issued international guidelines in 1982 (Brhilikova et al., 2007).

GxP were issued within Europe as EU-GACP in 2002, in China as China-GAP in 2003, and internationally by the World Health Organization as WHO-GACP in

2004 (Zhang et al., 2021). Taiwan informally followed WHO guidelines until they were officially adopted by the Ministry of Health and Welfare in 2013 (MOHW, 2019)

Although GxP advancements in legislation included improvements in where and how quality attributes of CHM could be determined, and sources of adulteration could be more efficiently and accurately identified, as discussed further in the next section, similar quality issues observed centuries earlier still persisted to the Contemporary Era.

1.10 Contemporary occurrence of CMP quality issues

From the beginning of the Contemporary Era, which began in the post-World War II period, considerable advancements in biochemical knowledge and technology revealed that many of the problematic CMP quality issues that were reported centuries before still recurred including widespread misidentification. Furthermore, newly emerged issues were uncovered including contamination with toxic materials.

1.10.1 The issue of misidentification

Misidentification is a common source of adulteration. It can unintentionally occur though human error when identifying CMP visually or selecting plants with a similar name. However, it also served as a means of obscuring intentional substitution, in particular where macroscopically similar whole plants and

individual parts were used in place of others (van der Valk, Leon and Nesbitt, 2017; Ye, Li and Sang, 2021).

In a series of articles, Zhao and colleagues comprehensively collated many misidentified species and summarised common types of misidentification arising from confusion and other sources of error when identifying CMP, *Table 1.5,* (Zhao et al, 2006).

TABLE 1.5 EXAMPLES OF MISIDENTIFIED CHINESE MEDICINAL PLANTS COLLATED BY ZHAO ET AL.

Reason for misidentification	Recorded example
Similarity in shape and appearance	In Hong Kong markets, Wei Ling Xian, 威靈仙, the root of *Clematis chinensis* and Osbeck., is confused with similarly shaped and toxic equivalent, Gui Jiu, 鬼臼, *Sinopodophyllum hexandrum* (Royle) Ying, leading to adverse events due to its aristolochic acid content that induces renal tubular epithelial cell degradation, and renal fibrosis (Liang, et al., 2006).
Mixed use of medicinal parts	The aerial portion of *Ephedra sinica* Stapf., Ma Huang, 麻黃, induces sweating, whereas its root inhibits sweating. (Zheng et al., 2023). The aerial part of *Belamcanda chinensis* (L.) DC., She gan Miao, 射幹苗, is commonly confused with root, She gan, 射幹. (Zhou et al., 2021).

TABLE 1.5 EXAMPLES OF MISIDENTIFIED CHINESE MEDICINAL PLANTS COLLATED BY ZHAO ET AL.

Reason for misidentification	Recorded example
Reversal of names	The medicinal flowers of *Flos albiziae*, He Huan Hua, 合歡花 is commonly mistaken for Ye He Hua, 夜合花. It has similar meaning in Chinese when the names are reversed. The Chinese term for flower is CP: Hua, 花. Similarly Zhou also lists confusion between; *Spatholobus suberectus* Dunn, Ji Xue Teng, 雞血藤, and *Sargentodoxa cuneata* (Oliv.) Rehd. et Wils., Da Xue Teng, 大血藤. *Lycopus lucidus* Turcz.var. *hirtus* Regel., Ze Lan, 澤蘭, and *Eupatorium fortunei* Turcz., Pei Lan, 佩蘭. (Brand, 2018).
Mixed use of similar species	*Abrus cantoniensis* Hance., Ji Gu Cao, 雞骨草, and *Abrus mollis* Hance, Mao Ji Gu Cao, 毛雞骨草. (Zhao et al., 2006). Similarly, *Polygonum aviculare* L., Bian Xu, 萹蓄 and *Polygonum plebeium* R. Brown, Xiao Bian Xu, 小萹蓄, (Schuster, Reveal, and Kron, 2011).
Antecedent mistakes from classical reference texts	In Ben Cao Gang Mu, 本草綱目, *Carthamus tinctorius* L., Hong hua, 紅花 is erroneously interchanged with Xi hong hua, 西紅花, *Crocus sativus* L. (Li & Liang, 2015).

TABLE 1.5 EXAMPLES OF MISIDENTIFIED CHINESE MEDICINAL PLANTS COLLATED BY ZHAO ET AL.

Reason for misidentification	Recorded example
Confused nomenclature	Mu Tong, 木通, refers traditionally to *Akebia quinata* (Thunb.) Decne (*Caulis akebiae quinatae*) that was not listed in the ChP prior to an update in 2002. It previously indexed two species, Guan mu tong 關木通, *Aristolochia manshuriensis* Kom. (*Caulis aristolochia manshuriensis*) and Chuan mu tong, 川木通, *Clematis armandii* Franch. or *Clematis montana* Buch.-Ham. (*Caulis clematidis armandii*). Guan mu tong was involved in a series of adverse cases with renal failure and urethral cancers, also related to aristolochic acid content (Lord et al.,1999).

Examples such as the *Akebia quinata* (Thunb.) Decne are mistakenly identified not only from confusion arising when compiling and referring to standard texts such as pharmacopeias, but also known substitutes are considered legally acceptable. These have become generally known as “unofficial” and “official” substitutes, respectively. Leon’s PhD thesis identified 99 unofficial substitutes and estimated that approximately 70% of the CHM contained in the 2005 edition of the ChP could be reliably identified visually through macroscopic examination by experts (Leon, 2017). However, this leaves potential for misidentification of a significant number, over 350 of the other 1,145 listed medicinal materials.

Acceptable substitution further adds to the proportion of CMP which can be “mistakenly” used, even when advanced testing and authentication is completed.

Wherein a species is allowed by a pharmacopeia however, is not considered similar in traditional CHM practice. The medicinal effects and consequences for many of these have not yet been determined. Conversely, the practice of intentional substitution of a sometimes unofficial medicinal by traditional herbal practitioners is both common and well-documented, as will be discussed in the next section.

1.10.2 The issue of acceptable substitution

Due to recent advances genetically similar species can be readily differentiated using DNA analysis techniques. Such species could not be discerned in the mid-20th century when many Chinese herbal medicines were integrated into China's biomedical healthcare system and when the use of specific herbal medicines were officially authorised. Many local species were included as acceptable substitutes for the "official herbal medicines", such as the commonly used CP: Jin yin hua, *Lonicera japonica* Thunb. In the fourth edition of the ChP in 1985, the first in English, Jin yin hua is listed alongside *L. hypoglauca, L. confusa, and L. dasystyla,*, and a further nine species as agreed substitutes (ChP, 1985; Foster and Chongxi, 1992). In recent times *Chrysanthemum* spp., *C. morifolium* and *C. indicum* L., and others are still interchangeably described in official sources as Ju hua, 菊花, however they possess varied phytochemical profiles and therefore potentially inequivalent medicinal effects that have not been as yet established (Gu et al., 2022; Hao et al., 2022).

Official substitution may be legally conducted under the instruction of a pharmacopeia, however unofficial substitution of one CHM for another is

inherently accepted in Chinese herbal traditional practice when composing formulas, wherein prescriptions are customised to match the health conditions for both different patients and the same patient seen at various stages of a disease (Yeung et al., 2015). In some instances, different species are substituted by herbal practitioners for clinical reasons. These can be derived from alternative species, such as *Codonopsis pilosula* Nannf., (CP: Dang shen, 黨參), in place of *Panax ginseng* C.A.Mey. (CP, Ren shen, 人參), where patients present with more lung-related health problems, to reduce financial cost, or due to scarce herbal resources (Chen et al., 2018; Cheung et al., 2021). In other cases, the substitutions are derived from the same genus, such as *Panax quinquefolius* L., (CP: Xi yang shen, 西洋參) with *Panax japonicus* (T. Nees) C.A.Mey. (CP: Zhu jie shen, 竹節參) (Yang et al., 2018). Those less botanically related sharing similar common names, such as American, Japanese, Chinese, Indian and Siberian ginsengs, are often found inter-substituted at markets (Ichim and de Boer, 2021).

There is, therefore, a continuum between what perhaps could be considered from a traditional herbal perspective that some CMP are mistakenly used but tolerated in practice through official acceptance by the ChP commission. Whereas from the perspective of more modern Chinese herbal practice, experts agree such CMP official substitutes are a progression in Chinese medicine prescription following considerable research and academic co-operation over a more than 70 year period of successive development and new Chinese pharmacopeias (Franz and Wang, 2015). Conversely, the clinical practice of intentional substitution by traditional herbalists with sometimes unofficial medicinals is not uncommon and documented, as discussed in the next section. There is justification for holding

either views. On one side of the argument, the medicinal effects should be based on selection using organoleptic assessment of aroma, taste or form of the plant, obtained from considerable antecedent knowledge and traditional use. While on the other side, more modern chemical characterisation of medicinal plants have validated some traditional uses and discovered novel modern clinical applications (Chassagne et al., 2019; Yuan and Lin, 2000).

The discrepancy is manifested in over-the-counter commercial herbal products requiring licence following rigorous pharmacopeial testing as part of the UK's EU market authorisation process or Traditional Herbal Registration scheme. While in contrast, Chinese herbal practitioners are allowed to prescribe formulas containing mixtures of CMP which may or may not contain licenced herbs (McIntyre, 2011; McIntyre et al., 2014). Although central to how CMP is prescribed, this complex disparity has not yet been resolved by researchers, legislators or practitioners. Therefore, as part of this thesis research, in Chapter Three the opinions of expert key informants were consulted to gain further insight and clarity into this area and how it may contribute to the problem of persistent of CMP quality issues.

Moving past debates over whether the identity of a medicinal plant is mistaken, acceptable, official or unofficial, the following section turns to more clear-cut occurrences of intentional substitution. Intentional substitution is sometimes required for pragmatic reasons but also results from nefarious profit-seeking activities.

1.10.3 The issue of substitution from scarcity and value

1.10.3.1 Scarcity substitution

Historically, herbal practitioners used herbs when seasonally available and where locally available. In times of scarcity or when cost of rarer herbs became unaffordable, substitutes were used (Cheung et al., 2021). Notwithstanding the commercialisation and considerable proportion to which international medicinal supply chains have expanded, CMP are still mainly sourced from natural, variable, and limited resources (Cunningham and Long, 2019).

The intentional substitution of one abundant CMP species for another is practiced to conserve the diminishing and limited supply of many medicinal plants, including some which have become endangered. Intentional substitution, together with cultivating endangered plants under controlled conditions optimal for their growth are the central strategies for preserving Chinese medicinal plant resources. This is of particular importance to plants in China where 80% of CMP are from wild sources and 11% of all land-based plants' existence is threatened in the country (Zhang et al., 2010; Qin et al., 2022).

An estimated 8,000 Chinese plants are recorded as possessing some medicinal property, either through detailed study or captured from oral tradition. Approximately 6,000 are well documented in the literature as being native to China and are classified as medicinal in nature. By individual family, most, more than 800 species are from the Lamiaceae, 700 species from Ranunculaceae family, Apiaceae, 500 species, Liliaceae about 560 species, Apiaceae 500 species, 300 from Papaveraceae, and approximately 260 species from the

Berberidaceae family. Of the 2,711 medicinals recorded in the 2020 ChP, about 600 are commonly used. About 33% of these are in cultivation settings, either *in-situ* within protected natural habitats or *ex-situ* intensive breeding settings, including various public and institutionally supervised botanical gardens (Huang, 2011).

The Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) is an internationally agreed framework to protect endangered animal and plant species. It provides a reference base from which to estimate and catalogue species that require special conservation attention. Additionally, it is a legal reference for regulating the trade of such medicinal plants. Approximately one-fifth of the world's medicinal plants have been assessed, and about one-tenth of these are considered at risk of extinction according to the CBDL criteria (Timoshyna et al., 2020). This CITES list classifies plants according to three threat levels in three respective appendices. The first is highly protected and restricted for which no commercial trade is allowed. The second are considered threatened but trade is limited trade under a permit system. The third group are not necessarily threatened however, they are protected and traded under approval and with special certification (CITES, 2023).

Cultivation species such as *Dendrobium fimbriatum* Hook., (CP: Shi hu, 石斛) has shown success. Although, being listed under CITES and threatened with extinction since the early 1980s, the orchid is more prevalent and commercially available as a result of controlled cultivation. Cultivation has been considered successful for many of the threatened species now available for general sale, including, *Fritillaria cirrhosa* D. Don, (CP: Chuan bei mu, 川貝母) , *Cistanches*

Herba (CP: Rou cong rong), and *Panax ginseng* C.A.Mey. (C.P., Ren shen, 人參) (Cunningham et al., 2018; Chandler and McGraw, 2020; Song et al., 2021).

To balance the need for justified commercial activities required to supply medicinal plants with the sharing of financial profits accrued from the global sale of these resources, the international community responded with the United Nations Convention on Biological Diversity. It is now considered the prime legal to guide for sharing the benefits accrued from their trade, and sustainable usage. The framework has been agreed by 196 countries (UN, 1992, 2023). On a national, local and inter-company level, many other initiatives have taken place, including the sustainable herbs programme of the American Botanical Council, Botanic Gardens Conservation International, and World Wildlife Federation. Organisations such as the Fair Wild Foundation works together with commercial entities in the UK such as Pukka Herbs and Neal's Yard Remedies (Kathe, Harter and Schippmann, 2018; Morgan and Timoshyna, 2016; Booker and Heinrich, 2016; Kumar, Kumar, and Khan, 2011).

Although many challenges remain to preserve scarce plant resources, these initiatives can only succeed if the ecosystems in which they grow are also protected. They face ever more significant challenges in the light of large-scale national industrial projects, changes to their habitat and natural disasters (Zheng and Cao, 2015; Xu et al., 2017). These influences significantly affect both the survival and the quality of many medicinal plants.

Organisations have gone one step further to ensure the future survival of plants by preserving seeds and DNA in case such scenarios arise. These include the

DNA and Tissue Bank at Kew Royal Botanic Gardens, Plant DNA Bank of Korea (PDBK), Australian Plant DNA Bank (APDB), NIAS DNA Bank, Japan, National Bureau of Plant Genetic Resources, India (NBPGR) and DNA Bank at Kirstenbosch (South Africa), (Rao, 2020). Additionally, they are reference material for both authenticating species and determining if substitution of CMP has occurred in part or whole. Detection methods that combine DNA analysis with highly sensitive analytical techniques such as electrospray ionisation-mass spectrometry (ESI-MS) together with multivariate statistical software, can now differentiate similar species not possible previously (Xin et al., 2014; Yang et al., 2015).

The dynamics between supply, demand and the effect on CMP resources became particularly apparent during the COVID-19 pandemic when the Chinese government officially recommended a number of CHM formulas which contained 125 plant species. *Glycyrrhiza* spp, including *Glycyrrhizae uralensis* Fisch. (CP: Gan cao, 甘草), is one of the most common ingredients contained in 11 of the formulas. Multiple other CITES-listed CMP were recommended, including *Aquilaria sinensis* Merr, (CP: Chen xiang, 沉香) and *Cibotium barometz* (Linn.) J. Sm., (CP: Jin mao gou ji, 金毛狗脊) (Timoshyna et al., 2020).

Cultivation usefully provided alternative sources for the commercial supply of medicine plants internationally. However, profit-motivated exploitation in the first instance is why many became threatened. Value substitution is established as a prime factor for both legal and illegal intentional substitution of CMP (Cunningham and Long, 2019).

1.10.3.2 Value substitution

The relationship between scarcity and the value of medicinal plants is complex. Scarcity can raises prices through both raising demand and creating prestige in obtaining that which is scarce (Cunningham and Long, 2019).

One of the most prized and, therefore, intentionally substituted groups of medicinal plants commonly termed “ginsengs”. When processed, packaged and marketed, they can sell for over €10,000 per kilogram (Amazon, 2020). Revered traditionally for their human-like roots, and belonging to the genus *Panax,* meaning “cure-all” in Greek, they have become one of the most consumed herbs worldwide (Alolga et al., 2020). The term “ginseng” describes botanicals from several taxa. However, *Panax ginseng* C.A. Mey., (Asian ginseng) and *Panax quinquefolius* L. (American ginseng) are the most frequently used for health indications (Uchendu et al., 2011). Even though the Panax genus is morphologically diverse with members, ranging from; “feather-leaf bamboo ginseng”, (*Panax bipinnatifidus* Seem.), “dwarf ginseng”, (*Panax trifolius* L.), some other species such as *Platycodon grandiflorus* (Jacq.) A.DC., *Codonopsis lanceolata* (Siebold & Zucc.) Benth. & Hook.f. ex Trautv., and *Pueraria montana* (Lour.) Merr., they are often used to replace similar looking substitutes in the marketplace, mimicking the familiar “human-like” root shapes and colours (Yun, 2001; Ichim and de Boer, 2021). Ginseng and the other CMP noted in this section are a subset of 17 Chinese medicinals listed under CITES that are commonly substituted for value purposes (Leon and Lin, 2017).

1.10.4 The issues of adulteration and contamination

The emergence of adulteration and contamination as quality issues is partly due to advances in the ability of analytical testing which allowed discovery of quality issues that were present historically but not detected. Whereas, other contaminants emerged as a consequence of the industrialisation required to meet increasing demand. More recent contaminants arose from attempts to preserve and extend shelf-life, and thereby value of CMP.

Contamination arising from adulteration that was intentionally perpetrated for centuries and discovered through improved testing by the analytical methods was described in successive pharmacopeias, which also set limits for the contaminants (Posadzki, Watson and Ernst, 2013; Commission, 2020). The aforementioned bulking agents used historically contained heavy metals such as lead, useful for increasing the weight of herbal products. Other heavy metal contaminants introduced into the CMP supply though industrial and domestic pollution, can be recently detected by analytical instruments at the cutting edge of instrument research (Zuo et al., 2020).

Recent and large-scale surveys across China and Taiwan found contamination more widespread than previously reported. More than 30% of 2,979 batches of CMP sampled contained multiple aflatoxins (Qin et al., 2020). Another survey of 1,773 widely collected samples agreed on the same percentage of contamination and heavy metals, including lead, cadmium, arsenic and mercury exceeding the Chinese pharmacopeia limits (Chen et al., 2020). Most, 88%, also contained pesticide residues. 59% of which were above levels set out by the European Pharmacopeia. Some, 43% of these contained 35 different types of banned

pesticides considered highly toxic, while others exceeded the limits more than five-hundred-fold (Luo et al., 2021).

Similarly, microbial spoilage, an inherent characteristic of natural product degradation, became better detected and previously unknown mycotoxins were discovered. Handling conditions and extended storage requirements for long journeys in international supply chains exacerbated their growth (Chen, et al., 2023).

1.10.4.1 Microbial contaminants

Bacterial and general microbial contamination is an unavoidable consequence of handling natural plant material, Throughout various controlled and less controlled stages of the supply, from cultivation and harvesting to ultimately, the customers who choose how they are stored. Generally, it is only when bacteria and mould occur at higher concentrations they become problematic. The limits for bacteria that preferentially grow in oxygenated conditions are set in the EP, ChP and THP, at up to a total of 10^1 CFU /g or ml of total aerobic microbial count (TAMC). Moulds and yeasts are permitted up to a maximum of 10^2 CFU /g or ml of the total yeast microbial count (TYMC). This accommodates the non-sterile nature of loose herbs handled by consumers who prepare them in aqueous decoctions. Although decoctions are boiled before use and any bacteria present might be expected to become denatured, some, including *Bacillus*, *Clostridium* and *Staphylococcus* spp.*,* can survive such conditions, particularly if encased in particles that can accumulate during the various stages of handling within a supply chain, or in herbs with fibrous roots and seed (Ting, Chow and Tan, 2013). Such bacteria are involved in significant health complications, including fatal outcomes (de Sousa

Lima et al., 2020). While the presence of some bacteria is accepted up to a limit, others, is completely prohibited, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella enterica* ssp. *enterica* serovar *Typhimurium* and *Candia albicans* (McMurray et al., 2020).

Contamination with mycotoxins such as aflatoxins is concerning due to toxicity, carcinogenic nature, and long-term effects. They derive from *Aspergillus flavus* and *Aspergillus parasiticus* fungi. Aflatoxin B1 (AFB1) is the most toxic of the thirteen currently noted in the EP, ChP, and TP pharmacopeias, ten times that of cyanide and sixty times than that of arsenic (Yan et al., 2020). It is mostly restricted by the EP to 2 micrograms / kg under the general limits, whereas as the ChP and THP allow more than double at 5 micrograms / kg. The EP also has a lower limit at 4 micrograms / kg for the total sum of B1, B2, G1 and G2 aflatoxins compared with 10 micrograms / kg of the ChP/THP. More stringent EP limits seem appropriate as CMP are more often stored for longer periods and transported over longer distances than within the Chinese mainland and Taiwan regions. Particularly as the few aflatoxins which are tested are indicators of general growth, and others which are not tested share similar optimal growth conditions.

In a review of 2,979 batches of 66 different types of CMP, more than 23%, 697 batches, contained AFB1. Some 30%, 2,734, had multiple aflatoxins. 70%, 486 batches, of those testing positive exceeded the EP, ChP and THP limits. *Massa Medicata Fermentata* and *R. Ophiopogonis* were those recorded highest at 50% over limit. *Zingiber officinale* and *Platycladi semen* were the most commonly

contaminated at 68% and 78% of samples, respectively. Roots, rhizomes, fruits, and seeds were most frequently contaminated (Qin et al., 2020). Furthermore, 67% of some flower species, such as *Lonicera japonica,* were detected at the highest aflatoxin level of 203 μg / kg (Tan et al., 2012). In general, CMP with high fat oils content were most susceptible, followed by those with higher polysaccharide and protein content. Those containing volatile oils were less contaminated, possibly due to their antibacterial properties (Zhao et al., 2016). As described further in the next sections, microbial and mycotoxins contamination is dynamic and changing that often occurs in conjunction with, and are affected by, other multiple contaminants in CMP such as heavy metals, pesticides, and synthetic adulterants.

1.10.4.2 Heavy metals

Heavy metal contamination can arise intentionally from addition of materials, such as the aforementioned bulking agents, and unintentionally through airborne particles, such as from engine fuel. Polluted water runoff and absorption from soil are also well-recognised sources. A low background of heavy metals occurs naturally, however contamination mainly derives from the demands of industrialisation, such as arsenic in fertilisers which does not degrade and accumulates over time (Soliman, 2015). The problem of contamination is compounded by industry and farming practised in close proximity (Pan et al., 2018). Heavy metals can enter the herbal supply at the cultivation stage through irrigation waters that have been affected by industrial processes, most often non-ferrous mining in coal discovery and rare-earth extraction (Sodango et al., 2018, p61).

Addition of fertilisers, pesticides, and sewage are well-recognised vectors for heavy metals, especially nitrogen-based agrochemicals containing high, 1,450 mg/kg levels of copper. Phosphate-based additives exceed 1,400 mg / kg of zinc content and others including manure can contain up to 300 mg / kg of lead (Alloway, 2012). Domestic and farm sources produce increasingly higher levels of pollutants such as cadmium, cobalt, chromium, nickel and lead. These are most often from battery and semiconductor components in consumer electronic devices and farm equipment (Duan and Shi, 2011; He and Xu, 2014). The significance of this problem was reported in a recent and comprehensive study which found more than 30% of CMP contained over-limit heavy metals tested in 1,773 samples from 86 commonly used herbal medicines sourced across 13 locations. The greatest concentrations found were for copper, arsenic, cadmium, mercury and lead, mainly in “herbal” CMP, and those herbs derived from the aerial part of plants including fruits. The highest level of Cu was found in *Schisandra chinensis* (Turcz.) Baill. at more than 34 mg / kg, as in *Plantago asiatica* L., 15 mg kg^{-1}, Cd in *Curcuma longa* L., 6 mg / kg) and Hg in *Chrysanthemum indicum* L. (9 mg / kg) and Pb in *Tetradium ruticarpum* (A.Juss.) T.G.Hartley, 50 mg / kg, (Luo et al., 2021). This is reflected in other studies finding high levels of heavy metals, particularly Cd, in other market surveys for Chrysanthemums (Gu et al., 2022).

However, not all heavy metal “contaminants” derive from pollution. They are often intentionally added as part of traditional practice. More than 7,000 species of Chinese herbs used in practice, ten of the 150 most commonly used, are toxic (Chan, 2003, p1532). Mercury, “Zhu sha”, as a sedative anti-convulsant. Lead in

“Mi tuo seng”, for abscesses and digestive disorders. Arsenic in “Xiong huang”, for skin conditions and anti-parasitic purposes. Lead oxide “Qian dan” for itching and as an anti-parasitic antispasmodic (Bensky et al., 2004).

Some heavy metals are ubiquitous in nature, including nickel, chromium, cadmium, arsenic, mercury, zinc and copper, which occur naturally in rocks and soils. As such, the World Health Organization makes allowances for up to 1, 50, 300 and 100 mg / kg of arsenic, copper, iron and zinc, respectively, in plant species for human consumption. However, as a consequence, plants provide a route for these heavy metals to enter the human body, wherein through being difficult to eliminate can accumulate throughout a lifetime. It is long-known that even low doses can cause significant health damage, and the additive effect of repeated trace doses over many years is of particular concern (Das, 1990).

1.10.4.3 Pesticides

Pesticides that are applied during cultivation not only contribute to heavy metal pollution but also harmful chemical residues. Sometimes these include a number of banned chemicals that can persist in CMP throughout the later stages of the supply. They are applied to enhance yields and therefore profit margins for cultivators who rely on them for their livelihood and to satisfy the demands of collectors, manufacturers, and ultimately consumers. More than half, 59%, of CMP recently tested contained levels higher than those allowed in the EP, and 43% of those detected 35 different types of banned pesticides in 1,771 samples of CMP from 503 cultivation sites. The most commonly detected pesticides in

more than 40% of cases found were bifenthrin, diphenylamine, and metolachlor. The majority, 49% of the residues, were found in roots and rhizomes herbs, 30% in the fruits and seed types, and 9% in leaf and bark derived herbs. The CMP most affected were *Chrysanthemi flos* with 37 different kinds of pesticides, *Crataegi fructus* with 29, and *Alpiniae oxyphyllae fructus* containing 27 types. The most commonly detected were general pesticides, 49% insecticides and 34% were fungicides (Luo et al., 2021).

Often sulphur-based fumigants are applied at the earliest stages of the supply, before sale to processors or middlemen, to preserve and resist pests in addition to enhancing the appearance of the CMP for more favourable sale prices. However, sulphur fumigation can also be a source of adulteration, adding up to 15% bulk weight to herb mass from its water retention effect (Jiang et al., 2013). Traditionally herbs were sun dried, but with increasing demands on time and cost, sulphur fumigation is now commonly conducted, often in the form of potassium or sodium sulphite, bisulphite or metabisulphite. Since 2005 the ChP has restricted these practices for processing CMP and removed the limit tests. However, sulphur fumigation continues undetected (Kan, Ma and Lin, 2011, p2). A large Chinese study of 862 batches of CMP found that more than half, 52%, of samples analysed in 35 different CMP had greater than 150 mg / kg, ChP, and THP limits (Kang et al., 2018).

1.10.4.4 Biomedical drug adulterants

CMP and biomedical drugs show synergistic benefits when combined and prescribed appropriately. Over-the-counter formulations, which contain both natural and synthetic drug compounds, can be purchased under non-prescription in pharmacies throughout China (Xian Zhou et al., 2016). However, in many areas outside Asia such as in the EU, the sale of CMP even without synthetic drug ingredients for medicinal conditions is restricted. Undeclared biomedical drugs are sometimes added to CMP to impart a more rapid or perceivable therapeutic effect (Tang and Easthope, 2000). However, inappropriate combinations can lead to drug-herb interactions with a potential range of side effects ranging from mild digestive upset to fatal outcomes (Choi et al., 2016; Singh and Zhao, 2017). These include both approved and unlicensed pharmaceutical drugs in addition to animal material such as thyroid tissue intended to enhance the natural medicinal plant efficacy or to compensate for poor quality and ineffectual herbal material (Chor Kwan Ching et al., 2018). In a review of the China National Institutes for Food and Drug Control database from 2003 to 2017, 166 different types of biomedical drug adulterants were detected in CMP and their products (Xu et al., 2019). This agreed with earlier reviews that found 24% of 2600 Chinese herbal medicines samples collected from 2003 to 2017 contained at least one form of synthetic drug (Ernst, 2002a). A comprehensive Hong Kong study of 487 adulterated proprietary CMP products identified 1,234 different types of adulteration. Most frequently, 18% nonsteroidal anti-inflammatory drugs, 15% anorectics, 14% steroids, 11% diuretics and laxatives, 10% oral antidiabetic agents and 6% erectile dysfunction drugs. Some 65% of consumers suffered adverse effects, 14 of which were classified as severe and two fatalities were

observed (Chor Kwan Ching et al., 2018).

Detection methods have advanced from basic techniques of macroscopic visual assessment to microscope-assisted authentication of plants, and through progressive advancements, determined finer chemical attributes to authenticate medical plants. They can determine when substitution, adulteration, and contamination has occurred. Although many incidences of quality CMP issues were discovered retrospectively through adverse events or following laboratory analysis of suspect CMP samples, a measure of progress in analytical testing capability is apparent in the types of detection that can be achieved, such as in clinical point-of-care settings where hand-held potentiometric sensors can now reliably detect many adulterant substances including sibutramine (Freitas et al., 2019).

The practice of biomedical drug addition and the other described types of adulteration continue, notwithstanding the many advances in testing and legislation. This is particularly concerning as the general response of the scientific community in the field of CMP field appears to have been directed towards innovating more sensitive analytical technologies, together with further legislative controls such as the European Directive THMPD and “Good Practices”, the GxP, described in the Chapter Two.

Yet, research into why such quality issues continue to recur despite the more capable detection and legislative measures is not so apparent. A literature review was conducted to better understand previous responses to problematic CMP quality issues. Firstly to clarify what the responses were, and identify towards

which quality issues they were directed. Secondly, contribute gain insight into why they persist, so that a solution to the general situation of persistent CMP quality problem could be informed, and formed.

Chapter Two Literature Review

2.1 Introduction

A literature review was conducted to more specifically explore the contemporary knowledge-base relating to Chinese medicinal plant quality from 1990 to 2022, the period in which CMP proliferated most widely throughout Europe (Ernst, 1998; Eisenberg et al., 1998; Xiang et al., 2022).

It was conducted in two phases. The first scoped the topic of CMP quality in general, followed by a second phase that further explored specific areas of CMP quality that appeared problematic in the first phase, such as misidentification, substitution and adulteration.

The literature was examined to explore the published knowledge-base to better define what aspects of CMP quality were previously researched and, more specifically, towards what quality issues this research directed. Furthermore, it explored why CMP quality issues recurred which inform a solution to persistent CMP quality problems.

This literature review clarified both areas that were well researched, and those not yet fully addressed which guided the formation of the thesis objectives to describe:

- what is the identity of the main CMP quality issues?
- why have they persisted?
- Is there a solution to the problem of their persistence?

This literature review considered both non-original research in published reviews, and primary research in journal articles.

2.2 Methodology

2.2.1 Objective

A scoping review was conducted to explore and analyse the contemporary peer reviewed published knowledge-base relating to the quality of Chinese medicinal plants. It was conducted in two phases. The first, exploring the topic of CMP quality in general followed by a second phase that explored specific problematic areas of CMP quality in more detail that were identified in the first phase review, such as misidentification, substitution and adulteration.

2.2.2 Design

The scoping review was guided by the process outlined by Tricco et al. (2018), to "*map evidence on a topic and identify main concepts",* wherein general themes from a published knowledge-base are identified as key topics in the field. Tricco and co-authors recommended the inclusion of objectives, design, sources of evidence, eligibly, charting methods, findings, and conclusion, described further in this section (Tricco et al., 2018).

2.2.3 Sources of evidence

Two online databases were used to conduct the review:

- Web of Science (WoS), hosted by Clarivate, at https://www.webofscience.com.
- PubMed hosted by National Library of Medicine, at https://www.ncbi.nlm.nih.gov.

2.2.4 Eligibly

All peer-reviewed literature included in the WoS and PubMed databases published between the dates 1st January 1990 and 31st December 2022 were examined (*Table 2.1*).

TABLE 2.1 DETAILS OF THE TWO LITERATURE SEARCH PHASES

Search Details	First Phase Literature Review Search	Second Phase Literature Review Search
Date and time	23rd January 2023, 4.23pm	27th January 2023, 9.06am
Terms and Databases	"Chinese herb" OR "Chinese medicine" AND "Quality", appearing in the title using the database specific search operators: ((TI=(Chinese herb)) OR TI=(Chinese medicine)) AND TI=(quality), for WoS, and, ((Chinese medicine[Title]) OR (Chinese herb[Title])) AND (quality[Title]), for PubMed.	"adulteration" OR "misidentification" OR "substitution" AND "Chinese medicine" OR "Chinese herb", appearing in the title for WoS, and in the title or abstract for PubMed, using the database specific search operators: TS=(adulteration OR misidentification OR substitution) AND TS=(Chinese medicine OR Chinese herb), for WoS, and, (((Adulteration[Title/Abstract]) OR (Misidentification[Title/Abstract])) OR (substitution[Title/Abstract])) AND (Chinese medicine[Title/Abstract]), for PubMed.

2.2.5 Exclusion criteria

Articles that the did not inform the questions set in the objectives of this investigation were excluded. Non-English language publications were also excluded.

2.2.6 Charting methods

The results were charted in tabular format, that illustrate the primary focus (referred to as major themes) or secondary focus of the publications reviewed (referred to as minor themes), together with the number of publications and the proportion they represent as a percentage of the total number that were examined. An overview of the search process was illustrated in a PRISMA flow diagram (Zhang et al., 2020).

2.3 Results summary

Literature found during the first and second phase search process is summarised in *Figures 2.1* and *2.2.* A complete record of the citations found, excluded and included is attached in the thesis appendix, appendix to the literature review (ALR), *Tables ALR 1* to *6*, inclusive.

An exploration of search terms was conducted before choosing those that produced the most relevant results, as minor alterations to search terms can produce quite different results. The search terms and results were saved and can be accessed directly for the first most general phase at:

- https://www.webofscience.com/wos/woscc/summary/3e4d6337-7bd3-4ffa-8188-7ae994d2db3a-749a31ce/relevance/1

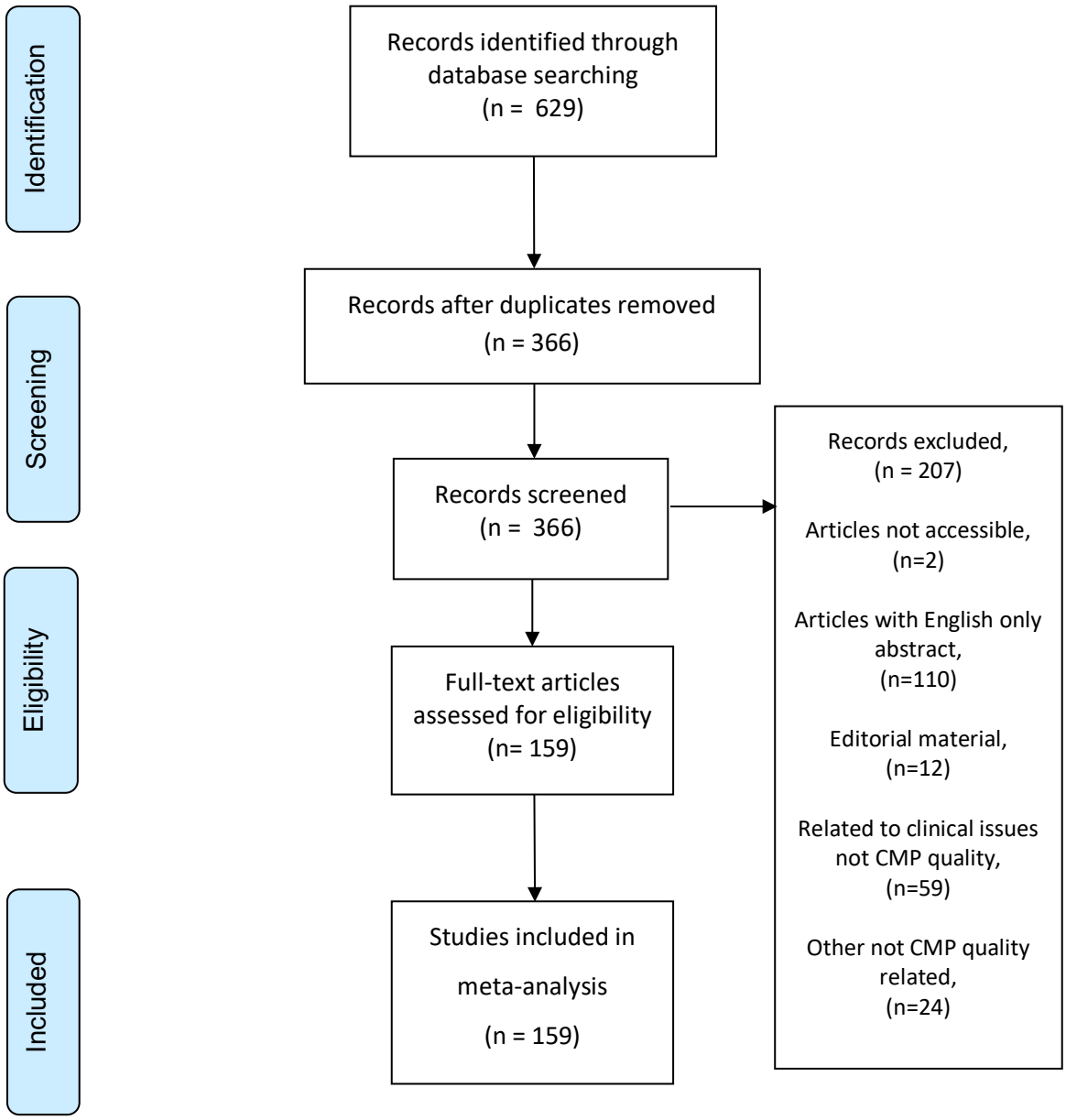
The second more general phase can be accessed at:

- https://www.webofscience.com/wos/woscc/summary/e6e5aac3-d08d-4b28-a069-340fe399cdb7-76d58661/relevance/1

2.3.1 Literature search phase one general review

FIGURE 2.1

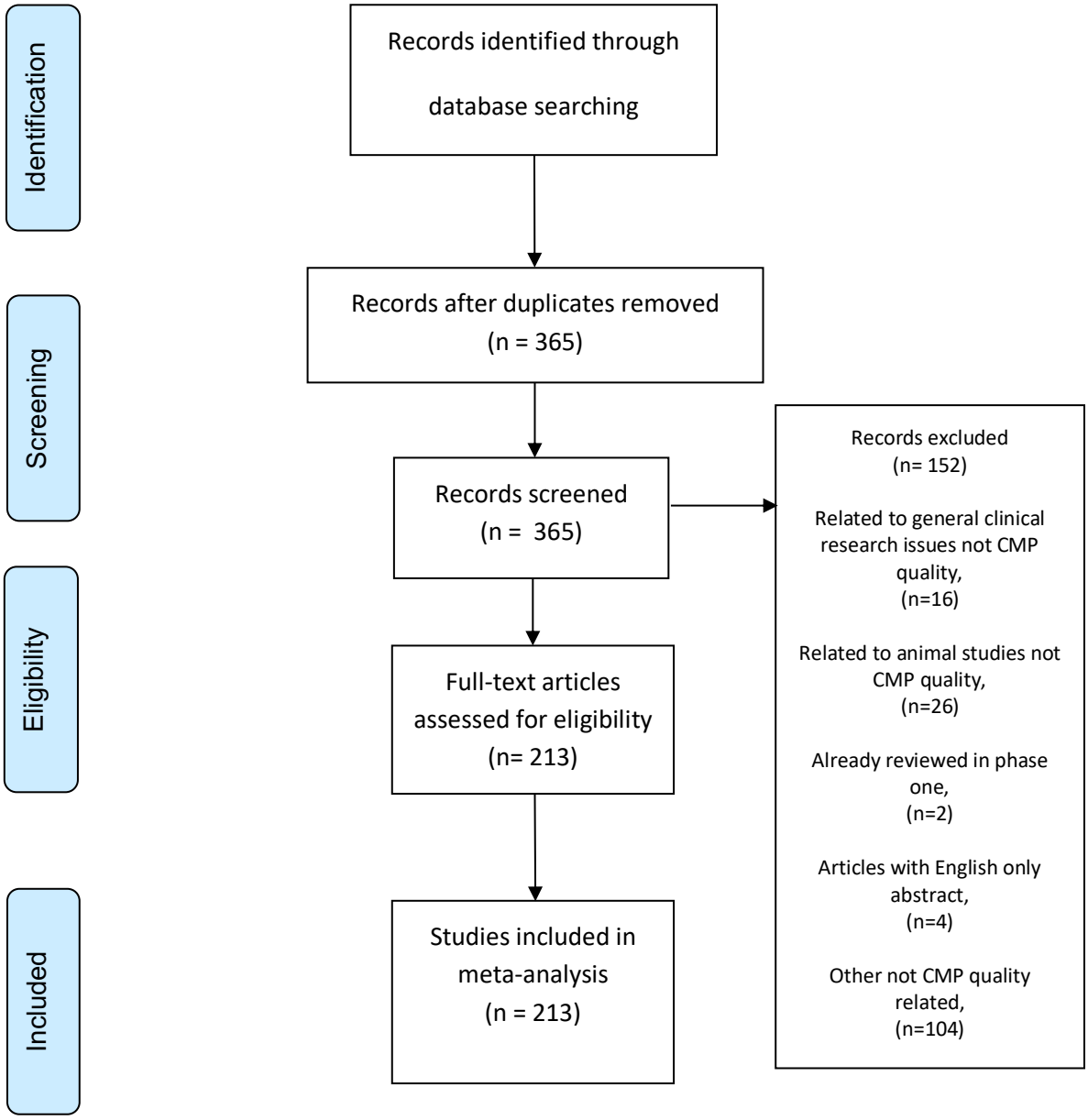
PRISMA FLOW DIAGRAM OF THE SEARCH PROCESS AND RESULTS FOR PHASE ONE OF THE LITERATURE REVIEW USING SEARCH TERMS: "CHINESE HERB" OR "CHINESE MEDICINE" AND "QUALITY",. ALL IN TITLE WITHIN WEB OF SCIENCE AND PUBMED DATABASES, FOR YEARS 1990 TO 2022, INCLUSIVE



2.3.2 Literature search phase two specific review

FIGURE 2.2

PRISMA FLOW DIAGRAM OF THE SEARCH PROCESS AND RESULTS FOR PHASE TWO OF THE LITERATURE REVIEW USING SEARCH TERMS: "ADULTERATION" OR "MISIDENTIFICATION" OR "SUBSTITUTION" AND "CHINESE MEDICINE" OR "CHINESE HERB", APPEARING IN THE TITLE WITHIN WOS, AND IN THE TITLE OR ABSTRACT FOR PUBMED DATABASES FOR YEARS 1990 TO 2022, INCLUSIVE



2.4 Analysis and Discussion

2.4.1 Phase one general review of CMP quality

The efforts and challenges to control the quality of CMP is manifest in the general emphasis of 37 reviews that were published between 1990 to 2022 with “Chinese medicine” or “Chinese herb” and “quality” in their title. A relatively high proportion, 65% of reviews of CMP quality, shared a common theme of controlling Chinese herbal quality, (*Table 2.2*), and in particular, 43% in researching various strategies to control CMP quality, *(Table 2.3*). The complete list of the articles are attached in the appendix to the literature review (ALR), (*Table ALR 3*).

TABLE 2.2 SUMMARY OF THE MAJOR THEMES (MAIN FOCUS) FOR 37 REVIEWS THAT WERE PUBLISHED BETWEEN 1990 TO 2022 WITH “CHINESE MEDICINE” OR “CHINESE HERB” AND “QUALITY” IN THEIR TITLE WITHIN WEB OF SCIENCE AND PUBMED DATABASES

Major theme of reviews	Number	Proportion of the 37 CMP quality related reviews (%) *
Quality control	24	65
Quality assurance	5	14
Quality assessment	4	11
Standards	1	3
Pharmacovigilance	1	3
Analytical methods	1	3
Markers	1	3

** For clarity, rounded upwards to nearest whole number (total rounding error 2%)*

TABLE 2.3 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 24 QUALITY CONTROL THEMED REVIEWS PUBLISHED BETWEEN 1990 TO 2022 WITH "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLE WITHIN WEB OF SCIENCE AND PUBMED DATABASES

Minor themes within the 24 reviews with a major theme of Quality Control	Number of Reviews	Proportion of the 37 CMP reviews relating to quality (%) *
Strategy	16	43
Marker	2	5
Fingerprinting	1	3
Regulation	1	3
Review	2	5
Markers	1	3
Procedure	1	3

** For clarity, numbers rounded (cumulative rounding error -0.5%)*

Some strategies proposed were highly specific whereas others were more general in their approach. The more specific involved using existing infrared and UV spectroscopy, HPLC, or GC instrumentation together with the novel use of chemical markers to identify the plant and determine the known effective CMP bioactive contents (Yuan et al., 2011; Sun et al., 2010; Gong et al., 2017). Benzylisoquinoline alkaloids markers were identified for the QC of *Coptis chinensis* Franch and *Phellodendron amurense* Rupr, and the berberines, jatrorrhizine, and palmatine for *Coptis chinensis* (Liu et al., 2017; Ren et al., 2020). Some extended the scope to include multiple markers simultaneously. (Zhu et al., 2017), including multiple analytical "fingerprints" of CMP chemical profiles (Liang, Xie and Chau, 2010; Zhang et al., 2018), and others proposed QC of the more

complex commercial products such as the Yigong patent Chinese medicine through measuring bioactive compounds such as baicalein, wogonin with up to ten simultaneous chemical markers in the form of a characteristic fingerprint (Gong et al., 2017). More general strategies proposed to control the quality of CMP were diverse. Some offered a system biology approach in which body fluids of those who have ingested CMP were monitored to gain knowledge of CMP with different biochemical profiles in-vivo. These were then used to predict in advance how future batches of CMP were likely to interact with other consumers (Wang et al., 2009). Whereas others were somewhat more removed strategies from the systems biology approach, including those that wished to define the production parameters under which CMP could be processed to produce more standardised products (Zhao, Ma and Li, 2018). Authors of broader reviews suggested research to better understand traditional practices and preparation methods to guide improved QC of CMP (Xie and Leung, 2009).

The second greatest group, 14%, of these published reviews focused on QA, and the third 11% on QAS (*Table 2.2*). Authors in the QA themed group of publications similarly attested to assuring QC quality through the development of analytical methods monitoring discrete chemical markers and fingerprints. However, their approach emphasised first monitoring and then excluding CMP that did not meet minimum standards, rather than primarily controlling their production (Li, Yang and Tsim, 2006; Zhao et al., 2007; Liu et al., 2019; Zhu et al., 2016). The use of standards early in the supply chain while the medicinal plants grew was noted by those in this QA themed group of literature, to authenticate and therefore assure the identity of CMP so that the intended or declared herb was as stated. This also

assured that it contained a minimum amount of active ingredients, as defined by the chemical markers selected (Song and Li, 2021). Others held the opinion that understanding the differences between European and Chinese pharmacopeia standards was critical to advancing testing, and therefore to assuring CMP quality, as differences in regional pharmacopeial standards could lead to unknown quality issues (Leong et al., 2020a). Adverse events and associated CMP quality issues during this time were captured in reviews of pharmacovigilance practices and their outcomes (Bensoussan et al., 2000; Posadzki, Watson and Ernst, 2013; Melchart et al., 2016).

The difficulties encountered controlling CMP quality observed in the reviews were also mirrored in the patterns of 122 primary research, peer-reviewed articles that were published in the 32-year period. Most, 56%, focused on attempts to control quality, the second largest group, 30%, on attempts assess the biochemical composition to better characterise CMP quality. 10% of the articles focused on assuring quality of CMP through establishing a standardised content and that was safe for consumption, yet still possessed bioactivity to impart an expected effect (*Table 2.4).* The complete list of articles are attached in the appendix to the literature review (ALR) (*Table ALR 4).*

TABLE 2.4 SUMMARY OF THE MAJOR THEMES (MAIN FOCUS) FOR 122 PEER-REVIEWED ARTICLES PUBLISHED BETWEEN 1990 TO 2022 WITH "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLE

Major theme of articles	Number	Proportion of 122 Articles (%) *
Quality control	68	56
Quality assessment	36	30
Quality assurance	12	10
Classification	1	1
Survey	1	1
Quality	1	1
Characterisation	1	1
Clinical trial	1	1
Clinical practice	1	1

** For clarity, numbers rounded (cumulative rounding error 0 %)*

Of the predominant group with a QC theme in the 122 articles, 43% related to researching strategies to control medicinal plant quality (*Table 2.5*).

TABLE 2.5 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 68 QUALITY CONTROL THEMED REVIEWS PUBLISHED BETWEEN 1990 TO 2022 WITH "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLE

Minor themes of the 68 major QC themed articles	Number of Articles	Proportion of 122 Articles (%) *
Strategy	53	43
Analytical methods	6	5
Review	2	2
Characterisation	1	1
Procedure	1	1
Fingerprinting	1	1
Standards	1	1
Holistic	1	1
Mechanism	1	1
Metabolomics / Chemometrics	1	1

** For clarity, numbers rounded (cumulative rounding error 1%)*

In addition to describing strategies for QC, the second largest proportion, 5%, indicated the importance of analytical development for QC (*Table 2.5)*. Analytical methods demonstrated better characterisation of CMP so that improved reference standards could be established (Chen, Zhao and Leung, 2009). Increased analytical instrument capability generated more detailed data from biological studies resulting in a more detailed understand their metabolic mechanisms. It further supported more comprehensive statistical analysis, including the aforementioned profiling or "fingerprinting" quality characteristics (Liu et al., 2015). Holistic perspectives on how CMP quality should be assessed and maintained were represented in a minimal 1% proportion of the articles that described a case study for the commercial herbal pills, Liu wei di huang (Wang et al., 2021).

A generally consistent progression in the capability of analytical methods to determine finer variations in CMP quality is apparent throughout the review period. Fingerprinting techniques employed progressively sophisticated computer algorithms. This is seen earlier when at first basic differentiation individual species was demonstrated (Liang et al., 2010; Chen et al., 2010), then later in profiling more complex extracts of herbs that were known to have adverse effects (Yang et al., 2014), then towards the end of the review period when a complete multiple species discrimination of (*Stephania*) was completed using DNA barcoding with multiple hybrid instrumentation. These hybridised techniques consisted of HPLC-QTOF-MS/MS and UHPLC-DAD; abbreviations of high performance liquid chromatography-quadrupole time of flight-mass spectrometry – mass spectrometry, and ultra-high performance liquid chromatography-diode array detection (Zhao et al., 2020). Resolving herbs such as *Tetradium ruticarpum*, which previously could only be analysed in isolation, were later fully differentiated in complex combinations with other CMP (Shan et al., 2020). This contributed to better understanding how the biochemical composition of CMP influenced efficacy and toxicity quality attributes.

Similar progressive sophistication is apparent in considering combinations of multiple chemical markers rather than previous approach with single markers to characterise medicinal plants (Liang, Xie and Chan, 2004). The previous basic concept of chemical “fingerprints” represented in earlier two-dimensional graphs were later presented in up to 18 dimensions. Furthermore, interpretation of the data by statistical computer algorithms enabled further discrimination of complex herbal ingredients became accepted by the WHO, FDA, EMEA, German Commission E, British Herbal Medicine Association, Indian Drug Manufacturers’

Association and others (Fan et al., 2006). Such as the milestone analysis of complex mixtures, Tianjihuang, Dang Gui, (Liang, Wu and Yuan, 2009), *Rehmannia glutinosa,* (Chang et al., 2006), and Shuang huang lian, (Cao et al., 2006), and proprietary formulas, (Leung and Fu, 2009).

However, together with further advancements and more detailed knowledge of plant quality also came greater realisation that more factors influenced variations in herbal quality than previously considered. These included the same plant, under the same conditions, being harvested at sunrise or sunset, which imparted a different phytochemical profile, as demonstrated with *Ginkgo* spp. A new appreciation was apparent of the seemingly infinite permutations in numbers and levels of secondary metabolites which could be produced and impart different clinical effects. This mirrored a new and clearer realisation of the limitations and difficulties with regulating and standardising herbal products (Wang et al., 2005, p175) .

As CMP quality became better understood and herbal extracts were more systematically screened for activity, comprehensive authenticated plant libraries were generated (Eisenberg et al., 2011). Such as for Yanghuo sanqi, and other *ginseng* spp. products (Zhu et al., 2013). In aggregate, this information illustrated the effects of ever-subtle factors, such as when repeatedly planting a herb in the same soil, minor variations in soil nutrients, microbiological and fungal changes affected the phytochemical profile and potential efficacy of CMP (Tang et al., 2015; Cao et al., 2020). By 2020, computational pattern matching could differentiate whether *Astragali Radix* was wild or farm-cultivated, and in many cases determine its original cultivation location within China (Wang et al., 2020).

Notwithstanding these accumulated and significant advanced insights and unprecedented analytical capability, additional similar quality issues and associated adverse reports from the use of CMP persisted by the close of the decade in 2020. Highly cited reviews continued to collate serious observed toxic effects in herbs in medicines and supplement forms (Han, et al., 2019; Charen and Harbord, 2020). Further adverse events appeared, such as recurrent nephrotoxicity cases more than 700 years after the same herb, *Aristolochia fangchi* was described and prohibited in China which demonstrated further that in this Contemporary Era attempts to understand and prevent such CMP quality issues are still both incomplete and significantly limited (Xu et al., 2020; Gaohua in Fleischer et al., 2017).

Notwithstanding the advancements which had taken place, basic practices of intentional adulteration remained difficult to detect. New knowledge of CMP quality accrued in this review period theoretically advanced the field. However, in practice its usefulness was somewhat offset by the changing circumstances of how CMP was processed and grown. As in the case of Wu Wei Zi *Schisandrae Chinensis Fructus*, and Nan Wu Wei Zi, *Schisandrae Sphenantherae Fructus,* both of which are similar visually in shape and form, in addition to their close biochemical profiles. New knowledge and testing could differentiate the species, but as they are not easily differentiated visually in clinical practice settings, the need to do so was not always apparent, and their phytochemical differences were diminished with the increasingly common processing of CMP (Jiang, Lu and Chen, 2016, p246).

Reliably identifying and authenticating herbs became both more difficult and

important. Herbs more frequently took on dried, powdered, capsulated or tableted forms often unrecognisable from the original. As CHM use significantly increased in the 1990s, evidence of adulteration continued into the 2000s (Ma et al., 2002; Ergil, Kramer and Ng, 2002; Lim and Thirumoorthy, 2005).

The corresponding increasing demand on relatively slow-growing herb resources, becoming ever-scarcer and in some cases endangered, had compelled suppliers to grow many herbs outside their traditional growing areas. Such as ginsengs, (*Panax ginseng*), Cistanches, (*Cistanche deserticola*), Magnolia (*Magnolia officinalis*), Orchids, (multiple *Dendrobium* and *Gastrodia elata*), Eucommia bark, (*Eucommia ulmoides*), and Liquorice root, (*Glycyrrhiza uralensis, Glycyrrhiza inflate, Glycyrrhiza glabra*) (Sodhi et al., 2004; Ding et al., 2008; Xu et al., 2009). Cultivation in new areas potentially influenced their efficacy, and variation in phytochemical profiles which made identification and authentication using pre-defined analytical fingerprints increasingly difficult (Yap, Chan and Lim, 2007). Demand required more manufacturers, who consequently introduced more variation in processes, additionally complicating standardisation and reducing the usefulness of analytical fingerprints (Harkey et al., 2001). Yet, attempts both within China and Europe continued to resolve the problem of defining and controlling a naturally variable CMP-type material, that was becoming increasingly variable due to new influences introduced from supply chain developments.

However, fundamental differences were apparent between the Chinese and European approaches to assessing and controlling CHM quality, which became progressively more distinct during the review period.

European regulators attempted to define CHM quality in a similar manner to synthesised biomedical drug products when harmonising legislation, both between existing EU countries and China. The European pharmacopeia commission since 2005 had sought to directly adopt the Chinese Pharmacopeia herbal monographs, however difficulties arose when importing the different structure, standards and naming system of the ChP. This necessitated the formation of expert working groups to resolve the differences (Franz and Wang, 2015). At the start of the review period, in preparation to later harmonise regulation, the newly formed European Medicines Agency under the remit of the EU commission reviewed the individual member states' legislation. Countries such as France since the 1980s already had some basic medicinal plant regulation in place through the Agence franqaise de securite sanitaire des produits de sante (Afs-saps). Austria already held an official list of "traditional status" herbs and their excipients (Arzneimittelgesetz), similar to Germany (Section 109a of the German Medicinal Products Act). Belgium used a simple annexed list system that was in place since the early 1990s and Sweden allowed the use of a "natural remedy" status for naturally derived ingredients, including herbs (Anquez-Traxler, 2011, p16). European harmonisation was initiated through the introduction of Directive 2001/83/EC (later amended to 2004/24/EC), with CHM used as medicines, as district from culinary status, and were now regulated under the traditional herbal medicinal products (THMPs) category. However, approaching the end of the 7-year precursory period, in 2010, 153 registrations were in place, representing only a fraction of herbal medicines that were previously on the market. The UK led the way with 48 registrations, mainly due to the proactive engagement of the UK Medicines and Healthcare Products

Regulatory Agency offering practical relevant guidance (MHRA, 2021). The new system proved difficult for CHM compliance as traditionally they were most often used as variable mixtures with non-standard preparations, including other excipients such as vinegar and honey. This contrasted much of Western herbal practice, which prepared discrete single herbs, often in the form of standardised alcoholic tinctures. However industry did adapt, with the first CHM (*Dioscorea nipponica* rhizome) receiving market authorisation in 2012, and 72 further monographs included in the subsequent European Pharmacopoeia. (Knoess and Wiesner, 2019, p26). Registration was largely completed through describing the chemical composition of the herb and assessing the safety risk to consumers on the basis of pharmacognosy and its longstanding use for a minimum of 30 years.

The rise in popularity of CMP throughout Europe combined with the increasing frequency and severity of its associated adverse events necessitated further efforts to regulate its availability and safety. By the late 2000s, a 38 EU member states group was formed, including representatives from DG Health & Food Safety, European Medicines Agency and observers from 27 additional regions and organisations such as the Taiwan Food and Drug Administration (TFDA) and the WHO (EDQM, 2017). The WHO continued its role to develop international harmonisation in pharmacopeias (WHO, 2018). Currently there are 2,711 herbal monographs in the 2020, 11th edition of the ChP. (CCP, 2019), and 73 specific CMP entries in the current EP 10th edition (Leong et al., 2020b).

At the close of the review period the use of CMP is significantly restricted. A fraction of the traditional herbs in the ChP and their mixtures in formulas are not allowed for general sale. However through registered herbal practitioners

hundreds of CMP and their mixtures are allowed to be dispensed, leaving a partial legal vacuum, where they can be prescribed but are relatively difficult to source. Many of the herbs prescribed through this route are therefore unlicensed, which raises the question as to whether this supply route to consumers is one through which quality issues arise. Particularly in light of self-directed, over the counter and non-registered practitioner prescriptions were found to be the most usual sources of herbal administration in cases of adverse events. As misidentification, substitution, and adulteration have been documented as common quality issues and seem to more commonly occur with CHM than in those from other traditions (Vickers and Zollman, 1999), it is likely that many more adverse events including fatalities from CMP have not been recorded due to difficulty in detecting, recognising and attributing their cause (Byard, 2010).

2.4.2 Phase two review of specific CMP quality issues

A second phase literature review was conducted with search terms of common quality issues reported in research found in the phase one review of CHM quality in general. The terms “adulteration”, “misidentification” or “substitution” were searched together with “Chinese medicine” or “Chinese herb” in the title of peer-reviewed publications within the Web of Science database. Identical terms were used to search a second database, PubMed, but the search criteria was expanded to include the terms in either the title or abstracts of publications to capture a greater number of relevant articles. Secondary research in review articles and primary original research were both included for examination over a period of 32 years, between 1990 to 2022 inclusive. In the first group, reviews were examined to identify the major themes reported by authors previously

reviewing the field. This was intended to clarify what main quality issues were identified. A further examination of the main major themes of the reviews included their secondary focus, or minor themes. Overall, this assessment was conducted to inform what proportion of different quality issues comprised the main themes reported by reviews, so that any apparent trends in the literature could be more clearly discerned. The primary research articles were examined similarly to the review articles, for both the primary, major and secondary, minor themes. A further more detailed analysis was conducted to explore if authors previously reported why CMP quality issues occurred, or persisted, together with previously proposed solutions.

2.4.2.1 Literature insights from reviews

Of the 40 published reviews included, 43% identified various types of CMP adulteration (*Table 2.6*). 15% of those with adulteration as their main theme described the addition of synthetic drugs, most often those for erectile dysfunction indications, including sildenafil, tadalafil, and vardenafil, or the slimming agents sibutramine (*Table 2.7*) (Ekar and Kreft, 2019; Singh et al., 2009).

A further 13% of the adulteration themed reviews described multiple combined adulterants (*Table 2.7*) (Posadzki, Watson and Ernst, 2013; Corns, 2003). 10% reported herbal substitution of specific species such as *Rhodiola sachalinensis* Boriss., and focused on the methods to authenticate CMP, including DNA analysis (Raclariu et al, 2018). Additionally, toxic contaminants such as heavy metals, and unexpected alkaloid content were identified in species such as *Tussilago farfara* L. (Ernst, 2002b; Kim et al., 2013). Adulteration from

prescriptions with unusually high doses of CMP containing arsenic sulphide were also reported (But, 1995). The complete list of the articles is attached in the appendix to the literature review (ALR) (*Table ALR 5*).

TABLE 2.6 SUMMARY OF THE MAJOR THEMES (MAIN FOCUS) FOR 40 REVIEWS THAT WERE PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES WITHIN WEB OF SCIENCE, AND TITLE AND ABSTRACT IN PUBMED DATABASES

Major theme of reviews	Number	Proportion of the 40 CMP quality related reviews (%) *
Adulteration	17	43
Adverse Events	9	23
Toxicity	9	23
Specific Reviews	5	13

** For clarity, numbers rounded (cumulative rounding error +2%)*

TABLE 2.7 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 17 ADULTERATION THEMED REVIEWS PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES IN WEB OF SCIENCE, TITLE AND ABSTRACT IN PUBMED DATABASES

Minor themes of the 17 reviews with a major theme of Adulteration	Number	Proportion of Reviews (%) *
Adulteration (Synthetic drugs)	6	15
Adulteration (Multiple types)	5	13
Adulteration (Substitution)	4	10
Adulteration and contamination	1	3
Adulteration and risk of incorrect prescriptions	1	3

** For clarity, numbers rounded (cumulative rounding error +1%)*

The second largest group of reviews, comprising 23%, mainly focused on the adverse events and their outcomes from such adulteration and prescription practices (*Table 2.8*). The reported effects were wide ranging, from a relatively mild nature such as digestive upset, to those that affected the central nervous system, heart, liver and kidney systems, some of which resulted in organ failure from toxic effects (Chou et al., 2018; But, 1995; Ernst, 1998).

TABLE 2.8 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 9 ADVERSE EVENTS THEMED REVIEWS PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES WITHIN WEB OF SCIENCE, TITLE AND ABSTRACT FOR PUBMED DATABASES

Minor themes of the 9 reviews with an Adverse Events major theme	Number of Papers	Proportion of Reviews (%) *
Adverse effects (CNS)	1	2.5
Adverse events (Cardiac and CNS)	1	2.5
Adverse events (Cardiac)	1	2.5
Adverse events (Digestive)	1	2.5
Adverse events (General)	1	2.5
Adverse events (Organ Failure)	1	2.5
Adverse events (Pain and CNS)	1	2.5
Adverse events (Systematic review)	1	2.5
Adverse events (Toxicity)	1	2.5

** For clarity, numbers rounded (cumulative rounding error +0.5%)*

The toxic effects themed reviews that represented 23% of the 40 reviews captured more specifically the toxic and significant adverse effects of the aforementioned heavy metals, synthetic drugs on liver and kidney health (*Table 2.9*). An increased awareness of the misconception that "natural is safe" within

Europe was illustrated in a review of the intrinsic toxicity of some aconitum species, and the seeds of *Strychnos nux-vomica* L., (Ekar and Kreft, 2019; Mosihuzzaman, 2012). Many of the species reported in recurrent toxic events due to intrinsic toxicity were those recorded in the classical CHM text Bencao Gangmu, 本草綱目, four centuries earlier that detailed 381 toxic medical plants that highlighted their historical persistence (Zhao and Liang, 2017).

TABLE 2.9 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 9 TOXICITY THEMED REVIEWS PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES IN WEB OF SCIENCE, TITLE AND ABSTRACT IN PUBMED DATABASES

Minor themes of the 9 reviews with a major theme of toxicity	Number of Papers	Proportion of Reviews (%) *
Toxic (heavy metals) and undeclared drugs	1	3
Toxicity (hepatoxicity)	3	8
Toxicity (intrinsic)	2	5
Toxicity (Renal carcinogenic)	3	8

** For clarity, numbers rounded (cumulative rounding error +1%)*

Particularly specific reviews comprised 13% of the 40 examined (*Table 2.7*). These were most often relatively narrow in scope and focused on the analysis of single plant genus such as *Panax ginseng* (Yap et al., 2005), or a particular area of healthcare, such as cancer (*Table 2.10*) (Chiu, Yau and Epstein, 2009). One review in particular took a broader historical approach in collating adverse events from incidents of adulteration throughout Europe and Russia, together with regional legislation (Sammons et al., 2016).

TABLE 2.10 SUMMARY OF THE MINOR THEMES (SECONDARY FOCUS) OF THE 5 REVIEWS OF SPECIFIC CASES OR SPECIES PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES WITHIN WEB OF SCIENCE, TITLE AND ABSTRACT FOR PUBMED DATABASES

Minor themes of 5 reviews with a major theme of specific cases or species	Number	Proportion of Reviews (%) *
Review of detection methods for Ginsengs	1	2.5
Review of quality issues in healthcare	1	2.5
Review of quality issues with CMP in Cancer treatment	1	2.5
Review of safety assessment of botanicals in food supplements in EU	1	2.5
Historical review	1	2.5

** For clarity, numbers rounded (cumulative rounding error -0.5%)*

2.4.2.2 Literature insights into the identity of quality issues

Peer-reviewed primary research journal articles resulting from the search "adulteration" or "misidentification" or "substitution" and "Chinese medicine" or "Chinese herb" in their titles produced publications directly related to the terms searched, as expected. Of interest is that the emphasis of the primary research in aggregate, in contrast to the review articles, was predominantly upon substitution, followed secondly by general adulteration (*Table 2.11*). This reversal of emphasis may not be particularly significant, as adulteration and substitution can be thought of as a continuum, wherein the presence at lower amounts of one plant in the bulk content of another could be considered as both substitution or adulteration, whereas in a case where all of the declared CMP is replaced, then it is more often considered as a complete substitution, as observed in 45% of the articles (*Table 2.11*). The complete list of the articles is attached in the appendix

to the literature review (ALR) (*Table ALR 6*).

The sources of many of the CMP quality issues appear interrelated, as described by 10% of the articles, in which medicinal plants are commonly misidentified (Xu et al., 2022; Kai et al., 2021), and 8% of articles outlining the potent medical effects of some plants in some instances misidentified that incorrectly prepared CMP are considered toxic (Doan et al., 2019; Grollman et al., 2007). The challenge to control quality in a similar manner to biomedical pharmaceutical manufactured products is highlighted in a few, 2%, of the articles that describe the natural variability of CMP (Gu et al., 2022; Scotti et al., 2019a). Although these articles indicate the identity of some common problems with CMP quality, as some of the problems can be causes of others, misidentification is related to erroneous substitution and is further relevant to potential toxicity and adverse events.

TABLE 2.11 SUMMARY OF THE MAJOR THEMES (MAIN FOCUS) FOR 173 PEER-REVIEWED ARTICLES PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES WITHIN WEB OF SCIENCE, TITLE AND ABSTRACT FOR PUBMED DATABASES

Major Theme of Articles	**Number of Articles**	**Proportion of Articles (%) ***
Substitution	77	45
Adulteration	48	28
Adverse Events	12	7
Misidentification	18	10
Toxicity	14	8
Variable quality	3	2
Traceability	1	1

** For clarity, numbers rounded (total rounding error +1%)*

2.4.2.3 Literature insights into why CMP quality issues occur

Examining the 173 articles further to gain insight into why these quality issue occurred generated a diverse number of reasons (*Table 2.12*). Most articles, 36%, either directly stated or inferred that intentional acts of substitution were involved in recurrent quality problems, and a related 25% due to misidentification which could lead to similar outcomes, albeit the former intentional and the latter unintentional resulting from erroneous substitution (Wei et al., 2019; Lin, Harnly and Upton, 2009). Combined they contribute to more than half, 61%, of articles that offer reasons why quality issues occur in CMP. Many, 20%, of the articles attest to difficulties with detecting CMP issues and its role as a challenge to controlling their quality (Zhao, Jiawei and Jihao, 2022; Ma et al., 2018). Less, 6%, direct attention to the role toxicity contributes to the general situation of CMP quality issues (*Table 2.12*). (Chen et al., 2010; Bensoussan et al., 2000).

TABLE 2.12 SUMMARY OF "REASONS QUALITY ISSUES OCCURRED" IN PEER-REVIEWED ARTICLES THAT WERE PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES IN WEB OF SCIENCE, TITLE AND ABSTRACT FOR PUBMED DATABASES

Reason why quality issues occurred	Number of Articles	Proportion of 173 Articles (%) *
Intentional substitution	63	36
Misidentification	43	25
Detection difficulty	34	20
Toxicity	11	6
Variability of botanicals	5	3
Not specified	5	3
Perception that "natural herbs are safe"	4	2
Insufficient data	3	2
Multiple causes	2	1
Difficult to trace	1	1
Unlicensed herbs	1	1
Information and packaging unreliable	1	1

** For clarity, numbers rounded (total rounding error +1%)*

Two aspects found in the phase one, more general review of CMP quality described earlier were also supported while examining the primary research articles. The first, that of the changing perception of naturally herbs being safe in 2% of articles, and secondly the natural variability of herbal quality in 3%, are highlighted as the reasons why quality issues occurred (Jordan, Cunningham and Marles, 2010; Xu et al., 2018; Zhang and Nie, 2010).

However, exploring the articles revealed a number of additional reasons related to gaps in current knowledge. In 2% of the publications authors expressed that there is insufficient data on CMP quality issues, such as adverse events as a result of deficiencies in recording and reporting (Drew and Myers, 1997; Patel et al., 2012). Further, in cases where investigations have occurred, there is insufficient data to draw firm conclusions on the causes of quality issues. In some cases herbs not likely causing adverse events may be ingested, but still implicated in the case, such as in the forensic examination of those poisoned from monkshood extract, therefore overestimating the effect of toxicity on consumers (Hofmann et al., 2020a). Whereas others emphasised that there may be many drug interactions with CMP that are still undiscovered, leading to an underestimation of their effects and contribution to quality issues (Bensoussan et al., 2000; Homma et al., 1995). This an area that requires further research. Reviewing both reviews and primary research over the 32-year period brings into question how much the general body of literature reflects the underlying and full extent of quality issues, and how accurately it represents the current situation. This is further suggested in other articles that communicate that much data currently published may be from “official” or “registered” sources that capture information related to herbal medicines that are more likely licensed, however, many are as yet still remain unlicensed, largely to an unknown scale and extent (Yee et al., 2005). Additionally, stated claims and information relating to the content of herbs on packaging may not be accurate, and therefore even in cases where a quality issue may be detected, attempting to trace the cause or relationship to other similar issues remains unknown (Calahan et al., 2016; Kim et al., 2013). One article described how misidentification may be more

widespread than currently documented, with new DNA analysis indicating likely mis-authentication and therefore inter-substitution of many unknown species, such as that demonstrated for *Gentiana* species, *G. dahurica*, *G. siphonantha*, *and G. officinalis* (Zhou et al., 2018). Some articles, 3%, did not clearly state or infer a cause why a CMP quality issue could occur (*Table 2.12*). (Wang et al., 2022; Yang et al., 2022).

Although examining original research to inform why the quality issues may have occurred, their occurrence does not necessarily reflect the reasons why they recurred and persisted. This prompts a question not adequately addressed by the general body of literature: if such quality issues are known, and therefore detectable, then why do they continue to recur or become persistent? This question emerged as a central focus for the investigation.

Another examination of the primary research publications was conducted to assess if insights could be gained to inform this question of persistence. Specifically, do authors report or infer why these known and detectable problems of misidentification, substitution and adulteration persist?

2.4.2.4 Literature insights into why CMP quality problems persist

Examining the 173 primary research articles generated 12 potential reasons why CMP quality could persist. These were based on interpretation: where, for example, authors clearly expressed difficulties with detecting quality issues, then “difficult to detect” was interpreted as a potential reason for such issues to persist; when authors indicted that a particular issue occurred due to the high value of a

CMP, this was interpreted as “value profit motivation”, and similar for the others shown in (*Table 2.13*). The complete list of the articles and individual analysis is attached in the appendix to the literature review (ALR) (*Table ALR 6*).

In examining the 173 articles related the CMP quality issues, a striking absence of authors addressing their persistence is apparent. This is in contrast to numerous examples and specific cases of quality problems occurring, suggestions for improvements, and further research.

TABLE 2.13 SUMMARY OF “INTERPRETED REASONS WHY QUALITY ISSUES COULD PERSIST” FROM PEER-REVIEWED ARTICLES THAT WERE PUBLISHED BETWEEN 1990 TO 2022 WITH; “ADULTERATION”, OR “MISIDENTIFICATION” OR “SUBSTITUTION”, AND “CHINESE MEDICINE” OR “CHINESE HERB” AND “QUALITY” IN THEIR TITLES IN WEB OF SCIENCE, TITLE AND ABSTRACT FOR PUBMED DATABASES

Interpreted reasons why CMP quality issues could persist?	Number of Articles	Proportion of 173 Articles (%) *
Difficult to detect	117	68
Value Profit Motivation	29	17
Error	3	2
Toxicity	6	3
Accepted practice	2	1
Perception	6	3
Incorrect Herb Usage	4	2
Variability of botanicals	1	1
Multiple reasons - complex	1	1
Unlicensed herbs not tested	1	1
Analytical fraud	1	1
Not investigated sufficiently	2	1

** For clarity, numbers rounded (total rounding error +1%)*

This interpretation shows that difficulties with detection and motivation for profit could combine as prime potential reasons why CMP quality issues might persist in 86% of articles reviewed. Error, toxicity and other reasons combined constituted the remaining proportion of articles reviewed (*Table 2.13*).

Notwithstanding the many demonstrated advances in analytical instrumentation, challenges detecting problematic CMP quality issue are still evident. Comprehensive studies showed that even with 184 well-developed standard and accepted testing methods that are capable of detecting 166 types adulterants over the 14-year period between 2003 to 2017, they were highly limited in capturing the full extent of global adulteration and counterfeit products, concluding that information available and therefore understanding of the situation is still “inadequate” (Xu et al., 2019). Ching et al. (2018) analysed 487 CMP products in the consumer marketplace, finding 1,234 adulterants were still present even though highly sophisticated analysis methods and extensive legislation were in place to test these products in advance of distribution to consumers. Still, 14 severe adverse events and 2 fatalities were documented. Deng (2002) further concluded that it is not just detecting quality issues that are problematic, but defining and determining the quality of complex CMP, even with advanced detection technology and regulation in place, primarily that there still remains “difficulties...[with identifying CMP]…substances and active ingredients”.

The motivation for profit featured highly for potential reasons why CMP quality issues could persist. This included high demand causing scarce CMP and therefore further motivation for its substitution (Cunningham and Long, 2019).

Desire for increased yields has also prompted higher amounts of fumigants (Fan et al., 2022). There is a predominance apparent in the substitution of more expensive CMP species, such as; *Ophiocordyceps sinensis* (Dunn) Dorr (Zhang et al., 2015), *Ganoderma lucidum (Curtis) P. Karst.* (Shi et al., 2022), *Panax notoginseng* (Burkill) F.H.Chen (Chen, Tan and Li, 2020; Zhou et al., 2020), *Panax ginseng* C.A. Meyer (Yap, Chan and Lim, 2007), and *Dendrobium huoshanense* Z.Z.Tang & S.J.Cheng (Hao et al., 2021). The relationship between quality, value and patterns of adulteration in the herbal supply chain has been established for *Rhodiola rosea* L. and *Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba, (Booker et al., 2016). Those seeking profit with an acquired knowledge of analytical testing requirements for CMP have fraudulently added material to increase their value, including species *Actaea racemosa* L. (Jiang et al., 2011), *Vaccinium myrtillus* L. (Penman et al., 2006), and multiple other species (Bessaire et al., 2019).

It appears that current approaches to detecting and preventing CMP quality issues still require further consideration to adequately meet the challenges presented. Particularly when it is apparent that the same CMP quality issues continue to recur despite advancements, and furthermore from the standpoint of CMP problems in aggregate it is a problem of persistence that has not been adequality addressed nor substantiated in the literature. Reconsideration of CMP quality issues from an alternative perspective to inform new types of solutions is warranted.

2.4.2.5 Literature insights into solutions to CMP quality problems

Assessing the literature specifically for previous solutions that have been proposed for well-known, recurrent and document CMP quality issues such as misidentification, substitution and adulteration shows that there is a central emphasis on the continued reliance upon analytical method development as a solution to CMP quality issues. This was found in the majority, 72%, of the articles reviewed, along with increased pharmacovigilance in 10%, and further legislative developments, 7%, (*Table 2.14*). However, as previously described, these approaches have significant limitations, and their success as a comprehensive solution when viewed historically is questionable. Furthermore, detailed descriptions of standard analytical test methods are available in the public domain which can be accessed by those who wish to circumvent detection and perpetrate nefarious acts which affect CMP quality, including those for profit motivated actions (Mudge, Betz and Brown, 2016). Pharmacovigilance is highly dependent on the detection that these somewhat limited analytical methods provide, and reporting quality issues is hampered by known low reporting rates (Pittler and Ernst, 2003), and insufficient data (Drew and Myers, 1997; Patel et al., 2012). Difficulties in ascribing cause to reported incidences adds to the already complicated situation (Chan, Zhang and Lin, 2015). Pharmacovigilance systems in place in Europe, UK and China are limited in their design as they are primarily based on recording biomedical pharmaceutical drug-adverse outcomes. Such systems require significant development to more fully capture plant based medicine outcomes and adverse reactions (Kim, Woo and Han, 2021). Although pharmacovigilance monitoring and recoding systems are essential, they do not likely to capture CMP quality issues which do not present in overtly apparent physical reactions, such as psychiatric disturbances (Ernst, 2003).

TABLE 2.14 SUMMARY OF "SOLUTION TO CMP QUALITY ISSUES" FROM PEER-REVIEWED ARTICLES THAT WERE PUBLISHED BETWEEN 1990 TO 2022 WITH; "ADULTERATION", OR "MISIDENTIFICATION" OR "SUBSTITUTION", AND "CHINESE MEDICINE" OR "CHINESE HERB" AND "QUALITY" IN THEIR TITLES IN WEB OF SCIENCE, TITLE AND ABSTRACT IN PUBMED DATABASES

Solutions in Articles	Number of Articles	Proportion of 173 Articles (%) *
Analytical development	124	72
Pharmacovigilance	18	10
Legislation	12	7
Not proposed	10	6
Education	5	3
Predictive toxicology and omics	1	1
Selective sourcing and regulation	1	1
Study quality issues in context of whole supply chain (value chain)	1	1
Supervised prescription by TCM Practitioner	1	1

** For clarity, numbers rounded (total rounding error +2%)*

Although researching the area of CMP quality issues appears somewhat challenging from the literature, some adopting more comprehensive and multi-disciplinary approaches appear to have advanced knowledge and contributed to solutions within the field. *Astragalus membranaceus var. mongholicus* (Bunge) P.K. Hsiao, when researched from a broader perspective that included its cultural, traditional use, supply chain, value, and commercial contexts, showed considerable advancement in knowledge around previous limited understanding of why, where and how it was commonly adulterated (Bi et al., 2020). These types of investigations incorporated multiple sources and methods, including interviews with stakeholders in the herbal supply chain to explore their varied perspectives,

together with considering how the testing and recording of quality is conducted in the supply chain as a whole. Such studies show that significant gaps in knowledge remain in the literature-base in considering the testing, recording and many practical considerations that influence CMP quality in herbal supply chains. These more muti-perspective investigations often proposed solutions orientated towards better integration of supply chains from producers to consumers (Bi et al., 2020). Similarly, this is shown in the case of *Cistanche deserticola* Ma., for which scarcity and reduced quality became problematic. More comprehensive research approaches studying the supply and value chain in combination with both qualitative ethnographic and quantitative analytical investigation techniques have led to more specific, relevant and potentially effective solutions. These included proposals for specific methods to increase traceability and more equitable benefit sharing in the supply chain to reduce reliance on adulteration practices for supporting livelihoods, in conjunction with tighter integration along supply chains (Jiang et al., 2021). The concept of “Ethnobotanical-assembly”, demonstrated for the Genus *Lycium* CMP, a term developed to describe a more comprehensive approach of inquiry when investigating together the cultural, value, medicinal, social and supply aspects of CMP, in order to better understand quality issues and develop more relevant and potentially more effective solutions (Yao et al., 2018, 2021). Explorations of medicinal plants and quality issues in other South Asian cultures using such multidisciplinary, mixed approaches have shown similar successes in advancing knowledge of the field. Particularly, around insights into the identity of what medicinal plants are used, how they were used traditionally, together with how their cultural context influences their quality and transmission into other cultures, including Europe and the UK (Bhamra, 2016).

Such studies have produced a rich and varied knowledge-base from which future researchers can draw, particularly those who wish to adapt existing, and develop new, medicinal uses based on known but inaccessible knowledge. These aspects support authenticating medicinal materials more reliably.

However, the successes apparent in these relatively recent publications comprise less than 1% of the combined in the literature-base reviewed in the field of CMP quality and problematic issues. More research is required to demonstrate their contribution to the wider knowledge-base. The successes apparent with these approaches that collate multiple perspectives of key informants, together with the benefits of analytical testing of medicinal plants from Chinese and other south Asian traditions, informed how the investigation of persistent CMP quality issues as documented in this PhD research was conducted.

2.4.3 International initiatives to solve CMP quality issues: GP-TCM and BAPP

Reviewing the literature from 1990 to 2022 suggests that attempts to deal with CMP quality issues predominantly centred around controlling their quality. Particularly through mandated pharmacopeia analytical testing, and to further restrict CMP from entering the EU-UK market through the process of licensing. This was also reflected in the foremost collective research initiative to date between the EU and China to identify important aspects of TCM practice, CMP quality, and its future place in the EU, conducted by the GP-TCM.

The “good practice in traditional Chinese medicine research in the post-genomic era group” (GP-TCM) was the first large-scale European Union financially supported consortium that focused specifically on coordinating research and actions of experts in traditional Chinese medicine globally. They discussed improving the practice of TCM by identifying “priorities, challenges and opportunities” through the collective work of approximately 200 researchers in 107 institutions from 24 countries. Their work represented a landmark in state-of-the-art research in the early 21st century that was documented in a seminal collection of 20 articles published in a special issue of Journal of Ethnopharmacology (Xu and Bauer, 2012).

A core activity involved collating opinions of those in the group and other experts to identify the “priorities, challenges and opportunities” through a survey and agreed voting system. Some 187 respondents comprised 77 GP-TCM members and an additional panel of 110 expert key informants identified by them, who mainly resided in the EU, 47%, including the UK, and some in China, 34%, the others, 19%, were based in regions world-wide including the USA, Canada, Australia, India and Switzerland.

The predominant challenge jointly agreed by the group, out the 13 in total proposed, was to control the quality of TCM. The specific primary agreed priority action of the group members was to better evaluate the quality of CMP in light of “frequent misidentification, adulteration and contamination”, after general points on improving clinical effects through study of the mechanisms to achieve better patient outcomes for diseases were agreed by all participants (Uzuner et al., 2012, p465).

The group's recommendations on how to advance the situation varied. Some thought improving the practice of CMP and its quality could best proceed through consolidating the current knowledge-base using conventional approaches, whereas others proposed novel approaches to gain new perspectives.

More conventional proposals included better characterisation of CMP quality by improving how basic research data is collected and reported to establish a more credible evidence-base to further support its integration into modern conventional biomedical practice. This included research to generate baseline data of how natural phytochemical variation is affected by the locations and climate in which CMP grow (Zhao, Guo and Brand, 2012), and their various preparation and formulation methods (Luo et al., 2012). It also proposed to more reliably collect data to further understand the relatively subjective methods and different diagnosis styles used by Chinese medicine practitioners when observing, listening, and questioning patients according to traditional Chinese methods in conjunction with pulse and tongue diagnosis (Jiang et al., 2012). These insights were hoped to inform improvements in clinical trials that could incorporate the individual diagnoses and more personalised prescriptions used by practitioners, in matching many diseases to one herb and many herbs used for one disease (Tejedor Garcia et al., 2012). The concept supported evaluating trial outcomes based on the individual intent of the practitioner and subjective improvement reported by each patient, rather than using single herbs for a single clinical indication in many patients and measuring a limited set of outcomes, yet still maintaining good research rigour and an emphasising evidence-based practice (Verpoorte, 2012; Flower et al., 2012). They collectively proposed consolidating

basic empirical data for CMP quality using existing methods to better define the phytochemical composition, variation, and clinical effects in the context of how the CMP is prepared and prescribed. This further informed proposals for improved standards in Chinese medicine training and practice (Robinson et al., 2012), in addition to regulation worldwide (Fan et al., 2012). The group collectively aimed to collect data relating to the quality of CMP beyond the scope of relatively limited and controlled conditions in clinical trials, to extend data collection while monitoring patients post-prescription in the varied conditions and influences of their daily lives (Shaw et al., 2012; Zhang et al., 2012).

In addition to these relatively conventional approaches suggested by the group, those adopting more novel strategies to assess quality variations in CMP were more wholistic and multi-disciplinary. Advances in analytical instrument and computer technology enabled analysis and identification of multiple chemical components in CMP simultaneously, that when visualised together produced a characteristic pattern or phytochemical “fingerprint”, that if altered could indicate a change in herbal composition and therefore quality (Sheridan et al., 2012). A similar concept was applied when changes in metabolic markers were observed in subjects who ingested multiple CMP that when combined represented metabolic fingerprints. This considered the effects of herbal medicines as a network of biological interactions as studied in the field of systems biology (Pelkonen et al., 2012). The exponentially increasing amounts of such data accumulated in computer databases relating the effects of individual chemical compounds on human metabolism were correlated to those in medical herbs through the field of bioinformatics using *in-silico* software algorithm-computer

processing techniques (Barlow et al., 2012). This aided understanding of the rationales for choosing specific CMP and their combinations in traditional practice retrospectively, in addition to prospecting new applications. It also supported the analysis and synthesis of the large amounts of data generated in clinical trials in the field of metabolomics (Liu and Cheng, 2012). A confluence of multiple disciplines occurred at this time in a considerable and focused effort to better understand CMP quality and its medicinal effects by combining advances in the chemical, biochemical and genetic analysis fields. This incorporated instrumental-computer analysis, statistical, chemometric, transcriptomics, proteomics and metabonomics, termed collectively as “omics” (Ouedraogo et al., 2012; Buriani et al., 2012). It marked a new era in combining a muti-disciplinary, wholistic approach to characterising natural variations CMP quality and linking them to their medicinal effects in the body.

The collective contribution and international collaboration within the GP-TCM was considerable and a landmark in CMP research. It successfully advanced proposals in strengthening research rigour and advanced standards in data collection, education and practice. It co-ordinated and focused the benefits afforded by multiple disciplines to better differentiate the natural variation of CMP quality from other non-natural factors that could influence its quality and clinical effects.

Although CMP quality was better characterised, and recommendations were proposed, the primary challenge identified by the group to control the quality of CMP was not yet significantly advanced in practice. Analysis methods and

strategies were much more clearly defined, and the priority identified by the group members to “evaluate the quality and safety” of CMP in light of frequent adulteration was theoretically advanced and did inform later research. However, pragmatic, effective actions to prevent the priority issue, that of similar types of frequently recurring adulteration, were still forthcoming and are still in progress.

Notable exceptions that advanced the field considerably were similar in approaches to those found in the previously described literature reviews. Some in the group studied individual CMP-specific metabolic changes, analysis methods and effects within the human body. Others generated new field-based data combining quantitative laboratory chemical analysis, spatial geographic variation of herbal quality together with more qualitative social sciences perspectives, in collecting the opinions of supply chain stakeholders and experts. This placed the analytical data in a wider context that informed on whom and why herbal quality varied, substantiating that the high value of herbs motivated action and influenced variation of herbal quality variation at different supply stages in the “value-chain” (Booker, Johnston and Heinrich, 2012).

Outside the EU-China axis, in the USA three non-profit groups formed the Botanical Adulterants Prevention Program (BAPP) in 2011: the American Botanical Council, the American Herbal Pharmacopoeia, and the University of Mississippi's National Centre for Natural Products Research (Blumenthal et al., 2019). This group is the foremost American collective initiative to identify, research and disseminate information relating to adulteration of herbal products. Although the BAPP doesn’t specifically focus on CMP quality issues, and is

inclusive of both many traditional practices and modern herbal products such as dietary supplements, it is a valuable source of information that has demonstrated adulteration practices are common both in frequency and among diverse types of medicinal materials. These include food supplements, teas, and products marketed as “natural” with various herbal constituents (Tripplett, 2019). In common with the GP-TCM the BAPP have identified the increasingly sophisticated methods by which those seeking to perpetrate economically motivated adulteration acts, that require an in-depth knowledge of analytical methods and testing requirements. These include using various non-authentic materials to simulate higher chemical content and therefore make them falsely appear to be of better quality and cost, due to the knowledge of over- or under-specific detection principles of the instruments used to test the medicinals. Their reports have included examining the CMP *Ginkgo biloba* L., *Hypericum perforatum* L., *Actaea racemosa* L. in addition to those from other medicine traditions (Gafner et al., 2018). Since 2012 the BAPP has formally collaborated with the High Performance Thin Layer Chromatography Association (HPTC Association), in recognition of the analytical method’s suitability and versatility in plant analysis. This technique is sensitive enough to identify plants and their adulteration, yet not overly specific to fraudulent materials that can be added to pass other analytical techniques using more sophisticated detection technology (Kowalska and Sajewicz, 2022). However, it can also be used effectively in combination with other techniques (Reich and Schibli, 2007).

The BAPP also recognised the limitations of primarily using pharmacopeia analytical method-based testing and legislation as a solution to the global

adulteration of medicinal plants. It acknowledged that a communal effort is required from those in all stages of the herbal supply to assure herbal quality, and that problematic quality issues in herbal medicine, and their solutions, necessitate a greater range and combination of principles that include training, aspects of human motivation, behaviour, value, and economic factors collectively (Blumenthal et al., 2019).

Successful approaches of researchers undertaking multi-disciplinary work (such as by Jiang et al., (2021), Bi et al., (2020), Yao et al., (2018), Bhamra, (2016), Booker et al., (2012) and Heinrich et al., (2010)), and the response of the GP-TCM and BAPP, informed the basis of this PhD thesis research. Their body of works together with others described in this literature review collectively advanced the field of herbal medicine and its quality. They characterised herbal quality variation, described their transmission in to Europe, and identified influences of value and economically motivated actions.

However, the question of why CMP quality issues can still continue to recur, even though these factors are known, still stands. The consequences are known and, further, these can be detected by highly developed analytical instruments in an environment of extensive regulation that mandates testing, yet this apparently basic question has still not been substantively answered.

2.5 Limitations of the literature review

This literature review has limitations, both those inherent in the nature of a scoping review and others specifically related to how it was conducted in this thesis. Literature reviews are often appraised in the context of more extensive "gold-standard" systematic reviews (Booth, 2001). Scoping reviews tend to be less focused than systematic reviews, require multiple stages within one review, and possess inconsistencies often not tolerated in the practice of systematic reviews, such as single rather than double reviewers (Waffenschmidt et al., 2019). Although scoping reviews are widely-published they still lack a universally agreed process and tend to have less critical narrative in favour of identifying trends in previously published literature (Peters et al., 2015).

These generally acknowledged drawbacks are also evident in this review that shifted from an initial highly general focus from scoping the field of CMP quality, to a highly specific area within the field, that of misidentification, substitution and adulteration, with many other areas overlooked. It is single-reviewer rather than multiple-reviewer. This review did not follow a specific methodology, and was concerned less with critically appraising researchers' work than identifying general trends and selective information. Furthermore, only two databases were included of the many that are available.

However, in retrospect and taking these limitations into account, the scoping review has completed the objective set out to explore and analyse the contemporary peer-reviewed published knowledge-base relating to the quality of Chinese medicinal plants. This broad scoped, part-historical, part-contemporary

field, with elements of legislation, analytical testing, adverse events, and dealing with an undetermined area such as medicinal plant quality, required a broad and adaptable review tool.

Specifically, it completed the main objective in that the review has highlighted that the identity of CMP quality issues have yet to be determined, and the reason for their persistence is not yet substantively established and requires further investigation. The review identified previous approaches that successfully advanced the field, particularly in combining multi-disciplinary research that take the perspectives of those within a herbal supply chain into account, and incorporated analytical testing such as HPTLC. A blend of these were chosen as a foundation on which to base and inform this investigation.

Of the many review types available (Grant and Booth, 2009), this scoping review completed its objective.

2.6 Conclusion

As CMP proliferated throughout Europe between 1990 to 2022, it brought with it considerable quality issues such as misidentified, substituted and adulterated medicinal plant material.

The predominant response centred around attempting to control the quality of CMP, particularly by using increasingly sophisticated analytical testing techniques, better supply handling practices in the form of GxP and restricting CMP to the consumer market through a licencing process. Although these

approaches were productive in better characterising CMP quality attributes, and informing what quality issues occurred, the strategy was not successful in stemming these specific quality issues.

Notwithstanding many developments in testing technology and legislation, similar quality issues documented historically in Chinese classical texts still recurred at the end of the review period in 2022, and persist in this Contemporary Era.

Foremost global strategies proposed to deal with CMP quality issues from the European medicines agency, Chinese National Medical Products Administration, and internationally by the World Health Organization are derived from, and based upon, previous similar approaches using increasingly sophisticated analytical testing, GxP, and efforts to harmonise the two internationally. However, as these are based on similar previous strategies they embody their inherent limitations. Consideration of other approaches through further research is warranted.

Multi-disciplinary research incorporating cultural, traditional use, supply chain, value, and commercial contexts of medicinal plants demonstrated significant advances to the field. Further research based on these approaches could perhaps advance investigation of why similar and well-documented Chinese medicinal plant quality issues that emerged centuries ago still recur in this Contemporary Era of advanced analytical testing and extensive regulation. The identity of CMP quality issues that occur, their scale, and why they persist require further investigation.

Chapter Three The KI Study

Consulting with Key Informants

3.1 Aim and objective of the KI study

This study aims to explore the knowledge of key informants expert in the field of Chinese medicine to gain insight into why similar, well-documented Chinese medicinal plant quality issues recur, and how this persistent problem can be improved.

Problematic CMP quality issues that emerged centuries ago still persist, notwithstanding the many apparent advancements in analytical testing and legislation. This investigation sought to explore why they persisted and to propose improvements by achieving the objective:

> To explore the knowledge of key informants expert in the field of Chinese medicine with questionnaire and interview tools using thematic analysis to acquire insight into why similar and well-documented Chinese medicinal plant quality issues recur, so that improvements can be proposed to the persistent problem.

The exploration was guided by three questions:

1. What are the main Chinese medicinal plant quality issues that persisted?
2. Why do the issues recur?
3. What improvements can be proposed?

3.2 Overview of the KI study

Consulting with key informants contributed to clarifying the identity and scale of the main quality problems, generated insights into why they recurred, and informed improvements for these persistent quality problems.

A trial questionnaire was conducted as a pilot study to explore key informant responses to questions intended to inform the three central thesis research questions. Although the opinions this captured were varied and detailed, the questionnaire format did not allow for further clarification and expansion of the points key informants raised. Therefore, follow-up interviews were conducted in a semi-structured format that allowed open discussion with questions that were found to elicit the most response during the questionnaire process.

Eighteen key informants completed a total of 20 consultations, five in the pilot study and 15 interviews. Two key informants completed both the pilot questionnaire and interview. Their opinions were explored using thematic analysis and visually illustrated in a heat-map, alluvial chart, and tabular formats. The investigation generated insights into the identity of the main quality issues, their scale and why they persisted. Improvements were proposed.

Figure 3.1 outlines the process from forming the initial research questions to developing the initial pilot questionnaire. *Figure 3.2* summarises the subsequent creation of the semi-structured interviews from the questionnaire findings to completing the KI study by informing the research questions.

FIGURE 3.1 OVERVIEW OF THE KI STUDY PROCESS FROM FORMING RESEARCH QUESTIONS TO COMPLETING THE PILOT QUESTIONNAIRE

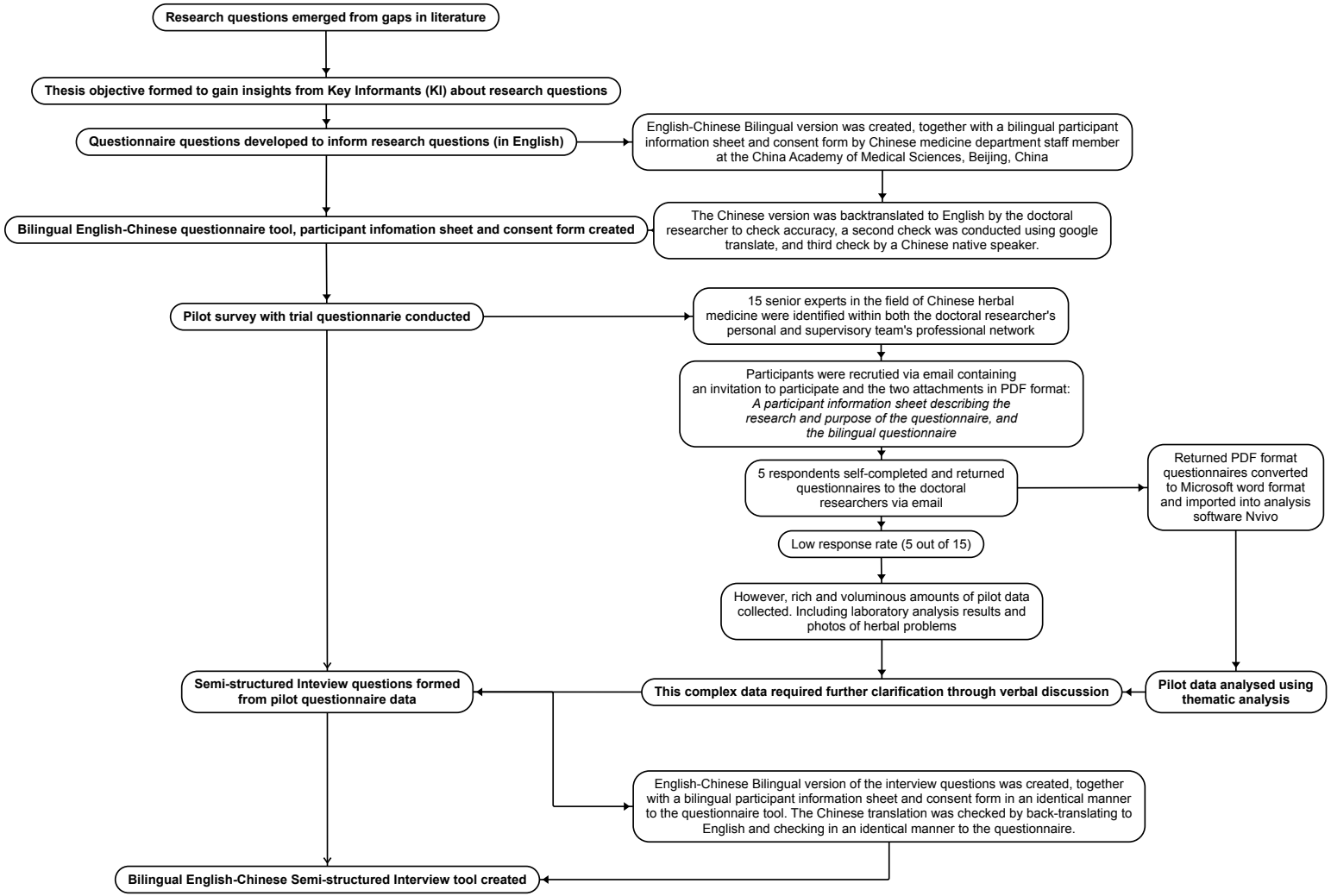


FIGURE 3.2 OVERVIEW OF THE KI STUDY PROCESS FROM FORMING THE SEMI-STRUCTURED INTERVIEW TOOL TO COMPLETING THE STUDY BY INFORMING THE RESEARCH QUESTIONS

3.3 Background

A number of research methods have been used to collect information from participants as a systematic means of inquiry (Crabtree and Miller, 1992). Some authors describe up to 28 approaches (Tesch, 2013), while others describe the process as a sequential “tree” of potentially unlimited possibilities (Wolcott, 2008). These have emerged from research explaining phenomenon (Munhall and Oiler, 1986), as a means develop theories based on experiences (Corbin and Strauss, 1990), creating records of observations (Morse, 1990) and developing multiple interpretations of such records or practices (Denzin and Lincoln, 1994), among others (Creswell and Poth, 2016). Their use has become increasingly blended in research (Denzin and Lincoln, 2005) and may broadly be considered as ethnographic research (Given, 2008).

Although ethnographic methods vary considerably in their approaches, when consulting with key informants they commonly converge in their practical application and suitability to this research around their basic requirement to sample information provided by participants with either an individual or combinations of survey, questionnaire or interview tools (Miles and Huberman in Creswell and Poth, 2016). Questionnaire and interview tools were adopted for this research as surveys typically require a large number of respondents not practically available for this relatively niche research area. Key informants have played central role in research as they possess specific, specialist and conceptually ordered expert knowledge relevant to the area studied (Marshall, 1996). The questionnaire and interview tools were used in this research to inquire specific, specialist and conceptually ordered knowledge from key informants

expert in the field of Chinese herbal medicine. Specifically, knowledge they possessed relating to the scale, identity, why they recurred, and any suggested improvements to the issues.

Questionnaires have been widely used in research, from commercial market research (Reynolds, Diamantopoulos and Schlegelmilch, 1993), evaluating political and social issues (Bradburn et al., 2004), education (Boynton and Greenhalgh, 2004), sociology (Eaden, Mayberry and Mayberry, 1999), and as clinical tools (Moskovitch, Mount and Davies, 2020), in addition to others (Lietz, 2010). Bell, Bryman and Harley referred to it as a "self-completion" tool of inquiry (Bell, Bryman and Harley, 2018), whereas Fowler considered the questionnaire a tool for measurement in surveys (Fowler, 2013) that allows relatively closed responses to be quantified. Whereas, Bell et al., referred to the questionnaire as a "self-completion" tool of inquiry (Bell et al., 2018), in which open responses could be expressed and qualified. In this research, both aspects were blended together in one questionnaire where some questions were intended to draw responses that can be quantified and others, more open, could be examined qualitatively from a number of perspectives.

An "interview", or exchange of views, has been described by Kvale as "a conversation, whose purpose is to gather descriptions of the "world" of the interviewee", so that it may be interpreted by the interviewer to inform their perspective (Kvale, 1996). Meuser and Nagel (in Flick, 2006) described the type of interview in this research as a "semi-structured...expert interview". They are semi-structured as the questions do not seek binary answers, instead they are

open, posed in manner which both allows and encourages expression of opinions and ideas.

The questionnaire used in this investigation was composed with the principles of posing clear and concise inquiry to elicit relevant responses, as described by Jones, Baxter and Khanduja (2013). The questionnaire were used to trial questions for subsequent use in an interview to consult with key informants, and collect pilot data. The number of questions were later reduced and used in a semi-structured interview format.

3.4 Ethical considerations

Ethical approval for this research was conducted under the University of Westminster application ETH1718-1510, completed, 27th March 2018, Class 1: research with no or minimal ethical implications. The ethics application is attached in appendix to the KI study (AKI), AKI 1 *Ethics application.*

The research was conducted according the university requirements that included: safeguarding participants; adverse events and incidents would be reported; there was valid consent and participant information; health and safety considerations were in place; and research data were protected and secure, among others (University of Westminster, 2018).

Some ethical considerations are warranted when engaging participants as they express their professional and personal opinions. Cohen considered interviews as an “intrusion into respondents’ private lives”, and that an ethical researcher should consider this highly, and at the very least obtain consent. The interview process could be intimate and create a space in which interviewees may regret or not be aware of the impact of the information they give. It can develop in to a “quasi-therapeutic” environment where unintended things are voiced (Cohen, 2007). Confidentiality and anonymity were therefore integral to this research. All participants were informed and consent was obtained in written format. Instructions were included in the consent form for all participants, which explained that they may choose to discontinue the interview at any stage without prejudice. Such concerns are also relevant to questionnaires as written responses are given in a private, relaxed context may, when viewed in other contexts, be interpreted differently from those intended. Choudhury also highlighted that participants may misinterpret questions and answer in an unintended manner, when responding without the benefit of the researcher’s presence to confirm intended meanings. Misinterpretation by the researcher may also occur, through lack of rapport, body and verbal language cues that would otherwise be present in a personal context (Choudhury, 2015).

Although these points may not seem as pertinent when dealing with a group of well-educated professionals, all of whom speak and present in public in the course of their work, it was still considered foremost during both the questionnaire and interview process.

3.5 Methodology

3.5.1 Development of the interview tool

A list of 17 questions were noted relating to issues with CMP quality apparent during the literature review and which contributed to forming the central thesis research questions. These 17 questions were initially trialled as a questionnaire in addition to introductory “warm-up” questions with five key informants (*Tables 3.1 and 3.2*). Eight of the questionnaire questions generated significantly verbose responses which highly informed the three central thesis research questions. These eight questions were chosen and formed the basis of a subsequent semi-structured interview conducted with 15 key informants.

The wording of the pilot questionnaire questions was guided by that of Jones et al., “answering the questions you want answered ....”with questions that are” clear, concise and without bias” (Jones et al., 2013). Clarity was achieved through the simplicity of the language used. Conciseness was achieved by avoiding double-barrelled questions and keeping them brief. Bias was minimised by prompting the respondent to give their view and not asking leading questions, for example, instead of asking “what are the problems associated with Chinese medicine quality?”, asking “Do you think there is a problem with the quality of Chinese herbal medicines...?” Clarity was considered foremost to maintain research rigour through credibility and transparency throughout this research (Green and Thorogood, 2018).

It was explicitly expressed that it was acceptable for both expansion of any answer, or not to respond to any individual questions, so that authentic responses were encouraged. It was intended to minimise responses not relevant to the questions posed from participants feeling obliged to offer a response.

The introductory section had 17 substantive questions. Section two, together with a participant information sheet and consent form, were translated to Chinese by Ms. Yuan Yuan, a Chinese medicine researcher at the Chinese academy of medical sciences, Beijing, China. The translations were back-translated to English by the doctoral researcher using Google translate to verify the content. A secondary check of the translations was conducted by native Chinese speaker Xixi Yang. No modifications were necessary.

The list of the bilingual participant information sheet, consent form and pilot questionnaire tool, together with the complete thematic analysis, are appended in the *Appendix to the KI study* (AKI), sections AKI 2, 3, 4, 5 and 6, respectively.

The first section of the questionnaire, 1.1 to 1.4, established the eligibility of the respondents possessing at least ten years' experience in the Chinese medicine field, and served as a "warm-up" for participants as they described their professional details in advance of offering more complex opinions (*Table 3.1).*

TABLE 3.1 SECTION 1 PILOT QUESTIONNAIRE QUESTIONS

Section 1	Pilot questionnaire questions
1.1	Please indicate which field(s) you feel most closely represents in your area(s) of expertise
1.2	Have you been working or studying in your own speciality field for more than 10 years?
1.3	Have you been involved in any capacity through work or study with Chinese herbal medicine?
1.4	What percentage of your career would you approximate has been spent involved or any way related to Chinese herbal medicine?

Questions in section two of the questionnaire aimed to draw opinions around topics relating to the three research questions. A tag question was included to create the opportunity to speak with other key informants, from which three further key informants were suggested. However, all three that were suggested by respondents had already been invited (*Table 3.2*).

TABLE 3.2 SECTION 2 PILOT QUESTIONNAIRE QUESTIONS

Section 2	Pilot questionnaire questions
2.1	Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?
2.2	If yes, what are the main issues?
2.3	On what scale would you say a quality problem exist?
2.4	Could you give examples of issues you have had to deal with personally?
2.5	What is the origin of the problems?
2.6	Are we effective at detecting these problems?
2.7	What circumstances or factors have allowed these problems to occur?
2.8	Are there specific Chinese herbs that you feel present higher risk?
2.9	Do you think there are higher risks at specific stages of the herbal supply from Asia to the UK?
2.10	Do you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?
2.11	What main problems would you say unlicensed Chinese herbal medicines present?
2.12	On what scale would you say unlicensed Chinese herbs exist?
2.13	How effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?
2.14	Are there non-quality related problems with Chinese herbal medicine?
2.15	Please give your thoughts on these including a sense of their scale.
2.16	Do people cause quality problems for Chinese herbal medicine?
2.17	If so, please give your thoughts including how big are these problems?
Tag question	Could you recommend anyone else in your field to complete this questionnaire?

The eight questions chosen for the interview tool were based on those of the pilot questionnaire findings that most informed the three central research questions following analysis as described later in this chapter.

The first section of the interview, 1 to 1e, was similar to questionnaire section 1 and was intended as an “ice-breaker”, to introduce themselves and their work details, in addition to again verifying their inclusion criteria of more than ten years’ experience in the field of herbal medicine (*Table 3.3).*

The participant information sheet, consent form sample and interview tool are attached in the *Appendix to the KI study* (AKI), sections AKI 7, 8 and 9, respectively.

TABLE 3.3 SECTION 1 DEVELOPED INTERVIEW QUESTIONS

Section 1	Developed interview questions
1	Could I ask you about the nature of your work?
1a	Positions?
1b	Area?
1c	Time?
1d	Expertise?
1e	Countries?

Questions in the second section aimed to illicit opinions around what Chinese herbal quality issues have emerged, their scale, controls on herbal quality and supply, personal experiences in addition to their views on why problematic issues occur despite existing legislation. Sub-questions relating to a main topic were sometimes included to explore an area in more detail, for example question 2a and 2b intended to investigate CMP quality in the context of regulated and unregulated medicine and between different supply chains, respectively.

A further tag question, number ten, was included to potentially identify further key informants not already invited. Four experts were suggested by the interview respondents during the process, however four were already invited, including one who previously completed a pilot questionnaire (T*able 3.4*).

TABLE 3.4 SECTION 2 DEVELOPED INTERVIEW QUESTIONS

Section 2	Developed interview questions
2	What do you think about Chinese medicine quality?
2a	Regulated and unregulated?
2b	Different supply chains?
3	What do you think about species of herbs being mixed up?
3a	Examples?
3b	Prevention strategies?
4	What do you think about species of herbs being replaced with others?
4a	Examples?
4b	prevention strategies?
5	Do you have personal experience of these issues?
6	Have you had much experience with aflatoxins?
7	What do you think the key issues are?
8	Why do you think these problems continue despite control measures being in place?
9	Do you think that CHM quality could be improved?
9a	If not — why?
9b	If yes- how?
10	Anyone else you would recommend to speak to?

3.5.2 Key informants targeted and eligibility

The key informants were selected on the basis of being well-known, recognised senior experts in the field of Chinese medicine or CMP quality testing, or closely related area.

The eligibility criteria was that informants worked in the area of Chinese herbal medicine for at least 10 years and were therefore considered an expert in their field (Ericsson, 2006).

3.5.3 Key informants sampling

Forty-four potential key informants were invited to participate in this research after consultation with colleagues, the supervisory team and the researcher's own network to identify experts in the field of Chinese herbal medicine. Fifteen were invited to complete the initial pilot questionnaire, and 29 to conduct an interview subsequent to completing to the questionnaire process. They were invited by email that included an English-Chinese bilingual participant information sheet, consent form, and questionnaire, or a list of interview questions in the case of the subsequent interview process. Five completed the questionnaire and 15 the interview. Two participants completed both a questionnaire and an interview.

3.5.4 Key informants' responses

The pilot questionnaire participants returned a completed questionnaire by email. In total, five Microsoft Word® document transcripts of questionnaires were returned.

Interview participants agreed to participate by email and meeting times for the interviews were similarly arranged through email. Eight interviews were recorded using an Apple™ iPhone model 6s Plus smartphone or Apple™ iPad 2019, 11 inch model, with either Apple FaceTime or Tencent WeChat application, as preferred by the participants. The responses of interviews for five participants for who did not wish to be recorded were directly typed into a Microsoft Word® document.

In total fifteen interview responses were recorded. Eight audio recordings of an interview were transcribed to a Microsoft Word® document. The content of the five additional interviews of those who did not wish to be recorded were directly typed into a Microsoft Word® document on the Apple™ iPad. All fifteen interview respondents that agreed to participate completed the interviews and did not withdraw during the interview. No adverse events were recorded during the process.

3.5.5 Data analysis

3.5.5.1 Data transcription and translation

All transcripts were formatted in Microsoft Word® to more easily distinguish questions from the responses. A sample of the transcripts together with their date, times, locations, data capture format and additional details are attached in the thesis in *Appendix to the KI study* (AKI), section *AKI 10*.

The interview audio data were transcribed by a specialist company, Gotranscript Ltd., using a triple-review process to verify the transcript content (Gotranscript, 2021). They were rechecked by the researcher by comparing the original audio with the final transcriptions during review of the text. Audio of one interview conducted in mandarin Chinese, Case 17, was translated, and similarly verified and rechecked by Gotranscript, the researcher and a second native Chinese speaker, Xixi Yang.

As this thesis is intended for general electronic distribution by the University of Westminster following submission, participant responses were anonymised by deleting section 1, the introductory responses and redacting some areas of text to preserve anonymity and identity, where clearly evident. The primary data are stored in University of Westminster's secure, password-protected server with the filenames coded in a manner that obscures the original participants' identity.

3.5.5.2 Coding of the key informant transcripts

All Microsoft Word® formatted transcripts were imported electronically into Nvivo 12 software™, a programme specifically designed to assist with document management, coding and thematic analysis (NVivo, 2020). Text containing words, phrases or passages of the key informant responses relevant to answering the research questions were selected and moved to a column in the software that created a folder called a “node” within the programme. A name assigned to this folder by the researcher was the code.

An example is shown for the fourth participant, case 4, where two areas of text were identified as most relevant to answering the question of what were the main quality issues with CMP. The first relevant text element was “Misidentification”, and second “deliberate use of the wrong herb” (*Figures 3.3 and 3.4*).

These were highlighted individually, then moved into two new folders that were later named, “Misidentification” and “ Substitution” respectively, which were considered further as two new codes *Figures 3.3* and *3.4* illustrate the coding process using Nvivo software ™.

FIGURE 3.3 CODING "MISIDENTIFICATION" FROM A NARRATIVE ELEMENT WITHIN QUESTIONNAIRE QUESTION 2.2 RESPONSE FROM EXPERT KEY INFORMANT CASE 4 IN THE NVIVO 12 SOFTWARE PROGRAM

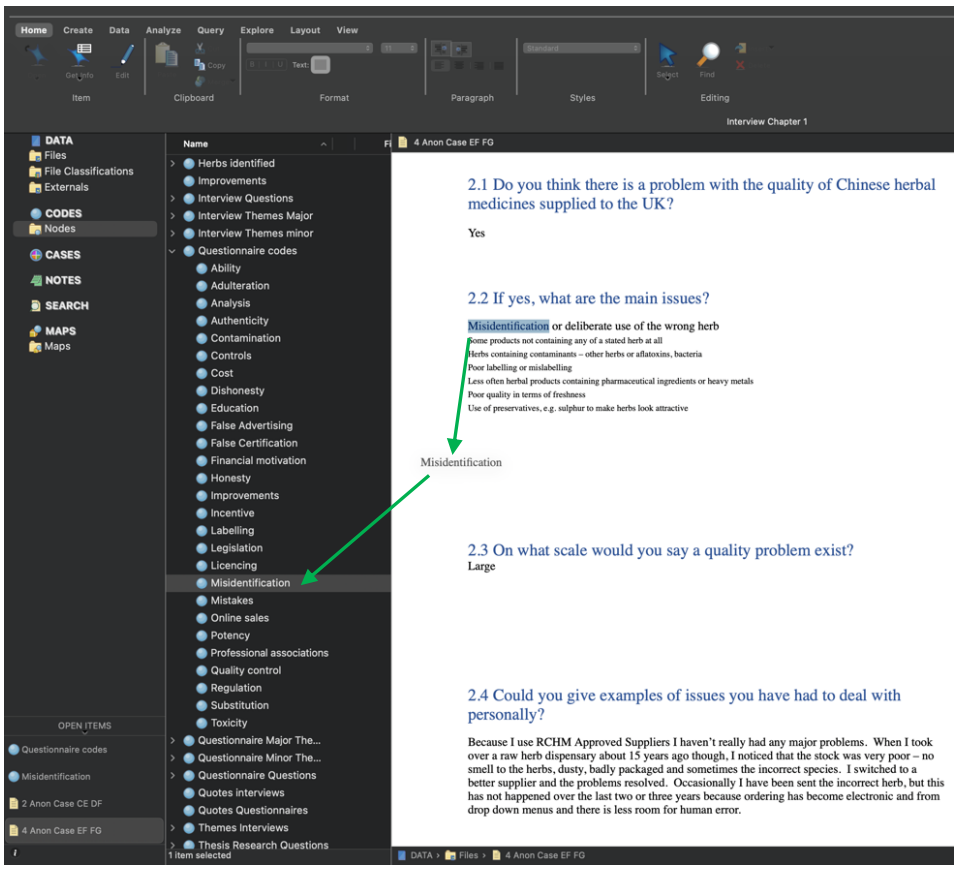
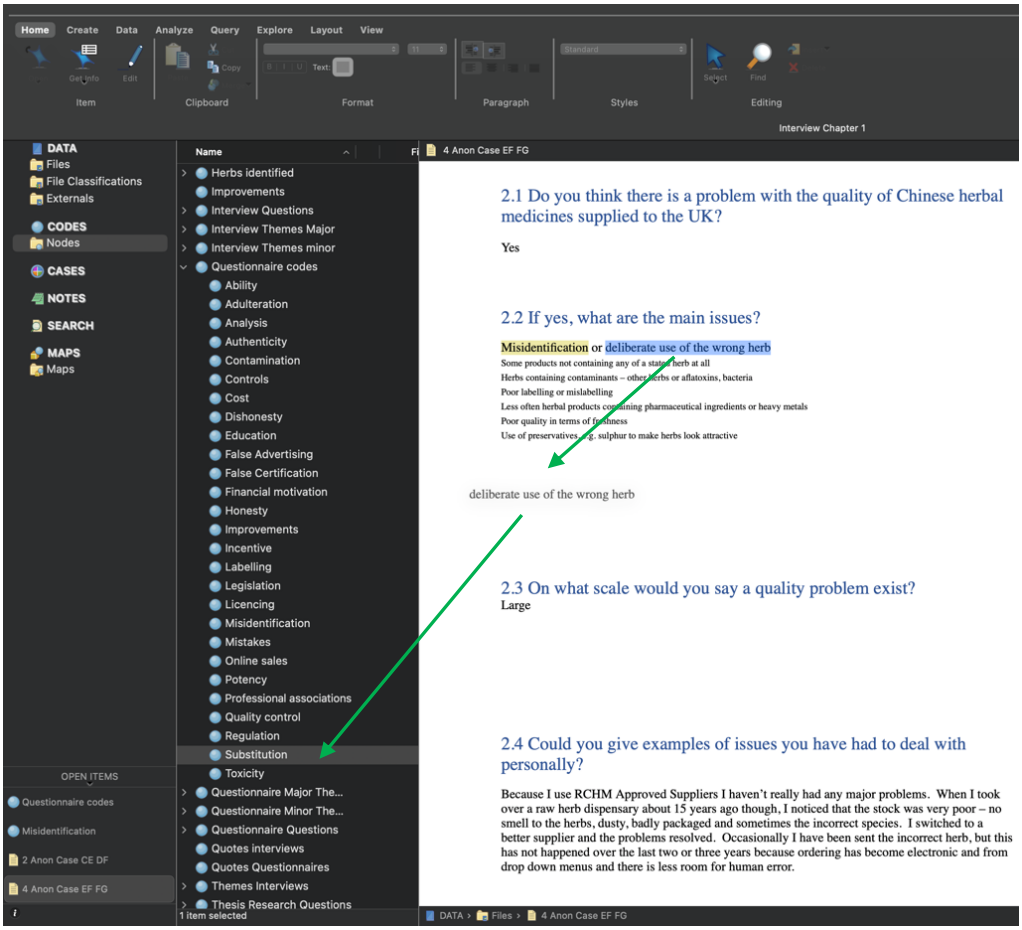


FIGURE 3.4 CODING "SUBSTITUTION" FROM A NARRATIVE ELEMENT WITHIN QUESTIONNAIRE QUESTION 2.2 RESPONSE FROM EXPERT KEY INFORMANT CASE 4 IN THE NVIVO 12 SOFTWARE PROGRAM



When the coding was completed and reviewed for all 15 transcripts, the codes that shared relevance were then further grouped into themes, upon which a new folder was created with the name of a themes. For example, the contents of the folders for the codes "Misidentification" and "Substitution", were transferred into a new folder assigned the name "Authenticity" as a theme. The software retained the full transcript content from where the codes were selected in both of the original folders and also generated a new copy of the contents for the folder for

the themes. This maintained a transparent data trail from the original transcript data through to the formation of codes and final themes.

3.5.6 Thematic analysis

Thematic analysis was used to analyse, synthesise and summarise the questionnaire and interview responses given by key informants. This method identifies and groups common patterns of meaning within narratives (Braun and Clarke, 2006, 2012). Thematic analysis was conducted in this research by first identifying sections of the key informant responses relevant to answering the research questions and tagging it with a word or short phrase referred to as a code. Weber described coding as an approach that “classifies textual material, reducing it to more relevant, manageable bits of data” (Weber, 1990, p5). Codes that shared similar relevance or meaning were then grouped together and tagged with a short word or phrase representing the theme. Grouping codes into themes may occur as many times as required by the researcher until forming further themes does not appear to provide any further benefit to the analysis. Themes were used during the analysis as means to efficiently group similar and relevant key informant responses into groups of opinions relevant to answering the research questions posed, that would not necessarily be apparent from a large body of uncoded text without pre-identified themes.

Thematic analysis has been used most commonly to facilitate the analysis of complex, rich and diverse sets of participant data in the social sciences area in a timely, efficient, meaningful and systematic manner that may not otherwise be

possible with other techniques (Davies et al., 2014). Thematic analysis was used in this research to produce credible findings based on the use of a clear, step-wise methodical coding process, and to maintain research rigour by transparently documenting each step of the coding in a manner that can be replicated.

The six steps of the systematic thematic analysis processes used in this research is that previously demonstrated by Braun and Clarke (Braun and Clarke, 2006, 2012), and are:

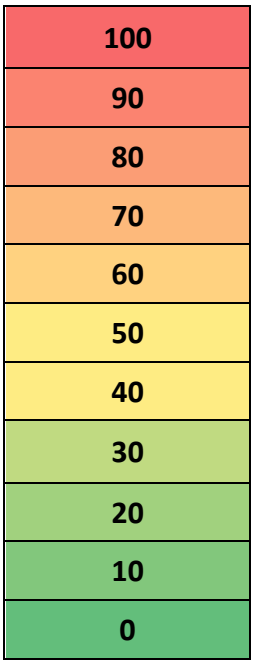
1. Familiarisation with the data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Producing the report

3.5.7 Heat map analysis

Thematic analysis is a transparent and systematic method for a researcher to analyse a large volume of complex narrative data. However, how often and what proportion of the original data the findings represent are obscured from those who are not familiar with the original data, that is, the reader's perspective. Therefore, the thematic analysis findings were presented together with a heat map. The frequency and proportion of the codes and themes represented in the original data are indicated side-by-side the thematic analysis findings. Heat-mapping further qualifies the data quantitatively, and contributes to the rigour of the research process by supporting the credibility and transparency of the findings.

Heat-mapping has been used to represent the relative contribution of narrative elements to findings in content analysis (Schatz, Bashroush and Wall, 2017) using software (Engle et al., 2017; Krippendorff, 2018). Colours of the visible spectrum from red to green signify "warm" to "cool", representing higher to lower relative contributions respectively. Each 10% of a selected data number range is indicated by a different colour from the highest 10% as red to the bottom 10% as green, as shown in (*Figure 3.5*). Readers are likely to perceive colours differently, therefore for accessibility purposes ordinal numbers are also included to denote the number of codes from which the themes were formed.

FIGURE 3.5 HEAT-MAP SCALE USED TO ILLUSTRATE THE PROPORTION CODES CONTRIBUTED FROM THE TOTAL NUMBER OF CODES (HIGHEST 10% OF NUMBER RANGE RED TO LOWEST 10% GREEN).



The number of codes for each question and themes were tabulated in Microsoft Excel® for Mac version 16.5, 365 edition, by selecting the numerical data then the "Home" menu followed by "Conditional Formatting" and "Colour Scales" options.

As an example in *Table 3.5,* 25 narrative elements called codes were coded to "Product integrity", from interview responses to question 2, and eight codes from question 3. Whereas one code was coded to the "Education" from question 2, and none from any interview response to question 3.

TABLE 3.5 EXAMPLE OF CODING THEMES

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the sum total of codes formed.

25 codes the highest, 0 the lowest

Interview Minor Themes	Q2 CHM Quality	Q3 Herb mixup
Control	9	2
Cooperation	1	0
Education	1	0
Error	9	9
Herb Care	5	0
Honesty	4	1
Human Behaviour	6	7
Incentive	9	0
Inertia	11	1
Opacity	22	2
Product Integrity	25	8
Reasons	25	2
Supply	5	1
Toxicity	6	0
Tradition	2	0
Understanding	10	5
Value	12	2
Variation	18	1

3.5.8 Tabulation of informant responses

Thematic analysis groups common patterns of meaning within the key informant narratives and heat-mapping represents the relative contribution of narrative elements to findings. However, on completion of these syntheses, specific and

individual contributions that may not form strong association with other responses will not be represented in the final analysis report. Further, the relatively large volume of data collected presents a challenge in maintaining traceability to original informant responses. Therefore, a table of the specific contributions of key informants was also presented by tabulating each individual example of CMP quality issues identified, a description of how the informants discovered this information, improvements proposed for each individual example, and individual opinions on why CMP problems persisted in tabular form. The master table from which the summary later in the discussion is derived is attached in *Appendix to the KI study* (AKI), sections AKI 12.

The thematic analysis and heat-mapping represents a wider perspective, “from top down view” of the key informant responses collectively, and tabulating individual contributions to a more granular standpoint, “from the bottom up view”. The content of the table is organised in order of relevance to each of the three chapter research questions later as presented later in this chapter.

3.6 Results and Analysis

3.6.1 Pilot Questionnaire findings

3.6.1.1 Questionnaire respondent profile

The expertise profile of the 15 invited key informants spanned the fields of manufacture (one), education (four), herbal supply (three), regulation (four),

herbal clinical practice (one) and research (two), The five respondents who participated were in the fields of manufacture (one), education (one), herbal supply (two) and regulation (one). Those invited from the fields of clinical practice and research did not participate in the questionnaire (*Table 3.6*).

TABLE 3.6 EXPERTISE PROFILE OF QUESTIONNAIRE INVITEES AND PARTICIPANTS

EXPERTISE FIELD	NUMBER OF INVITED KEY INFORMANTS (N=15)	NUMBER OF PARTICIPANTS RESPONDED (N=5)
Manufacture	*1*	1
Education	*4*	1
Supply	*3*	2
Regulation	*4*	1
Practitioner	*1*	0
Research	*2*	0

3.6.1.2 Questionnaire respondents profile

The participants possessed secondary expertise in areas of research, regulation, company management, herbal clinical practice, supply consultancy, herbal sourcing, and sales. The five questionnaire responses are referred to further as cases numbers one to five, abbreviated C1 to C5, inclusive (*Table 3.7*).

TABLE 3.7 OVERVIEW OF PROFILE PILOT QUESTIONNAIRE PARTICIPANTS

CASE NUMBER	PRIMARY EXPERTISE	SECONDARY EXPERTISE	ETHNICITY	RESIDENCY
C1	*Manufacturing*	*Research*	*China*	*China*
C2	*Education*	*Regulation*	*British*	*UK*
C3	*Supply*	*Company Management*	*China*	*UK*
C4	*Regulation*	*Practitioner*	*British*	*UK*
C5	*Supply*	*Sales*	*China*	*China*

Three of the five participants were of Chinese ethnicity, native mandarin Chinese and fluent English speakers. Two were of British ethnicity and native English speakers. Four were long-term residents in the UK and one (Chinese ethnicity) was a full-time resident in Taiwan. Residents in the Republic of China (ROC) and Taiwan and People's Republic of China (PRC) are, for the purposes of brevity, noted as Chinese resident throughout. All questionnaire responses were completed in the English language.

3.6.1.3 Participant contributions to the pilot questionnaire

Consultation with the participants using the pilot questionnaire with 17 questions generated a total of 27 unique codes formed from narrative elements that were relevant to answering the three research questions. These in summary described: areas relating to the influence of human actions on herbal quality; the controls on quality including legislation; issues affecting the integrity of CMP; and opinions on how to improve current quality issues, among others.

Table 3.8 shows the coding distribution for the pilot questionnaire questions in both numeric and heat-map format combined. The numbers indicate the number of codes formed from the participant responses to each of the 17 questions. The scale of colours from red to green represent the relative proportion of the number of questionnaire codes formed. Those coloured red are in the highest 10% fraction of the total number of codes formed from all questionnaire codes, and green for the lowest 10% proportion, respectively.

TABLE 3.8 OVERVIEW OF CODING FOR RESPONESES TO THE 17 PILOT QUESTIONNAIRE QUESTIONS FROM FIVE PARTICIPANTS

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the total number of codes formed. 9 codes the highest, 0 the lowest

Questionnaire Codes	Q2.1 Opinions on Quality	Q2.10 Licencing status	Q2.11 Unlicenced herb problems	Q2.12 Scale of unlicenced herbs	Q2.13 Effectiveness of legislation	Q2.14 Non-quality related issues	Q2.15 Scale of Non-quality issues	Q2.16 Human influence on quality	Q2.17 Human degree of influence	Q2.2 Main quality issues	Q2.3 Scale of quality problems	Q2.4 Personal experience with quality issues	Q2.5 Origin of quality issues	Q2.6 Effectiveness at detecting problems	Q2.7 Circumstances for problems to occur	Q2.8 Higher risk herbs	Q2.9 Risk stages of supply chain
Ability	0	1	0	0	0	3	2	0	0	0	0	0	0	1	0	0	0
Adulteration	0	0	1	0	0	0	0	0	1	2	0	0	2	0	1	1	0
Analysis	0	0	0	0	0	0	0	0	0	3	0	0	2	2	1	0	1
Authenticity	0	0	0	0	0	0	0	0	0	2	0	0	0	0	1	1	0
Contamination	0	0	1	0	0	0	0	0	0	5	0	1	1	0	0	0	0
Controls	0	2	0	0	0	1	1	0	3	2	0	0	2	2	4	0	2
Cost	0	0	1	0	0	0	0	1	1	1	0	1	0	0	2	0	0
Dishonesty	0	0	0	0	0	2	0	1	2	0	0	0	3	0	2	1	0
Education	0	0	0	0	0	9	0	2	7	0	0	0	3	0	1	0	0
False Advertising	0	0	0	0	0	3	1	1	2	1	0	1	0	0	0	0	0
False Certification	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	1
Financial motivation	0	0	1	0	0	0	0	1	2	0	0	0	5	0	1	0	0
Honesty	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	1
Improvements	0	0	0	0	1	1	1	0	0	0	0	0	0	2	2	0	0
Incentive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	1
Labelling	0	0	0	0	0	0	0	1	0	4	0	2	1	0	0	0	0
Legislation	0	0	0	0	3	1	0	0	1	0	0	0	0	0	0	0	0
Licencing	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Misidentification	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0
Mistakes	0	0	0	0	0	2	0	0	0	0	0	0	3	0	0	0	0
Online sales	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Potency	0	0	0	0	0	0	0	0	0	1	0	3	0	0	0	0	0
Professional associations	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
Quality control	0	0	1	0	0	0	0	0	0	2	0	7	2	1	1	0	0
Regulation	0	0	0	0	3	1	1	0	0	3	0	0	2	0	5	0	0
Substitution	0	0	1	0	0	0	0	0	1	2	0	1	0	0	0	1	0
Toxicity	0	0	0	0	0	0	0	0	0	3	0	3	0	0	0	1	0
Sum of number of codes	0	11	6	0	7	25	8	8	23	33	0	19	26	11	28	5	6

The majority of the coding (175 codes) were attributed to questions 1, 2, 5 and 7 that related to general opinions on Chinese herbal quality (88 codes from Q2.1 to 2.17 inclusive), identifying the main CMP quality issues (33 codes from Q2.2), origin of these issues (26 codes from Q2.5) and opinions on the circumstances in which quality issues emerged (28 codes), respectively. These are followed by question 4, personal experiences of herbal quality issues (19 codes), question 6, how effectively problematic quality issues are detected, (11 codes), question 9, identifying higher risk stages of supply chains (6 codes) and question 8, seeking to identifying the more problematic herbs (5 codes) (*Table 3.8*). These most informative questions were the basis on which the subsequent eight interview questions were formed. Supplementary details of the pilot questionnaire responses and analysis are attached in *Appendix to the KI study* (AKI), section *AKI 6.*

3.6.2 Interview findings

3.6.2.1 Interview invitee profile

The expertise profile of the 29 invited key informants spanned the fields of education (12), herbal supply (five), regulation (three), manufacture (two), research (four) and herbal clinical practice (three). The 15 respondents who participated were from the fields of education (eight), herbal supply (three), regulation (one), manufacture (one), research (two) (*Table 3.9*).

TABLE 3.9 EXPERTISE PROFILE OF INTERVIEW INVITEES AND RESPONDENTS

EXPERTISE FIELD	NUMBER OF INVITED KEY INFORMANTS (N=29)	NUMBER OF RESPONDENTS (N=15)
Education	12	8
Supply	5	3
Regulation	3	1
Manufacturing	2	1
Research	4	2
Practitioner	3	0

The participants possessed secondary expertise in areas of research, regulation, company management, herbal clinical practice and sales. The 15 questionnaire respondents are referred to further as cases 6 to 20, abbreviated to C6 to C20, inclusive.

3.6.2.2 Interview respondents profile

Ten of the 15 participants were of Chinese ethnicity, mandarin Chinese and fluent English speakers. One was ethnic Chinese and spoke in mandarin Chinese. Four interview participants were of British ethnicity. Eight were long-term residents in the UK, and eight full-time residents in either mainland China or Taiwan. Residents in the Republic of China (ROC) and Taiwan and People's Republic of China (PRC) are, for the purposes of brevity, noted as Chinese resident

throughout. Fourteen of the 15 interviews were completed in the English language, and one case (17) in Mandarin Chinese (*Table 3.10).*

TABLE 3.10 OVERVIEW OF PARTICIPANTS PROFILE FOR INTERVIEW

CASE NUMBER	PRIMARY EXPERTISE	SECONDARY EXPERTISE	ETHNICITY	RESIDENCY
C6	*Regulation*	*Research*	*British*	*UK*
C7	*Education*	*Practitioner*	*British*	*UK*
C8	*Education*	*Regulation*	*British*	*UK*
C9	*Education*	*Regulation*	*Chinese*	*China*
C10	*Education*	*Supply consultant*	*Chinese*	*China*
C11	*Education*	*Research*	*Chinese*	*China*
C12	*Education*	*Research*	*Chinese*	*China*
C13	*Education*	*Research*	*Chinese*	*China*
C14	*Supply*	*Sales*	*Chinese*	*UK*
C15	*Supply*	*Company Management*	*Chinese*	*UK*
C16	*Manufacturing*	*Supply*	*Chinese*	*China*
C17	*Education*	*Research*	*Chinese*	*China*
C18	*Supply*	*Herbal sourcing*	*Chinese*	*UK*
C19	*Research*	*n/a*	*Chinese*	*China*
C20	*Research*	*Author*	*British*	*UK*

3.6.2.3 Participant contributions to the interview

The contributions of the participants to the interview varied with their expertise, ethnicity and residency profile, as shown in *Table 3.11.* Consulting with key informant participants covered 8 interview questions that generated a total of 42 unique codes coded from 507 narrative elements in their responses. The narrative elements were cross-coded a further 109 times, comprising a total of 616 coding incidences. Cross-coding was completed where the response to one question informed another. For example, when asking question 5, about personal experience of quality issues, descriptions of incidences of herbal substitution were further coded to other questions 2 and 3 intended to identify quality issues and seek examples of substitution (*Table 3.11).*

TABLE 3.11 OVERVIEW OF CODING FOR INTERVIEW RESPONESES TO QUESTIONS FROM THE 15 PARTICIPANTS

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the sum total number of codes formed. 25 codes, highest, 0 codes, lowest.

Interview Codes	Q2 CHM Quality	Q3 Herb mixup	Q4 Herb substitution	Q5 CHM issue personal experience	Q6 Aflatoxins	Q7 Key CHM Issues	Q8 Issues Persistence	Q9 Improvements
Adulteration	7	1	0	4	0	2	0	0
Aflatoxin	3	0	0	0	5	0	0	1
Apathy	1	0	0	0	0	0	0	0
Authenticity	5	2	1	2	0	1	1	0
Business focus	8	0	0	0	0	0	6	0
Change	17	0	2	9	0	9	21	10
CHM is complex	1	1	1	0	0	1	1	0
Contamination	1	0	0	2	0	2	0	1
Cooperation	0	0	0	1	0	1	1	4
Cost	18	2	2	5	0	2	17	3
Dishonesty	3	0	0	3	0	1	3	0
Education	1	0	0	2	0	2	5	12
Fake documentation	1	1	0	3	0	0	1	0
Herb Care	5	0	0	0	0	1	2	1
Incentives	1	0	0	0	0	1	4	18
Inertia	11	1	2	4	0	7	22	6
Labelling	4	4	3	1	0	0	3	0
Legislation	2	1	1	1	0	1	7	2
Misidentification	9	9	3	5	0	1	3	0
Mistakes	4	5	1	1	0	0	3	0
Motiviation	0	0	0	0	0	1	2	9
Opacity	4	1	0	0	0	0	1	1
Perspective	7	1	1	0	0	1	3	0
Processing	1	0	0	0	0	0	1	1
Purity	11	1	1	0	2	1	1	0
Pyrrolizidine alkaloids	3	0	0	0	1	1	1	1
Quality definition	11	0	0	0	0	1	3	0
Reasons	25	2	1	3	0	2	14	0
Regulation	1	0	0	1	0	0	2	0
Responsibility	0	0	0	0	0	0	0	2
Scarcity	3	1	1	0	0	0	1	1
Siloed knowledge	1	0	0	1	0	1	1	0
Substituion	2	3	2	1	0	0	0	0
Substitution Acceptable	4	7	7	3	0	1	5	0
Supply chain	2	0	0	0	1	2	2	1
Sustainability	1	0	0	0	0	0	1	10
Synthetic drugs	1	0	0	0	0	0	0	0
Toxicity	2	0	0	0	1	0	0	0
Tracability	0	0	0	0	0	0	0	2
Traditional practice	2	0	0	1	0	1	0	0
Trust	1	0	0	1	0	0	0	0
Understanding	10	5	2	2	0	0	8	1
Sum of number of codes	194	48	31	56	10	44	146	87

The majority of coding, 427 codes, were attributed to questions 2, 8 and 9, respectively that relate to identifying CMP quality issues (194 codes), reasons why these issues persisted (146 codes) and opinions on improvements to herbal quality (87 codes). These were followed by personal experiences of herbal

quality issues (56 codes), herbal substitution (48 codes), beliefs about key issues in quality (44 codes) and the presence of aflatoxins in herbs (10 codes) (*Table 3.11*).

3.6.2.4 Participant contributions to the interview, by expertise

The greatest contribution was made by those in the field of education (245 codes) and supply (140 codes). The least from those in research (46 codes) and manufacturing (16 codes) (*Table 3.12*).

TABLE 3.12 OVERVIEW OF CODING FOR ALL INTERVIEW RESPONESES FOR EACH QUESTION BY OCUPATION, EHTNICITY AND RESIDENCY

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the sum total number of codes formed. 113 codes, highest, 0 codes, lowest.
n=number of participants.

Interview respondents profile		Q2 CHM Quality	Q3 Herb mixup	Q4 Herb substitution	Q5 CHM issue personal experience	Q6 Aflatoxins	Q7 Key CHM Issues	Q8 Issues Persistence	Q9 Improvements	Sum of number of codes
OCCUPATION	**Education** (n=8)	67	12	12	22	4	16	70	42	245
	Supply (n=3)	36	5	2	40	1	13	31	12	140
	Regulation (n=1)	24	4	1	3	1	2	18	7	60
	Manufacturing (n=1)	7	0	0	4	0	0	5	0	16
	Research (n=2)	18	1	1	2	0	1	14	9	46
ETHNICITY	**Ethnicity = Chinese** (n=11)	75	9	9	62	3	23	63	25	269
	Ethnicity = British (n=4)	77	13	7	9	3	9	75	45	238
RESIDENCY	**Residency = China** (n=8)	39	4	7	22	2	10	32	13	129
	Residency = UK (n=7)	113	18	9	49	4	22	106	57	378

The types of responses varied highly with the expertise of the participants. Those in the fields of education, regulation and research responded mostly to questions around general opinions on herbal quality and why issues persist. While those in supply and manufacturing more often related personal experiences of herbal quality issues.

3.6.2.5 Contributions to the interview by ethnicity and residency

Chinese and British ethnicities were approximately equivalent contributors to the in volume to interviews, however as there were four British respondents compared with 11 Chinese, each British participant was more than twice as verbose as Chinese. Both ethnicities mostly responded to questions of quality issues and their persistence, with British participants favouring to speak of further of improvements to quality while Chinese participants preferred descriptions of personal experiences of problematic issues. The least informed question by all related to the problem of aflatoxins in herbs.

UK and China residents both focused similarly on responses concerning the identity of quality issues and their persistence. UK residents contributed more than triple to that of Chinese residents overall to the interviews, with Chinese residents concentrating more on personal experience of quality problems while UK residents spoke more about improvements to herbal quality issues.

A review of expert responses of eight interview questions generated a total of 42 unique codes. These codes described aspects of how human behaviour

influences herbal quality, how the natural environment and circumstances in herbal supply change can impart variations in quality and challenge the natural integrity of herbs both as plants and as medicine products, among others as further in this chapter.

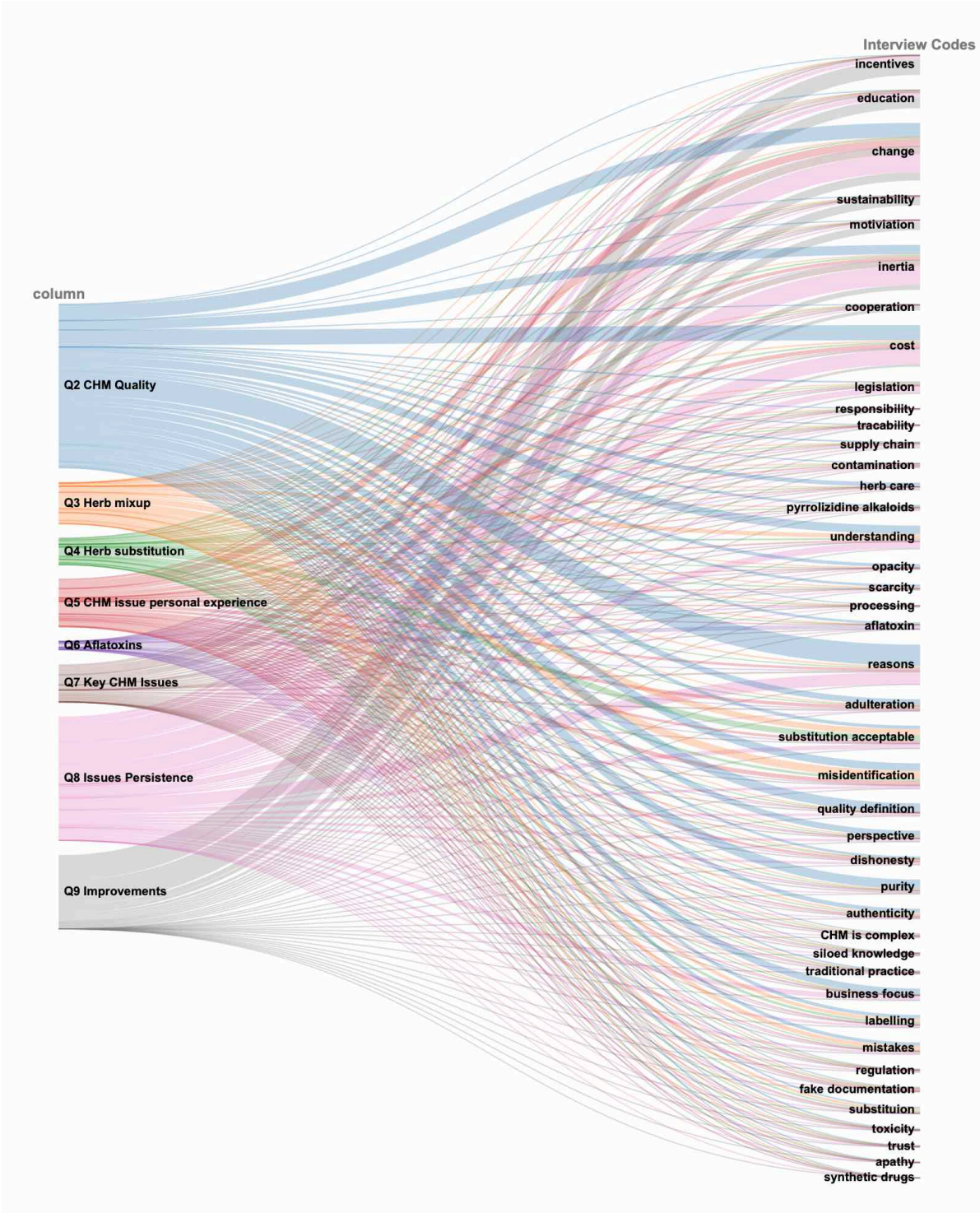
3.6.2.6 Thematic analysis of the interview responses

The preceding sections represent steps one and two of the thematic coding methods process, those of familiarisation and generating the initial codes.

Figure 3.6 illustrates the relationship between these two steps, where each coloured strand represents an instance where a narrative element in a response to a question on the left has been formed each code on the right.

FIGURE 3.6 ILLUSTRATION OF THE RELATIONSHIP BETWEEN NARRATIVE ELEMENTS CODED FROM INTERVIEW QUESTIONS AND CODES

Each strand represents one narrative element in response to a question (left) has been coded to a new code (right)



The following section documents the further three steps:

3 Searching for themes

4 Reviewing themes

5 Defining and naming themes

These are summarised in *Table 3.13.*

The final step six, producing the report is shown in *Figure 3.7*

TABLE 3.13 STEPS 3 TO 5 IN THE THEMATIC ANALYSIS PROCESS FROM CODES TO THEMES FOR THE INTERVIEW RESPONSES

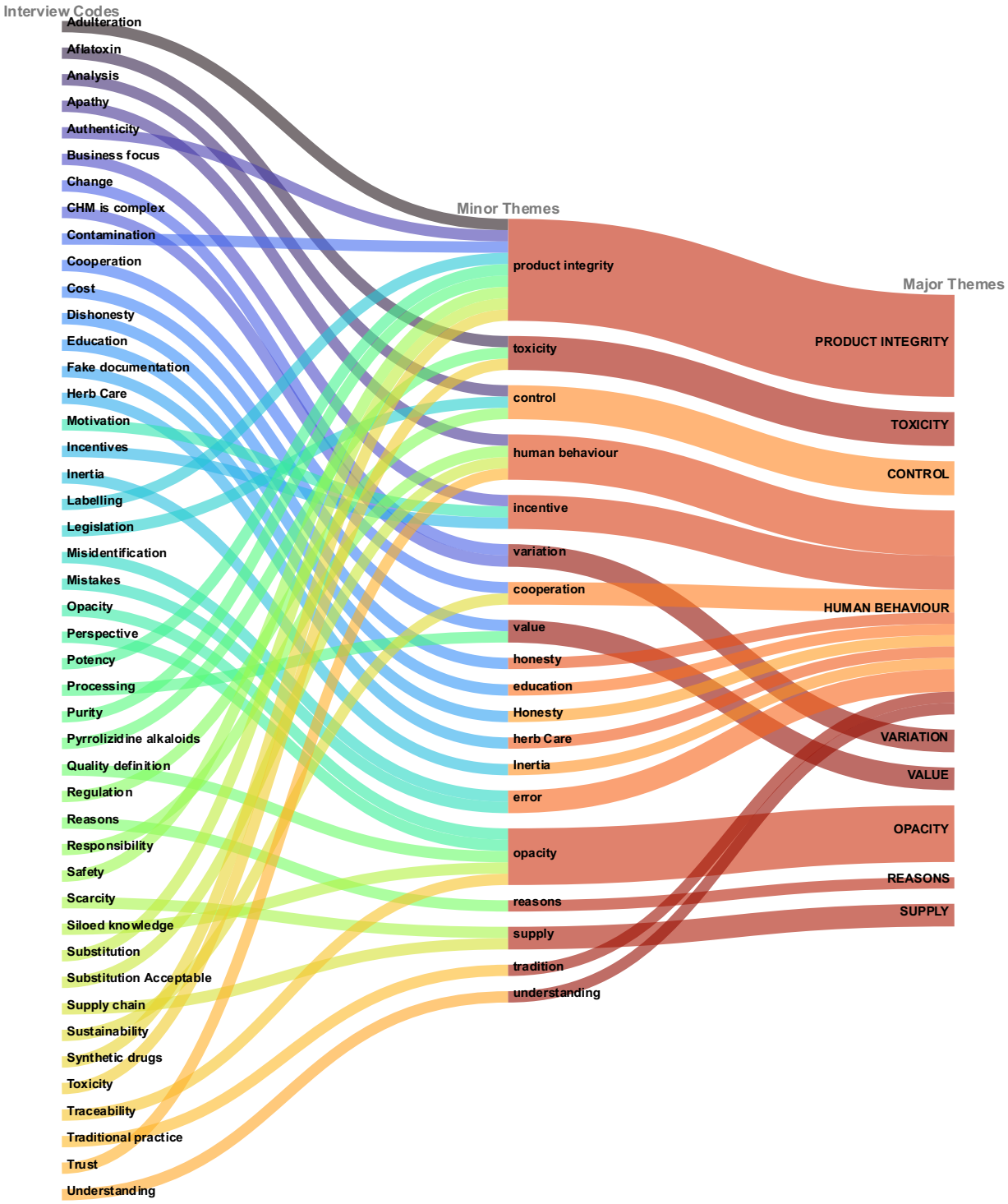
Initial codes	STEP 3 Searching for themes	STEP 4 Reviewing themes	STEP 5 Defining and naming themes (minor)	STEP 5 CONTINUED Defining and naming themes (major)
Analysis	*quality control*	*controls*	**control**	**CONTROL**
Legislation	*legislation*	*controls*		
Regulation	*regulation*	*controls*		
Education	*education*	*education*	**education**	**HUMAN BEHAVIOUR**
Misidentification	*mistakes*	*error*	**error**	
Mistakes	*error*	*error*		
Cooperation	*cooperation*	*cooperation*	**cooperation**	
Sustainability	*sustainability*	*cooperation*		
Apathy	*human response*	*human behaviour*	**human behaviour**	
Dishonesty	*honesty*	*honesty*	**Honesty**	
Fake documentation	*honesty*	*honesty*		
Herb Care	*herb care*	*herb care*	**herb Care**	
Responsibility	*human behaviour*	*human behaviour*	**human behaviour**	
Substitution Acceptable	*substitution*	*substitution*		
Trust	*human response*	*human behaviour*		
Business focus	*profit focus*	*incentive*	**incentive**	
Motivation	*incentive*	*incentive*		
Incentives	*incentive*	*incentive*		
Inertia	*inertia*	*inertia*	**Inertia**	
Traditional practice	*tradition*	*tradition*	**tradition**	
Understanding	*understanding*	*understanding*	**understanding**	

TABLE 3.13 CONTINUED STEPS 3 TO 5 IN THE THEMATIC ANALYSIS PROCESS FROM CODES TO THEMES FOR THE INTERVIEW RESPONSES

Initial codes	STEP 3 Searching for themes	STEP 4 Reviewing themes	STEP 5 Defining and naming themes (minor)	STEP 5 CONTINUED Defining and naming themes (major)
Opacity	*opacity*	*opacity*	**opacity**	**OPACITY**
Perspective	*separate perspectives*	*opacity*		
Quality definition	*unclear definition*	*opacity*		
Siloed knowledge	*separate knowledge*	*separate understanding*		
Traceability	*opacity*	*opacity*		
adulteration	*adulteration*	*purity*	**product integrity**	**PRODUCT INTEGRITY**
Authenticity	*authenticity*	*product integrity*		
Contamination	*purity*	*purity*		
Labelling	*labelling*	*identification*		
Potency	*potency*	*potency*		
Purity	*added value*	*purity*		
Safety	*safety*	*product integrity*		
Substitution	*substitution*	*substitution*		
Synthetic drugs	*purity*	*purity*		
Aflatoxin	*toxicity*	*toxicity*	**toxicity**	**TOXICITY**
Pyrrolizidine alkaloids	*toxicity*	*toxicity*		
Toxicity	*toxicity*	*toxicity*		
Reasons	*reasons*	*reasons*	**reasons**	**REASONS**
Scarcity	*supply*	*supply*	**supply**	**SUPPLY**
Supply chain	*supply*	*supply*		
Cost	*value*	*value*	**value**	**VALUE**
Processing	*processing*	*added value*		
Change	*change*	*variation*	**variation**	**VARIATION**
CHM is complex	*variable content*	*variation*		

FIGURE 3.7 STEP 6 OF PRODUCING THE THEMATIC ANALYSIS REPORT

Illustration of the relationship between codes (left) formed from interview responses to forming minor themes (centre) and major themes (right)



3.6.2.7 Thematic emphasis within the findings

The major themes that are formed from a synthesis of minor themes represent a relatively greater emphasis in findings of the key informant responses than the minor themes from which they are comprised. Each major theme also varies in emphasis to other major themes dependent on the number of minor themes and code from which they are formed. Minor themes are also comprised of a greater or lesser number of codes from which they are formed and therefore vary in the level of emphasis they represent relative to other minor themes. Although thematic analysis provides a systematic and transparent manner to analyse voluminous and complex narrative data, the drawback is that various emphasis of the findings is not always clearly apparent, and it does not indicate "the wood from the trees". Here, the emphasis for all key informant data combined is examined to further qualify the relatively voluminous and rich key informant findings so that the research questions may be more concisely and meaningfully answered. The themes are underlined to differentiate from other text.

The nine major themes formed from the key informant contributions in the interview process, in order from the highest to lowest number of unique codes, were: human behaviour, product Integrity, opacity, control, toxicity, variation, value, supply, and reasons.

The theme of greatest emphasis from the interview process was human behaviour influencing the quality of CMP and, secondly, how these actions challenged herbal product integrity which led to recurrent quality problems. The third most common contribution was the theme of opacity, from participants'

descriptions of how herbal quality problems arose from both human actions and natural photochemical variations that were obscured from detection and consequently the effect of legislation. The four themes of variation, control, supply, and reasons, formed from descriptions of how variation in CMP quality imparted by both nature and human actions, complicated the production of consistent and well-controlled products in herbal supply chains. The theme of toxicity was formed from explanations of how this variation in quality leads to toxic herbs reaching consumer as they remained undetected and sometimes result in adverse events.

The 19 minor themes emerging from the interview process formed the nine major themes. Six minor themes, those of control, toxicity, variation, value, supply, and reasons, respectively, were of significantly different thematic content to form single major themes.

Two minor themes of opacity and product integrity were formed from thematically similar but comparatively diverse content. The theme of opacity was formed from explanations by participants of how the different perspectives and siloed information held by those in various roles and stages across a supply chain can hold different definitions of herbal quality. These resulted in divergent goals and efforts that may not be towards maintaining herbal product integrity, or conducted in the same manner. Opacity along supply chains could obscure the detection and effect of legislation, an environment in which nefarious practices affecting herbal quality for profit gain could perpetuate. The theme of product integrity was formed from the many quality issues and was synthesised into a single concept

that described any significant alteration to the authenticity, potency, or label descriptions to a medicinal plant product through adulteration, substitution, contamination that could impact its purity, safety or efficacy.

The most diverse major theme of human behaviour was formed from 11 related minor themes; education, error, cooperation, human behaviour, honesty, herb care, human behaviour, incentive, inertia, tradition, and understanding. Human behaviour emerged twice as a minor theme from the different types of responses. One related to actions, and another identically named from explanations of how inaction from apathy can also lead to quality problems. This included a lack of vigilance, reporting, or concern regarding the health effects of herbal quality problems on patients' health that are often geographically distant and may arise many years after the herbs are handled and consumed.

The minor theme of education that featured in many of the participant responses contributed to the major theme of human behaviour. Insufficient education or that not specifically related to CMP directly influencing human actions and their effect on herbal quality, such as herb care during cultivation, processing, preparation, and general handling in the herbal supply. Education was associated by respondents with human error, such as herb misidentification in the absence of the relevant expertise together with lack of understanding of CMP traditional knowledge gathered over many years, which similarly affected how herbs were collected, processed and prescribed, and which consequently affect their quality. Value of herbs featured as a theme in creating an incentive for dishonest practices for profit gain that affected herbal quality, including various adulteration

and substitution. Herbal value and insufficient education together created barriers and inertia to co-operation between those in various steps of the herbal supply chain, affecting herbal quality such as adulteration and substitution. Education and co-operation were central contributions to the improvements suggested by participants to persistent CMP quality issues, including sustainable practices and raising awareness of the value created though the collective effort and benefit sharing for those working in supply chains.

The relatively slow rate at which legislation and scientific advancement in analytical detection methods proceeded was highlighted as a source of inertia that created opportunities around which quality issues could occur. In particular, by relatively agile nefarious actors who could evade legislation when implemented as regulation, and the novel testing methods it mandated. Therefore presenting the circumstances and environment in which similar and recurrent quality issues in CMP could perpetuate.

3.7 Discussion

3.7.1 Discussion of the findings

Consulting with key informants clarified the identity and scale of the main CMP quality problems and generated insight into why they persisted. It informed improvements for these recurrent quality issues. The following figures show the major and minor themes formed (*Figures 3.8* and *3.9*).

FIGURE 3.8 MAJOR THEMES FOUND IN THE KI STUDY

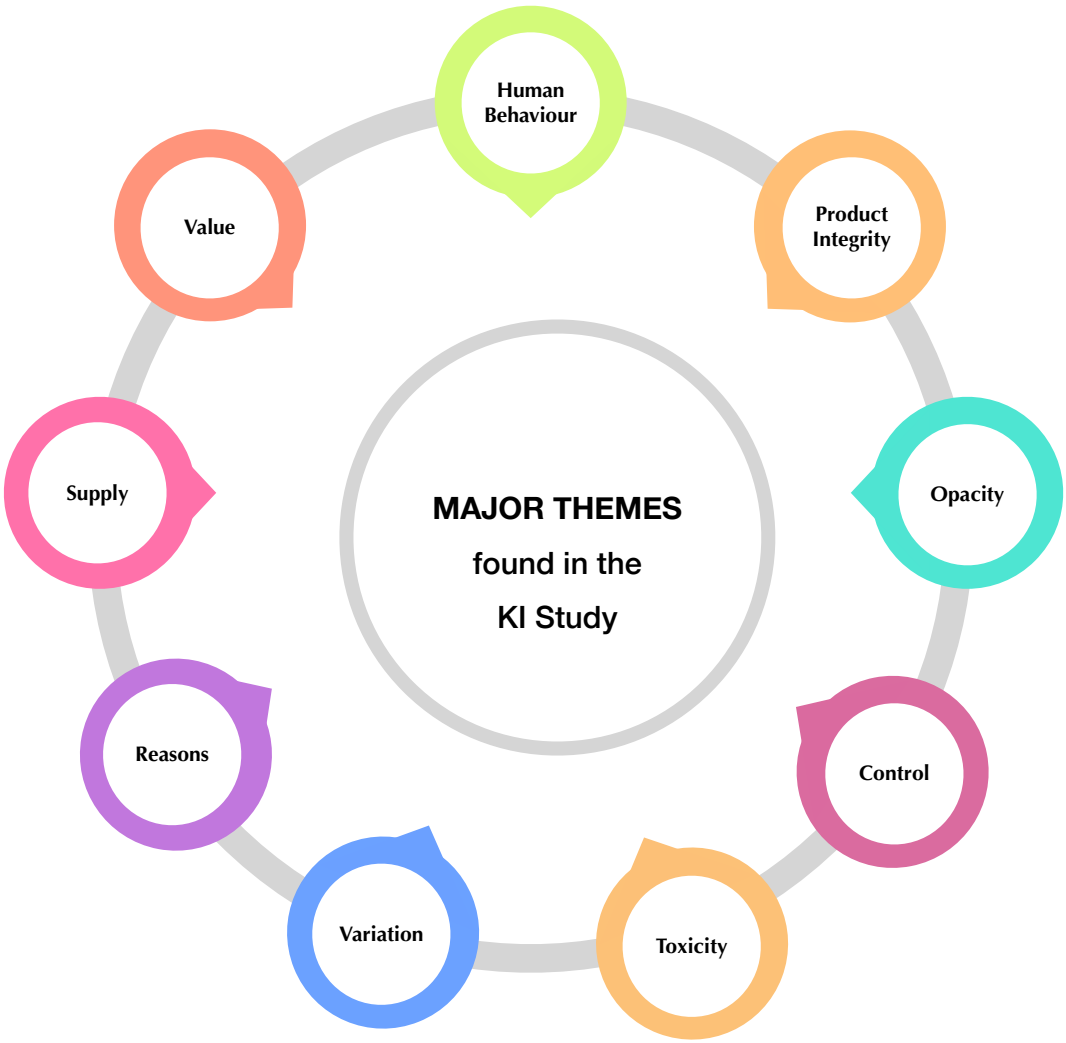


FIGURE 3.9 MINOR THEMES FOUND IN THE KI STUDY

The most prominent themes related the role of human behaviour in challenging the integrity of CMP and, consequently, quality. The problem of toxicity is particularly complex and should be considered separately from other product integrity issues such as contamination or adulteration, as naturally and inherently toxic medicinal herbs do not constitute a quality issue. However, if not identified, prepared and prescribed appropriately within a supply chain it could be problematic. Whereas in other cases it is the product integrity issues, such as

contamination or adulteration, that impart toxic effects to CMP. This was reflected in the majority, 94%, of specific examples of CMP quality issues reported by key informants during the combined questionnaire and interview processes. The full supplementary details are attached in *Appendix to the KI study* (AKI), section AKI 12, and are summarised in *Table 3.14*. Twenty-three related to substitution, 21 adulteration and 44 to toxicity out of a total of 95 examples given. Four additional examples related to three incidence of high variation in quality, and one of rejected material resold to another country.

TABLE 3.14 SUMMARY OF QUALITY ISSUES REPORTED BY KEY INFORMANTS FROM THE COMBINED QUESTIONNAIRE AND INTERVIEW PROCESSES FROM 95 SPECIFIC EXAMPLES OF CMP QUALITY ISSUES

Identified CMP quality issues	Number of Examples	Proportion of Total (%)
Toxicity	44	46
Substitution	23	24
Adulteration	21	22
Quality variation	3	3
Rejected material resold	1	1

Convergence was apparent between the questionnaire and interview findings in participant contributions that related to inadequacies of analytical testing and legislative controls in place to maintain herbal quality, which contributed to the persistence of quality issues. Contributions from both the questionnaire and interview process agreed that quality issues are related to supply chain

considerations, particularly those that provide opportunity for profit gain. This was reflected in the specific examples given by key informants. Some 78% of the opinions for the 95 example specific quality issues given of why these CHM quality issues persisted either related to non-detection or were unknown in 43 examples, and 31 due to value or profit motivation. Seven examples cited by respondents highlighted insufficiencies in both GxP regulations and in pharmacopeias that allowed practices that adversely impacted CMP quality as the reason for quality problems persisting. Four percent of the specific examples were not highly apparent in the thematic analysis. Three of these, over harvesting, supply and demand, and rapid commercialisation, collectively relate to the effect on quality form supply constraints. One example was given as persistent due to non-adherence to traditional Chinese herbal medicine preparation methods (*Table 3.15).*

TABLE 3.15 SUMMARY OF REASONS WHY QUALITY ISSUES PERSISTED BY KEY INFORMANTS FROM THE COMBINED QUESTIONNAIRE AND INTERVIEW PROCESSES FROM 95 SPECIFIC EXAMPLES OF CMP QUALITY ISSUES

Why CMP quality issues persisted	Number of Examples	Proportion of Total (%)
Not detected / unknown	43	45
Value or profit motivation	31	33
Difficult to detect	7	7
Acceptable practice as per GxP regulations and pharmacopeia	7	7
Oily nature susceptible to Aflatoxins	3	3
Overharvesting	1	1
Rapid commercialisation	1	1
Supply and demand	1	1
Lack of traditional preparation	1	1

The theme of improvements was most divergent in both the questionnaire and in the examples specified by informants. Respondent suggestions centred around improving both testing and legislation, so that the natural integrity of CMP could be better preserved, and reducing opacity between workers in the supply chain so that authentic CMP reached consumers. This was reflected in the specific examples given by the informants, where in 82% out of the 95 improvements suggested for the specific examples were those around better analytical testing and practitioner surveillance for quality issues. Education featured highly in the thematic analysis of responses as a solution, but respondents gave only specific

examples of how this would practically apply to 5% of the examples. Raising the question of how practical and applicable education could act as an effective improvement, although theoretically relevant in discussions of CMP quality problems (*Table 3.16*). Some single and individual suggested improvements were not apparent from the thematic analysis, that favoured more similar narrative elements over those that are different. Those not highly apparent were: conservation; adopting food regulation for medicinal herbs; reducing vulnerability in the supply chain; and more harmonisation in global legislation. It also did not capture that seven of the 95 examples where informants did not know or specify a solution. However, the key informants consulted in this research were both experts and professionals and therefore perhaps would not be expected to give a response for the purposes of answering without some meaningful, relevant or authentic reply.

TABLE 3.16 SUMMARY OF PROPOSED IMPROVEMENTS TO RECURRENT CMP QUALITY ISSUES BY KEY INFORMANTS FROM THE COMBINED QUESTIONNAIRE AND INTERVIEW PROCESSES FOR 95 SPECIFIC EXAMPLES OF CMP QUALITY ISSUES

Proposed Improvements	Number of Examples	Proportion of Total (%)
Analytical surveillance / regulation	62	65
Analytical / practitioner surveillance	14	15
Not specified or don't know	7	7
Education	*5*	*5*
Conservation	1	1
Harmonisation of legislation	1	1
Practitioner surveillance	1	1
Reducing vulnerability of the supply chain	1	1
Regulation and increased practitioner surveillance	1	1
Regulation from food industry examples	1	1
Use of traditional preparation methods	1	1

The pilot questionnaire responses elicited more specific descriptions than those of the interview, such as in defining supply routes including the online retailers bypassing testing and regulation requirements. Whereas the interview responses around supply were somewhat more conceptual in nature, as when describing that different views held by those in the supply chain that imbued an sense of opacity that affected how they handle herbs, and consequently the quality.

The areas of highest divergence between the pilot questionnaire and interview findings could also be considered to arise from the differences in the either the

more specific or conceptual nature of the responses. Questionnaire contributions, particularly around potential improvements to the problem of persistent quality issues, were more clearly defined. Interview responses referred more to generalised ideas of variation in quality attributes creating difficulties in quality control, opacity in supply chains obscuring quality issues, and how the value of herbs motivate nefarious practices and consequently influence quality. These differences are best considered in light of the differences in the tools. A questionnaire in many aspects is a more specific tool that requests respondents to write information in their own time, location, and unprompted by an interviewer. Although informants were encouraged to write as much as they wished, the space is limited in the questionnaire tool under questions by a specific boundary and visual space in which to write. An interview, particularly when partially structured as used in this research, is comparatively less specific, and the responses were verbal and prompted, simulating a space that approximated a more natural discussion, with more open-ended and general responses. The tools, though doing so differently, both contributed to a detailed, varied and rich collection of responses that supported the research objectives.

3.7.2 Contributions to the research objective and three guiding questions

In general, both the pilot questionnaire and interview responses converged on contributing to the first question, in identifying the main CMP quality issues. Interview responses more extensively informed the second question in clarifying why the quality issues persisted than the other two questions. The questionnaire defined aspects of question three most clearly, around improvements to the

situation of persistent CMP quality issues. Collectively and in summary, the consultation of key informants informed the three guiding research questions as follows. Themes are highlighted in bold and underlined.

Question one: What are the main Chinese medicinal plant quality issues that persisted?

The main Chinese medicinal plant quality issues that persisted are**:**

- **Product integrity** compromises that affected CMP
- **Authenticity** and **Potency**

Including

- **Adulteration**
- **Substitution**
- **Contamination**

And

- **Toxicity**

Question two: Why do these problems recur?

The main CMP quality issues described in response to question one, recurred due to:

- **Product integrity** challenges recurring,

arising from

- **Human behaviour,**

often motivated by

- **Value** of CMP

that resulted in

- **Variation in quality** and
- **Toxicity**

that persisted due to

- **Opacity** in the supply chain obscuring detection and effect of,
- **Controls**

Question three: Can improvements be proposed?

Improvements proposed are through concentrating future research and efforts towards:

maintaining

- **product integrity**,

and ensuring

- **authenticity** of CMP

by addressing the effects of

- **human behaviour** through
- **education**

to reduce

- **error**

and

- **incentives** for nefarious practices

so that there would be an improvements in

- **capability** of those within the
- **supply chain** and
- **understanding** of Chinese medicine in context of
- **traditional** knowledge

and

- **herb care** standards and communal value of,
- **cooperation** effort and
- **honesty**

Further, by applying more Chinese medicine appropriate

- **legislation controls** so that
- **opacity** in obscured areas of the supply may be reduced, information shared and
- **controls** for testing and therefore detection could be rendered more effective for CMP more widely across the whole supply chain.

The contributions of key informants found in this chapter will be assessed in the context of a case example in Chapter Four.

3.8 Limitations of the KI study

3.8.1 Participant bias and sampling issues

Consulting with Key informants (KI) was central to this research. KI are those who possess specific, specialist and conceptually ordered knowledge relevant to an area studied (Marshall, 1996). However, their focus on specific areas related to their expertise is known to influence their views and therefore introduce participant bias. Over-emphasis in one area could lead to misinterpretation by the researcher (Kumar, 1989). To minimise the effects of such bias, points that were raised by multiple participants, indicating a degree of saturation across different participants, were captured while coding participant responses. Multiple incidences of a similar points were illustrated by “hotter” parts of the resulting heat-map. These points of opinion with higher frequency coding were emphasised in the findings by the thematic analysis process which groups together expressions of common meaning.

Further, as all the questionnaire and some interview consultations were not conducted face-to-face some misinterpretation by the researcher could also occur, through lack of rapport, body and verbal language cues that would otherwise be present in a personal context (Choudhury, 2015).

Although these aspects could have presented during the study to an unknown extent, they were acknowledged in the design of the questionnaire and interview tools to minimise the effects of participant bias effects. Specifically, the clarity and simplicity in the content and phrasing of the questions were considered foremost

to maintain good research rigour by maintaining transparency, and to minimise any bias effects from leading or non-specific lines of questioning (Green and Thorogood, 2018; Jones et al., 2013).

Consulting with key informants intends to inform questions asked by collating specific responses in a narrow context, and in some instances assume that they generalise to a wider context (Guest, Bunce and Johnson, 2006). This relies on an assumption that data collected is accurate and can be extrapolated in a general sense to represent a larger population. It is difficult to evaluate what influence this aspect had while interpreting data in this study. Furthermore, including a greater number of KI could perhaps have offset any limited or overly specific responses to questions by comparisons with a greater number of participant responses, yet this study employed a relatively low sample number, 18 participants in 20 consultations.

To alleviate these influences somewhat, firstly, the approach taken was to capture the KI responses both quantitatively and qualitatively. This allowed interpretation of the findings in context of how lesser or greater they were emphasised by all participants collectively. Secondly, answers that were given to questions which repeated similar points and themes were considered of greater priority and considered as “major themes”, whereas those of lesser similarity were regarded as “minor themes” in synthesising the contributions of KI. There are ongoing debates in agreeing on the optimal number of participants for questionnaires and interviews. Some researchers pose that as little as 4 to 6 participants are suitably representative in such studies (Muellmann et al., 2021),

others hold that somewhere between approximately 20 (Green and Thorogood, 2004) to 60 is optimal (Ritchie et al., 2003; Britten, 1995). While there is considerable difference of opinion around the topic of specific numbers of participants, there is general consensus that the central and critical requirement is evidence of information saturation, rather than the number of participants, as the most important aspect in such studies (Hennink, Kaiser and Marconi, 2017; Francis et al., 2010; Miles and Huberman, 1994). Such saturation was observed in this research and was indicted quantitatively in the findings in the KI study, using the heat-map visualisation which indicated the specific number of repeated contributions to a similar theme.

3.8.2 Limitations of the interview participant information sheet

All invitees were invited to participate in an interview and were provided with a detailed participant information sheet in advance. On reflection, an incorrect assumption held by the researcher, given the references to confidentiality in the interview participation information sheet, was that the participants would also assume that the interviews would take place individually, one-to-one. However, when three professors from an undisclosed research organisation in China were being interviewed, they arrived together and expressed that they wished the other professors to be present also. Even after explaining that the research tool was designed for individual interviews and the contributions were confidential, they insisted on completing the interview together. When asked why they preferred this arrangement, one professor responded that it was “more comfortable” that way and further requested that they were not asked any political questions.

Chinese cultural sensitivities and difficulties arising during research interviews in China have been well-described (Lawrence, 2022), and researchers experienced in conducting interviews in China recommend engaging in as much a natural manner as possible and adapting to the situation at hand as best as is practicable (Eckhardt and Bengtsson, 2010). A clearer indication that the interview would be conducted one-to-one should be included in future participant information sheets for further follow-up research. Notwithstanding the unplanned events, the interviews were completed, and the contributions were informative.

3.8.3 Limitations of the thematic analysis approach

Drawbacks of using the thematic approach are manifest in its slow acceptance by the research community as a method. For some time it lacked a clear basic definition and consensus on how it should be performed (Attride-Stirling, 2001). Some proponents claimed that themes could “emerge” while reading data, implying that the researcher somehow played a passive role in interpretation which conflicted with the often qualitative research contexts in which it was used and presented (Taylor and Ussher, 2001). However, many of these opinions were based on perspectives informed by earlier prevailing analysis methods topical at the time. Such as grounded theory by proponents Glaser, Strauss and Corbin, (Glaser, 1992;Strauss and Corbin, 1998). Once thematic analysis was better philosophically and practically defined, in particular by Braun and Clarke (Braun and Clarke, 2006), it saw not only acceptance and experienced more widespread use throughout different fields of inquiry, it also achieved credibility through its increasingly rigorous application (Castleberry and Nolen, 2018).

Its strengths lie in its transparency and credibility, in addition to the flexibility imparted by its unsupervised nature, that is, it does not require pre-classified concepts to be constructed in advance, as in the case of hypothesis-driven investigations. This research was predominantly investigative and exploratory in nature. It required a method that supported the examination of a body of rich and complex data in a transparent and credible manner collected from a variety of sources across a number of disciplines within the field of Chinese herbal medicine. In retrospect it was suitable for the type of research conducted in thesis, which did not begin with a preconceived hypothesis of the research outcomes at the outset.

3.9 Conclusion of the KI study

Consulting key informants contributed in great detail, to more clearly defining the problematic CMP quality issues that emerged and persisted and the reasons why these quality issues persisted. Specific improvements could be proposed that built both upon the work of previous researchers, and formed from the collective opinion of experts in the field consulted in this study.

CMP quality issues occurred on a medium to large scale mainly due to challenges to the integrity of the herbal product and toxicity, that led to variable quality. They recurred due to the influences of human behaviour often incentivised by the value of herbs, recurring in an environment where such issues were obscured by variable circumstances at multiple stages in the supply chain. The CMP quality issues perpetuated in an environment of inadequate testing and legislation.

Improvements suggested focused on more suitable testing and legislation that better accommodates the specific and practical concerns of Chinese medicines in a global supply chain, such as more suitable and distributed testing in supply chains. Raising awareness through education of the communal benefits of cooperative effort, honest practices and maintaining the quality of CMP could reduce incentives for nefarious practices and human error that perpetuate CMP quality issues.

A case example with a number of problematic CMP quality issues was suggested by multiple of key informants, *Eleutherococcus nodiflorus*, could be examined to further evaluate the findings of this KI study.

Chapter Four The EN Study

Eleutherococcus nodiflorus Case Example

4.1 Aim and objective of the EN study

The aim of the EN study was to investigate why an unexplained case example of adulteration recurs in the Chinese medicinal plant, *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu adulteration with cardiotoxic *Periploca sepium* Bunge and a related plant, *Eleutherococcus senticosus*, so that a solution to the problem of its persistence may be proposed.

The objectives of the EN study was to collect Chinese medicinal plant samples; *Eleutherococcus nodiflorus, Periploca sepium* and *Eleutherococcus senticosus* from the global supply chain across mainland China, Taiwan and United Kingdom; then analyse the samples using high-performance thin-layer chromatography to determine their authenticity and investigate why this unexplained adulteration recurs, so that solutions to the problem of its persistence may be proposed. This is the second of the three main thesis objectives.

4.2 Background to the EN study

Eleutherococcus nodiflorus (Dunn) S.Y.Hu has been long used clinically to treat arthritic knee and back pain-type indications, termed bi-syndrome in Chinese medicine practice. The Chinese name, Wu jia pi (五加皮) refers to its physical five-leaf form, “wu” five, and “pi”, meaning skin, the outer root bark plant part used for medicinal purposes. It is more commonly known as *Eleutherococcus gracilistylus*, one of its 20 synonyms, meaning in Latin, “free-berried slender and sharp” that describes its physical form. The *nodiflorus* species Latin name refers to its flowers

which bloom from nodes in a knot-like fashion. Most of its other 18 synonyms are variations of *gracilistylus* and its former name, *Acanthopanax gracilistylus* (Plant list, 2022). EN is one of 37 species in the genus *Eleutherococcus* and a member of the Araliaceae Family. It grows throughout China on the edge of forests, in scrubland and sloping fields, including mountainsides, valleys, river and roadsides. It is normally found in eastern areas at less than a thousand meters (Committee, 2007; Li et al., 2023).

Periploca sepium Bunge is used for similar clinical conditions to EN and ES, however it is more specifically used for non-sinew joint pain in patients presenting with oedema. Apocynaceae is the current accepted family name of the genus *Periploca* and has no synonyms. It also grows well in forest edges and slopes throughout China, however in contrast to EN it grows well in flat plains, and does not generally grow well in Guangdong, Guangxi, Hainan, and the Taiwan regions (Committee, 1995). Confusion arising from its similar Chinese name and clinical usage has been suggested as the reason it has been substituted in place as EN. The colloquial terms used for PS are “bei wu jia pi”, (北五加皮） “bei” meaning “northern” and “nan wu jia pi”, （南五加皮） or “southern” wu jia pi for EN. Although this is a justifiable basis for potentially confusing species and is suggested by authors as the main reason for substitution, the findings in this study, as detailed later, demonstrate otherwise (Foster, 2011, 2016; Huang et al., 2019). A bias was found in this study for inter-substitution of PS and EN, that is not accepted by the ChP monographs for either species.

The glycoside content in PS, specifically periplocin, is the main concern with potential for a cardiac adverse event as an adulterant. Case reports documented

PS substitution causing high serum digoxin which can affect heart function (McRae, 1996; Awang, 1996). These naturally occurring cardioactive glycosides are present in nine plant families, most commonly; Apocynaceae, Asclepiadaceae, Brassicaceae, Fabaceae, Hyacinthaceae, Leguminosae, Malvaceae, Scrophulariaceae and Solanaceae (Botelho et al., 2019). The cardiac glycoside content of PS and related phytochemistry was previously well researched, although most were in the Chinese language. This Chinese research has recently and extensively been reviewed in English (Huang et al., 2019, p32). These reports suggested that PS was both associated with adverse events and occasionally found in market surveys as an adulterant. However, the extent and reasons for PS adulteration in the EN supply remained undetermined.

Notwithstanding the cardiotoxicity of PS, adverse reports associated with its use are not widespread. This may be a consequence of low reporting rates, however it is likely due in part to periplocin possessing low oral availability and therefore, even when present, it is not easily absorbed (Yi et al., 2010). Previous studies indicated that a relatively high concentration (15.20 mg of periplocin for every / kg of body weight) was necessary to effect fatalities in half the mice population to which it was administered. However, cardiac abnormalities were observed in other animal studies at a relatively low concentration of 0.39 mg / kg (Sun et al., in Huang et al., 2019). Notably, the amount of PS root bark extracted in water, similar in preparation to that used in routinely in human herbal prescriptions, demonstrated the highest correlation with toxic effects, and not the Chinese pharmacopeia (ChP) quality marker 4-methoxysalicylaldehyde, which did not result as an indicator of the relative toxicity of the PS. Of greater concern is that

cardiac glycosides, including periplocin, are more soluble and exhibit greater toxicity in ethanol than water (Huang et al., 2019, p38; Sun, Wang and Huang, 2010; Yong, Xiao-lu, Zhi-ye and Rong, 2012). EN has been commonly used for centuries to make Wu jia pi wine, CP: “Wu jia pi jiu” (五加皮酒), (Li et al., 2023). The wine typically contains 55% ethanol by volume, an approximate alcohol concentration long known optimal for extracting cardiac glycosides (Jacobs and Hoffmann, 1928, p524; Dzyubak et al., 2001, p8). While EN does not present a cardiotoxic risk in such wine preparations, the effects of the commonly found substitute PS have to date not been determined (Li et al., 2023).

EN’s long-use has been documented in Chinese medicine classical texts for at least one millennia, however attention was drawn to adulteration of its Araliaceaea plant family with PS following a high-profile case of a “hairy baby” in 1990, when a paediatrician and others reported the observation of a significantly androgenised baby born to a mother taking high doses of *Panax ginseng* C.A.Mey., adulterated with PS. Verification of samples by Canadian health authorities found it was more likely as a result of excessive consumption of ES, which imparted a steroidal effect, mistakenly identified as ginseng, and with no PS involved (Waller et al., 1992). Later, this was refuted and declared as being due to PS, further contributing to the confusion surrounding EN and PS adulteration which already included a series of anonymous journal letters, contradictory findings and erroneous scientific reports of mistaken species (Koren et al., 1990; Fong, 2002; Foster, 2011). Therefore, ES was also sampled in this investigation as a potential adulterant.

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim., is a relative of EN in the Araliaceae family, sometimes referred to as the ginseng family, which includes Panax ginseng. The 11 synonyms of ES are mainly variations of *senticosus* and was formerly known as Acanthopanax senticosus, a Latin derivative meaning “prickly ginseng" bearing similarity to its Chinese name, Ci wu jia, (刺五加), Ci meaning “thorny”. It became better known as Siberian ginseng in the 1960s when marketed as an alternative to the more expensive panax counterpart following Soviet Union research in the 1940s which found equivalent phytochemical properties and clinical use cases (Davydov and Krikorian, 2000). It grows extensively in Russia, Korea and Japan, and throughout China in scrubland, forests, roadsides, valleys, mainly below 2000 meters (Committee, 2007). ES is used in Chinese medicine practice for similar indications as EN, but is used more for patients observed with weaker constitutions and those with difficulty adapting to stress, as an “adaptogen”.

The botanical synonyms for the EN and ES species together with their Chinese names and accepted synonyms are summarised in *Table 4.1.* PS has no synonym.

TABLE 4.1 LATIN BOTANICAL PLANT NAMES AND SYNONYMS FOR *ELEUTHEROCOCCUS NODIFLORUS* (DUNN) S.Y.HU *AND ELEUTHEROCOCCUS SENTICOSUS* (RUPR. & MAXIM.) MAXIM

Plant name Latin	***Eleutherococcus nodiflorus (Dunn) S.Y.Hu***	***Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.**
Chinese (Pinyin, Characters)	Wu jia pi, 五加皮	Ci wu jia, 刺五加
Synonyms	*Acanthopanax spinosus* Pavol. *Acanthopanax gracilistylus* W.W.Sm. *Acanthopanax gracilistylus* var. major G.Hoo *Acanthopanax gracilistylus* var. trifoliolatus C.B.Shang *Acanthopanax gracilistylus* var. villosulus (Harms) H.L.Li *Acanthopanax hondae* Matsuda *Acanthopanax hondae* var. *armatus* Nakai *Acanthopanax hondae* var. *inermis* Nakai *Acanthopanax nodiflorus* Dunn *Acanthopanax villosulus* Harms *Aralia palmata* Lour. *Aralia scandens* Poir. *Eleutherococcus gracilistylus* (W.W.Sm.) S.Y.Hu *Eleutherococcus gracilistylus* var. *major* (G.Hoo) H.Ohashi *Eleutherococcus gracilistylus* var. *nodiflorus* (Dunn) H.Ohashi *Eleutherococcus gracilistylus* var. *nodiflorus* (Dunn) K.L. Zhang *Eleutherococcus gracilistylus* var. *trifoliolatus* (C.B.Shang) H.Ohashi *Eleutherococcus gracilistylus* var. *villosulus* (Harms) Q.S.Wang *Eleutherococcus villosulus* (Harms) S.Y.Hu *Hedera scandens* (Poir.) DC.	*Acanthopanax asperatus* Franch. & Sav. *Acanthopanax senticosus* (Rupr. & Maxim.) Harms *Acanthopanax senticosus* var. *brevistamineus* S.F.Gu *Acanthopanax senticosus* f. *inermis* (Kom.) Harms *Acanthopanax senticosus* f. *subinermis* (Regel) Harms *Acanthopanax senticosus* var. *subinermis* (Regel) Kitag. *Eleutherococcus asperatus* (Franch. & Sav.) Koidz. *Eleutherococcus senticosus* f. *inermis* Kom. *Eleutherococcus senticosus* var. *subinermis* Regel *Eleutherococcus senticosus* f. *subinermis* Regel *Hedera senticosa* Rupr. & Maxim.

Adapted from the world of flora consortium database and Flora of China database (Committee, 1995), (Committee, 2007), (WFO, 2022)

EN adulteration is detectable, known and reported (Hoarau, 2014; Leon and Lin, 2017; Wagner et al., 2010). Foster, Hosbas and Brinckmann previously attempted to clarify confusion around the adulteration of EN, PS and ES species. They compiled historical accounts and contemporary examples relating to *Panax* spp., and ES. However, specific study of EN, its supply and substantive laboratory analysis of adulteration with PS was not completed (Foster, 2016; Hosbas, 2022). The research presented here is intended to contribute further insight into this area through the collection of specific samples in greater sample numbers than previously conducted over a wider global area. This study

determined the extent of inter-substitution adulteration that occurs between the three species, and highlights where, why and how likely it recurred. It found that cardioactive PS is likely consumed unknowingly by patients who consume EN, even though this adulteration is known, and testing is mandated by regulation. Improvements and solutions are suggested to this problematic quality issue in this chapter.

4.3 Methodology

4.3.1 Sample collection

A total of 106 samples of EN, PS and ES herbal material were sampled between 29th December 2017 and 28th June 2020, from a combination of the two largest international CMP markets, in Bozhou, Anhui, Anguo in Hebei, and a convenience selection of outlets along the EN supply chain including the Taiwan and the UK regions (*Table 4.2*). Although it was hoped sampling could be conducted at the third and fourth largest international CMP markets in Yuzhou, Henan and Chengdu, Sichuan, they could not be accessed due to a global outbreak of COVID-19. Due to the uncertainly of the global pandemic situation, analysis and reporting was progressed with samples from the two largest markets. In total 61 EN, 20 PS and 25 ES samples were collected from 18 cities in three global regions: 71 from mainland China, 22 London and 13 Taiwan (*Tables 4.2* and *4.3*).

Ninety eight were purposefully convenience sampled by the doctoral researcher. A further eight samples (S1, S2, S6, S7, S8, S15, S104, and S105) were collected by proxy by the researcher's friends living in the mainland China and Taiwan region between 3rd January 2018 and 23rd February 2018 in the order of: Zhejiang (Kunyang) -> Gansu (Baiyin) -> Liaoning (Shenyang) -> Yunnan (Kunming) ->Taipei (Taipei).

TABLE 4.2 SAMPLE COLLECTION LOCATIONS, DATES AND SAMPLE IDENTIFICATION (ID) ASSIGNMENT

Region	Province	City	Dates	Sample ID numbers
Mainland China	Sichuan	Dazhou	29/12/2017 to	**3,4,5,9**
	Zhejiang	Kunyang	3/1/2018	**1,2**
Mainland China	Guangdong	Foshan, Dongguan, Guangzhou	3/1/2018 to 15/1/2018	**10,11,12,13,14**
	Gansu	Baiyin	07/02/2018 to	**6,7**
	Liaoning	Shenyang	13/2/2018	**8**
	Yunnan	Kunming	23/2/2018	**15**
Taiwan	Taiwan	Taichung, Taipei	1/8/2018 to 17/8/2018	**16-26**
Mainland China	Shanghai	Shanghai	20/08/2018	**27**
Taiwan	Taiwan	Taipei	13/9/2018	**104, 105**
Mainland China	Jiangsu	Nanjing	20/10/2018	**28 - 34**
UK	Greater London	London	10/6/2019 to 12/6/2019	**35-47**
Mainland China	Hebei	Anguo	18/8/2019	**60-80, 91,92**
	Anhui	Bozhou, Hefei	1/9/2019 to 2/9/2019	**81-90, 93-100, 108,118**
	Hubei	Qizhou, Hubei	2/9/2019 to 9/9/2019	**101-103**
	Beijing	Beijing	29/12/2019	**106,107**
UK	Greater London	London	23/6/2020 to 29/6/2020	**109-117**

TABLE 4.3 GEOGRAPHICAL DISTRIBUTION OF SAMPLES COLLECTED

Region	Province	City	*Total sample count*	Number of samples collected for each species		
				EN	PS	ES
Mainland China	Hebei	Anguo	***23***	8	7	8
	Anhui	Hefei	***12***	7	2	3
	Anhui	Bozhou	***8***	4	3	1
	Jiangsu	Nanjing	***7***	3	1	3
	Sichuan	Dazhou	***4***	3	1	
	Guangdong	Guangzhou	***3***	3		
	Hubei	Qizhou	***3***	2	1	
	Beijing	Beijing	***2***		1	1
	Gansu	Baiyin	***2***	2		
	Zhejiang	Kunyang	***2***	2		
	Guangdong	Dongguan	***1***	1		
	Liaoning	Shenyang	***1***	1		
	Guangdong	Foshan	***1***	1		
	Shanghai	Shanghai	***1***	1		
	Yunnan	Kunming	***1***	1		
Taiwan	Taiwan	Taichung	***8***	4	3	1
	Taiwan	Taipei	***5***	4		1
United Kingdom	Greater London	London	***22***	14	1	7

Fifteen of the 18 cities were in mainland China, two in Taiwan and one in the UK. The CMP materials were sourced from a distribution of ten outlet types, mostly (43 samples) from markets and traditional Chinese pharmacies (34 samples). The others from contemporary pharmaceutical drug pharmacies (14 samples), herbal suppliers (six samples), a botanical research facility (three samples), a farm (two samples), a hospital, (one sample), a manufacturing company (one

sample), a university (one sample), and a single sample from a private herbal medicine clinic (*Table 4.4).*

TABLE 4.4 SAMPLE COLLECTION DISTRIBUTION BY SOURCE OUTLET

Outlet	Abbreviation	Total sample count	Number of samples collected for each species		
			EN	*PS*	*ES*
Clinic	*CL*	**1**	1		
Manufacturer	*CM*	**11**	1		10
Traditional herbal pharmacy	*CP*	**23**	15	8	
Farm	*F*	**2**	2		
Hospital	*H*	**3**	2		1
Botanical research institute	*KS*	**13**	2		11
Market	*M*	**34**	22	10	2
Modern pharmacy	*P*	**13**	11	1	1
Supplier	*SP*	**5**	4	1	
Univeristy	*US*	**1**	1		

4.3.2 Sample name assignment

A sample naming convention was adopted to identify the sampling trip number, species, outlet type and sample analysis sequence. For example, CT8–XJP–M–S108 referred to a sample from the eight-collection trip, sourced as a Xiang jia pi herb (PS) at a market outlet, incrementally numbered as 108 in sequence. For brevity and clarity the samples are referred to throughout simply by sample sequence number, S1-47, S60-118 inclusive. The 106 samples were named in sequence from 1 to 118, with 48 to 59 omitted to avoid confusion with another concurrent project at the laboratory.

4.3.3 Materials and methods

All Botanical Reference Material (BRM) was obtained from Sun Ten Pharmaceutical Company, Ltd. Taiwan, for the three species: *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu, *Periploca sepium* Bunge and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.

All samples and BRM were deposited at the University of Westminster life sciences herbarium, 115 New Cavendish Street, London, UK.

4.3.4 HPTLC analysis equipment

The high-performance thin-layer chromatography instrument was supplied by CAMAG Ltd., via Omicron Ltd, UK., comprising: a TLC4 automatic sampler,

AD2C automatic development chamber with humidity control unit, twin trough development chamber 20x10 cm, chromatogram immersion device III (dip tank), plate heater model III and visualiser model 2.

Stationary phase HPTLC glass 20x10 cm plates, Si 60 F254 Merck HX258909 purchased from Sigma Ltd., UK.

Analytical Balance AG245 Mettler-Toledo Analytical Balance was used for weighing.

A coffee grinder was used for grinding samples, model De Longhi KG200 purchased from Argos Ltd., UK.

All solvents and acids were HPLC grade, purchased from Sigma Ltd. UK together with the system suitability markers and HPTLC visualisation spray kit. Sigma Ltd., catalogue numbers as noted in brackets. Toluene (650579-1L), dichloromethane (650463-1L), heptane (34873-1L-M), methanol (34885-2.5L-M), ethyl acetate (650528-1L), dimethyl sulphate (49497-10X1ML), ethanol (1009800500), sulphuric acid 98% (5438270250), acetic acid (45754-100ML-F). System suitability markers were borneol (15598-5G) and thymol (PHR1134-1G). Anisaldehyde spray reagent kit (SRA1-1KT).

4.3.5 HPTLC sample analysis

All samples and BRM were analysed using the HPTLC Association method, (HPTLC Association Method Adapted from Monograph 2432, European Pharmacopeia. 8.0., titled: Acanthopanax root bark, wu jia pi (*Eleutherococcus gracilistylus*) as developed by HPTLC association and the International Association for the Advancement of High Performance Thin Layer Chromatography (Association, 2015).

Test samples and BRM solutions were identically prepared. Approximately, 12 g to 15 g portions of material was ground in the coffee grinder for 30 to 40 seconds to a fine powder then sieved through a 0.70 mm metal mesh. 300 mg of this powdered material were accurately weighted and then mixed with 3 mL of methanol in a 5ml Eppendorf AG., tube. They were sonicated for 5 minutes and heated in a water-bath at 60°C for 5 minutes, then filtered using a 0.45 micron PDVF syringe filter Millipore Ltd. The filtrate was the solution analysed.

System suitability solution preparation used 5 mg of thymol accurately weighed on a weighing boat, then washed and made up to 5 mL in a volumetric flask with methanol. 8 mg of borneol was similarly weighed and made up volumetrically in 5 mL methanol.

The HPTLC plates and solvents were prepared on the same day in advance of the analysis. On the HPTLC plates a horizontal pencil-line was drawn from approximately 30 mm left and right edges at a height at 70 mm to mark the full

chromatographic separation distance. 98:2 v/v dichloromethane: ethyl acetate mixture was used for the mobile phase.

The chromatography conditions and instrument data acquisition were set for the HPTLC system using the preinstalled CAMAG Vision Cats software. The HPTLC plate was saturated for 20 minutes in the development tank with approximately 10 ml mobile phase. The system was activated for 10 minutes with a saturated $MgCl_2$ aqueous solution and the humidity was set to 33% in the software.

The sample run injection sequence was set up in a table of twelve columns (C1-12) representing twelve sample tracks on each test plate. They comprised three groups; the first, SST solutions, C1, Borneol and C2, Thymol, the second group BRM, C3, WJP, C4, XJP and C5 CWJ. The third group, C6 to C12 inclusive, were the test samples.

1µL of all solutions were applied by the autosampler. Development stopped automatically when the mobile phase reached the 70 mm pencil mark line. The Chinese name initials WJP, XJP and CWJ were used in favour of EN, PS and ES for the purposes of clarity to minimise the risk of confusion between similar sample initials EN and ES.

Detection of the samples separated on the HPTLC plates was completed by derivatising each plate to more clearly visualise the chromatogram bands. The derivatisation reagent was prepared using 170 ml of ice-cooled methanol with 20

ml of acetic acid and 10 ml of sulphuric acid (slowly and carefully) added. A further 1 ml of anisaldehyde was added.

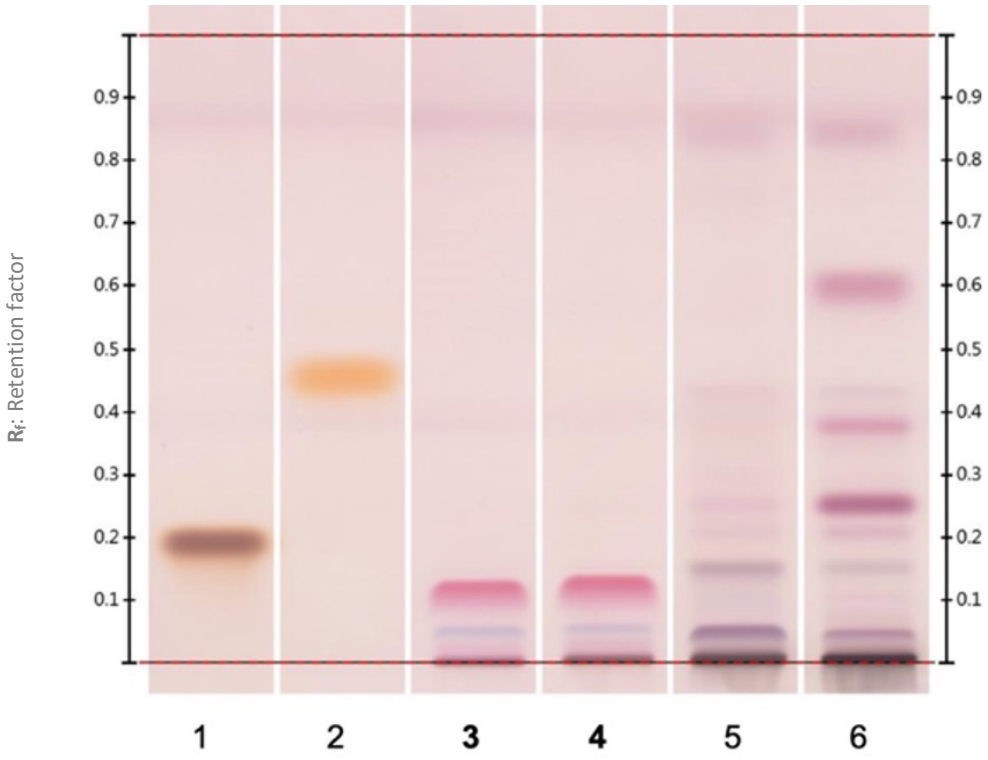
The dip tank was filled with the derivatisation solution. Each HPTLC plate was then submerged into this with the automated dipper using the settings; time 0, speed 5. The plate was left to hang in place for approximately 30 seconds, then excess solution was wiped from the bottom edge. The plate was heated to effect derivatisation by placing flat on the hotplate pre-set to 100^{o}C for exactly five minutes. Each derivatised plate was examined under white remission and transmission tungsten (RT) light in the instrument visualiser module. The relative retention (Rf) values were automatically determined by the software by moving a cross-hair cursor manually to the centre of each visible chromatogram band of interest.

Verification that the analysis had completed sufficiently according to the pharmacopeia methods was indicated by separation of the two SST solutions on each analysis plate, which indicated that appropriate chromatographic conditions and test sample separation conditions were met. The separation was considered valid when the results were within the SST criteria, as stated in the method: “System suitability test: Brown zone at around Rf 0.20 for borneol and orange zone around Rf 0.45 for thymol”, where Rf indicated retention factor, the distance travelled by the band of interest divided by that of the solvent.

4.3.6 Evaluation of HPTLC data to determine sample authenticity

The pattern of the coloured bands, or “fingerprints” of the BRM reference solutions, were visually compared with the test solutions to determine if they contained matching (authentic), or a set of non-comparable bands (adulterated). The assessment was further verified by comparing the results of the BRM and test solutions with the published validated method example fingerprints in *Figure 4.1.*

FIGURE 4.1. EXAMPLE HPTLC PLATE FROM THE HPTLC ASSOCIATION METHOD ADAPTED FROM THE EUROPEAN PHARMACOPEIA 2013, 8TH EDITION, MONOGRAPH NUMBER 2432



Track	Volume	Sample
1	1 µL	Borneol
2	1 µL	Thymol
3	**1 µL**	**Acanthopanax root bark 1 BRM**
4	**1 µL**	**Acanthopanax root bark 2**
5	1 µL	Eleuthero root
6	1 µL	*Periploca sepium* root bark

Acanthopanax root bark = EN, Eleuthero root = ES, *Periploca sepium* = PS

4.3.7 Identifying where authentic samples were supplied

The authenticity results were tabulated where the number of samples passing the HPTLC authenticity test was expressed as a percentage of the total samples collected for each of the three species, EN, PS and ES.

The percentage authentic samples were then tabulated together with the collection location and source outlet type for further consideration of where adulteration of EN occurred in the supply chain.

4.3.8 Calculating distances between sample collection locations

To assess if authenticity was related to distance from the market sources in the supply chain, the distances between each sample collection location was calculated using the Haversine formula and assuming a straight line distance between global positioning satellite (GPS) co-ordinates in decimal units, and a 6,371 kilometres average radius of the earth (Chopde and Nichat, 2013; Frank, 2006)

A Microsoft excel spreadsheet software was used for the formula calculations:

"=ACOS(COS(RADIANS(90-LAT1)) * COS(RADIANS(90-LAT2)) + SIN(RADIANS(90-LAT1)) * SIN(RADIANS(90-LAT2)) * COS(RADIANS(Long1-Long2))) * 6371"

Where: all co-ordinates are in decimal units.

And: LAT1= latitude co-ordinate of the first sampling location
LAT2= latitude co-ordinate of the second sampling location
Long1= longitude co-ordinate of the first sampling location
Long2= longitude co-ordinate of the second sampling location

Result: Theoretical straight line distance in kilometres between the two calculated sample collection locations.

To preserve confidentiality of the herbal traders and collaborators, a random approximate +/- 5 km error was applied to the GPS co-ordinates in the calculation, and wherever possible the nearest town or city centre location was used, as referenced by the Google Maps software program. Any remaining GPS co-ordinate correlation to an individual or company in operation is strictly coincidental, unintentional, and does not identify any particular individual trader.

4.3.9 Assessing if adulteration recurs due to intended clinical substitution or unintended misidentification

The medicinal properties of each CMP from a classical Chinese medicine perspective were tabulated for comparison, namely their nature, functions and indications.

Reference books were used to authenticate and differentiate EN adulterants, ES and PS, from two groups, the first, historical and the second, contemporary sources were also reviewed.

The first group were ten eminent classical Chinese herbal medicine collections used for reference over an approximately 600-year period selected following consultation with, and through the assistance of, staff at the Beijing Academy of Medical Sciences (CAMS), based on their expertise in the field of frequently referenced Chinese medicine historical sources (*Table 4.5*).

TABLE 4.5 TEN EMINENT CLASSICAL CHINESE HERBAL MEDICINE COLLECTION REFERENCED OVER A 600 YEAR PERIOD

Ten Classical Chinese herbal medicine collections
Shen Nong's Herbal Classic (神農本草經), pre-CE 25
Mingyi Bielu(名醫別錄), CE 498
Bencao Tujing (本草圖經), CE 1061
Zhenglei Bencao (證類本草), CE 1116
Bencao Mengquan (本草蒙筌), CE 1565
Bencao Gangmu (本草綱目), CE 1578
Bencao Yuanshi (本草原始), CE 1612
Bencao Huijian (本草匯箋), CE 1660
Bencao Congxin (本草從新) CE 1757

Records in the CAMS library catalogue were first searched electronically using the keyword "五加皮" (wu jia pi the Chinese name for EN), selected and then further inspected visually in-person.

Descriptions or illustrations from each reference text were noted, or in the case of drawings, photographed. They were tabulated together with any additional

details in the texts relevant to authenticating EN for further comparison and evaluation.

The second group were EN, ES and PS monographs published in contemporary pharmacopeias that included all ten Chinese pharmacopeias from 1963 to the current in edition in 2020.

Descriptions relevant to authenticating and detecting adulterated EN, PS and ES species were tabulated. For conciseness in summarising the large amount of textual material, the initial descriptions beginning with the first edition and further incremental changes in the monographs in subsequent editions over the 57-year period were denoted in the by the preface “+” or “-“, to indicate successive additions or omissions, respectively.

Additionally, six recent regional pharmacopeias spanning the years 2016 to 2020 were reviewed for inclusion of EN, ES and PS monographs. These included Europe (EP, 2019), Hong Kong (HKP, 2016), Taiwan (TP, 2019), Korea (KP, 2016), Japan, (JP, 2016) and the UK (BP, 2020).

Descriptions relevant to authenticating and detecting adulteration EN, PS and ES species were tabulated for further comparison and evaluation. The presence or absence of a monograph in each Pharmacopeia was denoted in the table by “✓” and “✕” , respectively.

4.3.10 Assessing if substitution recurs due intentional value-based substitution

The market values of EN, PS and ES from July 2019 to July 2022 inclusive, were plotted using a Microsoft Excel for Mac version 16.64 spreadsheet function, from a survey of sale prices listed in the Kangmei Bozhou market, published online at: https://www.kmzyw.com.cn/jiage/month_price_0103-0001.html, accessed 3rd August 2022, 10.34am.

4.3.11 Assessing analytical testing detection gaps in the EN herbal supply

The likelihood of adulteration recurring at an individual supply point along the EN supply chain stages, and cumulatively reaching a consumer, was calculated by tabulating nine common types of adulteration together with nine supply chain steps adopted from a simplified Booker-Heinrich supply chain model (Booker et al., 2012).

A three-star Likert scale was applied in a table form based on the general principles of Choudhary et al., (2022) and EMA (2016) for capturing and ranking risk in a supply chain. The Likert scale was generated using a combination of two variables. The estimated likelihood of a specific type of adulteration occurring at a supply stage, and whether the pharmacopeia method testing for the specific type of adulteration was required by Good Practice (GxP) regulation.

The sum of the stars was the score of how likely adulteration could recur (*Table 4.6*).

TABLE 4.6 SCORING SYSTEM FOR RANKING THE LIKELIHOOD OF ADULTERATION RECURRING

Ranked Likelihood of adulteration recurring	**Adulteration likely?**	**Testing required?**	**Score**
More Likely	✓	✕	★★★
Less likely	✓	✓	★★
Unlikely	✕	✓	★
✓ = Yes, ✕ = No			

For the purposes of scoring an assumption was adopted, that if testing is required by legislation for a known and detectable adulterant, then it is somewhat less likely to recur, and conversely, if adulteration is likely to occur and testing is not required, then it is more likely to recur.

The likelihood was calculated and ranked in order for the substitution of EN with CMP such as PS and ES.

The sum of the number of stars across each column represented the ranked likelihood of nine types of adulteration recurring at a single supply chain step.

The sum of the number of stars across each row represented the ranked likelihood of nine types of adulteration recurring and reaching the consumer.

4.4 Results and Discussion

4.4.1 Verification of the HPTLC system suitability for analysis

The fingerprint pattern and position of the HPTLC chromatographic bands for the reference substances successfully separated in all of the HPTLC plates analysed, verifying the analytical method's expected performance and suitability to identify EN and its adulterants ES and PS, (*Table 4.7).*

TABLE 4.7 SYSTEM SUITABILITY TEST RESULTS FOR HPTLC ASSOCIATION METHOD FOR *ELEUTHEROCOCCUS NODIFLORUS* (ACANTHOPANAX ROOT BARK, WU JIA PI (*ELEUTHEROCOCCUS GRACILISTYLUS*), ADAPTED FROM EUROPEAN PHARMACOPEIA 2013, 8TH EDITION, MONOGRAPH NO. 2432

SST Criteria (For Relative Retention Time for white Light plates)	Borneol brown zone at R_f ~ 0.20	Thymol orange zone at R_f ~ 0.45	Pass / Fail
Plate 1 Samples S1 to S10	0.17	0.43	Pass
Plate 2 Samples S11 to S20	0.19	0.46	Pass
Plate 3 Samples S21 to S30	0.19	0.46	Pass
Plate 4 Samples S31 to S40	0.19	0.47	Pass
Plate 5 Samples S41 to S46	0.23	0.49	Pass
Plate 6 Samples S47 to S68	0.17	0.44	Pass
Plate 7 Samples S69 to S78	0.16	0.42	Pass
Plate 8 Samples S79 to S88	0.18	0.45	Pass
Plate 9 Samples S89 to S98	0.17	0.43	Pass
Plate 10 Samples S99 to S108	0.18	0.44	Pass
Plate 11 Samples S108 to S118	0.18	0.44	Pass
Test Overall: Pass / Fail		**Pass**	

All HPTLC analyses passed the SST requirements. The SST varied slightly but acceptably around the expected relative retention factor of 0.20 and 0.45 by a maximum of +/- 0.04. This variation is likely due to HPTLC plates exposed to slightly different levels of moisture in the laboratory on different days before being placed in the controlled humidity and temperature conditions within the enclosed HPTLC system.

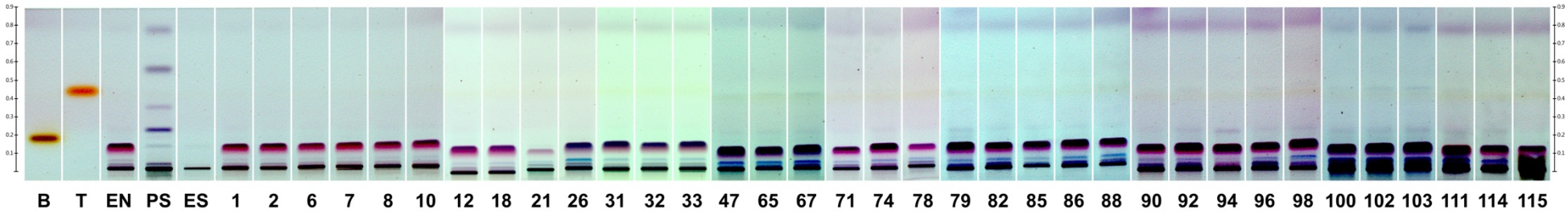
The HPTLC fingerprint patterns of the EN, PS and ES botanical reference material in all analysed samples compared similarly with that of published in the HPTLC association method, shown previously in *figure 4.1*.

4.4.2 HPTLC results for authentic, non-authentic, and unidentified samples

HPTLC plate tracks for the results are shown in *figures 4.2* to *4.6 inclusive*, grouped as follows;

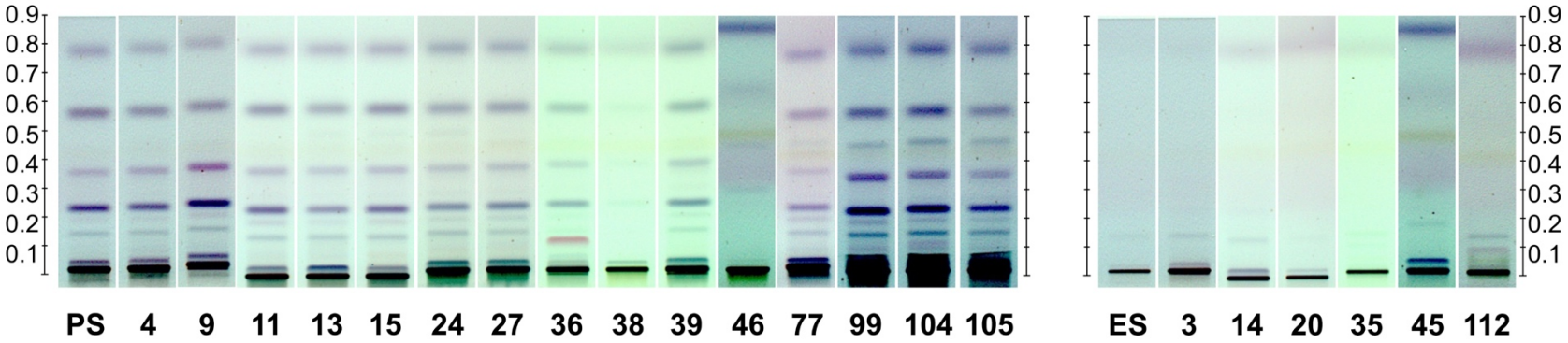
- Samples sourced as EN resulting as authentic, in *figure 4.2*.
- Samples sourced as EN resulting as non-authentic and identifying as PS or ES, in *figure 4.3.*
- Samples sourced as PS resulting as EN, in *figure 4.4.*
- Samples sourced as ES resulting as authentic, non-authentic and identifying as EN or PS, in *figure 4.5.*
- Samples which could not be identified, *figure 4.6.*

FIGURE 4.2 HPTLC ANALYSIS IMAGES FOR SAMPLES SOURCED AS *ELEUTHEROCOCCUS NODIFLORUS* AND RESULTING AS AUTHENTIC, VIEWED UNDER VISIBLE LIGHT



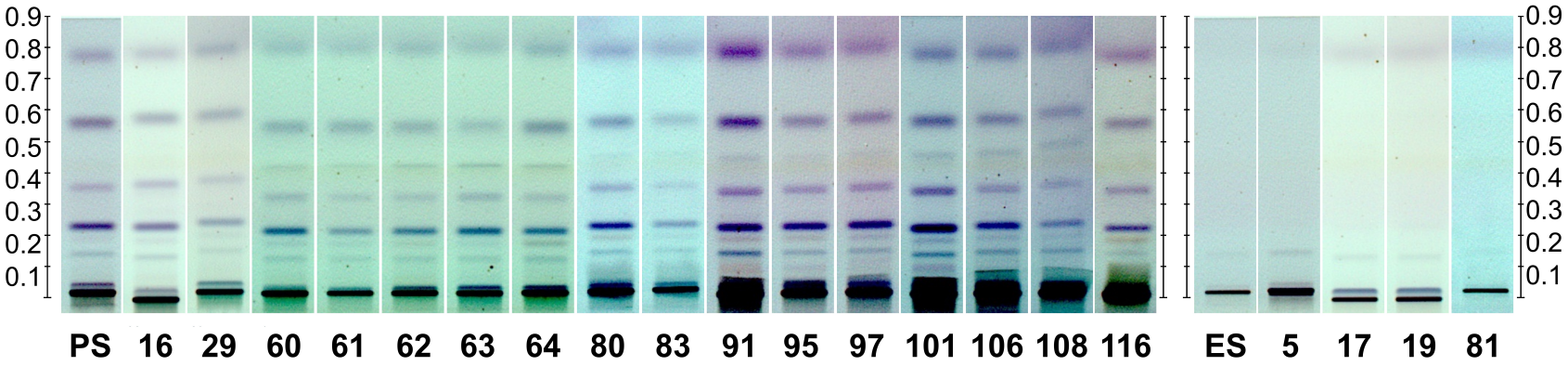
B= Borneol standard, T= Thymol standard. EN, PS and ES= *Eleutherococcus nodiflorus*, *Periploca sepium* and *Eleutherococcus senticosus* botanical reference material, respectively.

FIGURE 4.3 HPTLC ANALYSIS IMAGES FOR SAMPLES SOURCED AS *ELEUTHEROCOCCUS NODIFLORUS* RESULTING AS NON-AUTHENTIC AND IDENTIFIED AS THE SPECIES *PERIPLOCA SEPIUM* (LEFT) AND *ELEUTHEROCOCCUS SENTICOSUS* (RIGHT)



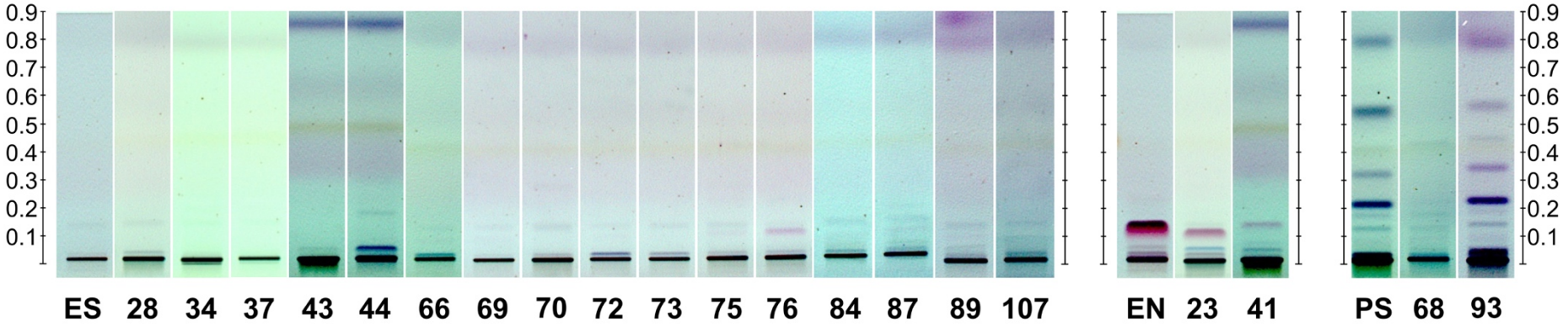
PS and ES= *Eleutherococcus nodiflorus*, *Periploca sepium* and *Eleutherococcus senticosus* botanical reference material, respectively.

FIGURE 4.4 HPTLC ANALYSIS IMAGES FOR SAMPLES SOURCED AS *PERIPLOCA SEPIUM* RESULTING AS AUTHENTIC (LEFT), AND NON-AUTHENTIC (RIGHT) IDENTIFIED AS THE SPECIES *ELEUTHEROCOCCUS SENTICOSUS*



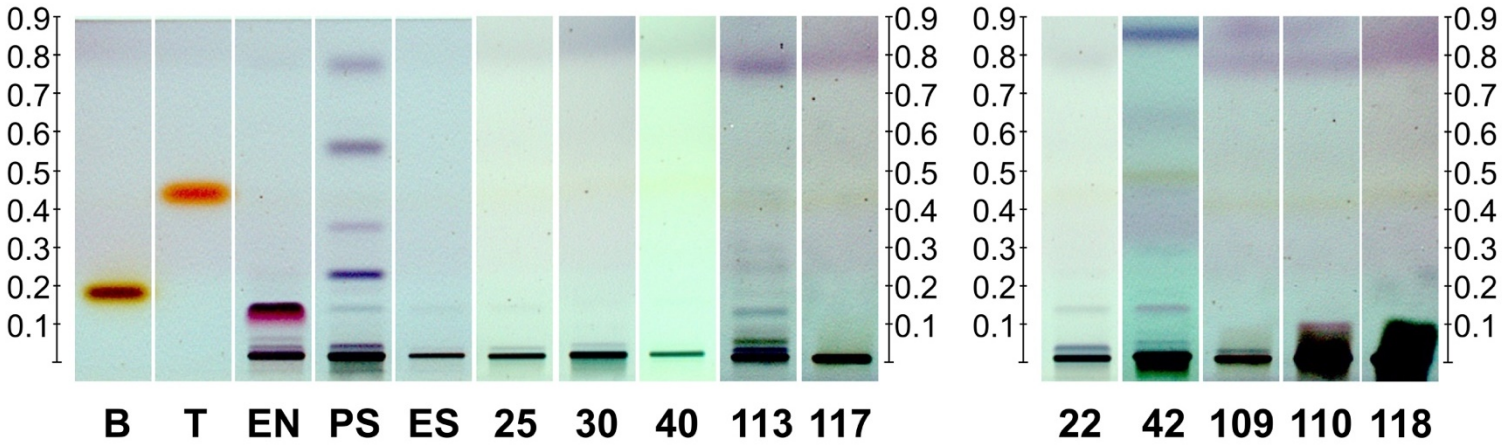
PS and ES= *Periploca sepium* and *Eleutherococcus senticosus* botanical reference material, respectively.

FIGURE 4.5 HPTLC ANALYSIS IMAGES FOR SAMPLES SOURCED AS *ELEUTHEROCOCCUS SENTICOSUS* RESULTING AS AUTHENTIC (LEFT), AND NON-AUTHENTIC IDENTIFIED AS THE SPECIES *ELEUTHEROCOCCUS NODIFLORUS* (MIDDLE), AND *PERIPLOCA SEPIUM* (RIGHT)



ES, EN and PS= *Eleutherococcus senticosus*, *Eleutherococcus nodiflorus*, *Periploca sepium* botanical reference material, respectively.

FIGURE 4.6 HPTLC ANALYSIS IMAGES FOR SAMPLES WHICH COULD NOT BE IDENTIFIED



B= Borneol standard, T= Thymol standard.

EN, PS and ES= *Eleutherococcus nodiflorus*, *Periploca sepium* and *Eleutherococcus senticosus* botanical reference material, respectively.

Differences in brightness and colour tone were observed in the HPTLC plate image backgrounds. This was also evident in other published HPTLC data, possibly due to the sensitivity of highly oxidisable p-anisaldehyde used in the derivatisation solution to temperature and exposure to air. Slight irregularities in the time periods between completing the heating step and captaining the image can also cause variation of this type, however the sensitivity and variations observed were minor and have been previously documented (Reich and Schibli, 2007, p234; Gayathri, 2014). Such analysis variations could perhaps be minimised by the use of automated HPTLC instrument modules that store and load analysis plates, together with dipping, heating and image capture steps, in a temperature-humidity controlled environment.

Improvement of the inter-analysis colour reproducibility is of particular importance as the EP commission endorsed the use of HPTLC for semi-quantitative analysis of Chinese medicine (Commission, 2023). It is expected HPTLC will be included in future monographs for assessing the content and purity of CMP (Noviana, Indrayanto and Rohman, 2022).

4.4.3 Summary of the HPTLC analysis results

Some, 67 of the 106 samples collected (63.2%) resulted as authentic, 39 samples (36.8%) non-authentic, of which 10 samples (9.4%) could not be identified (*Table 4.8*).

TABLE 4.8 SUMMARY OF HPTLC ANALYSIS RESULTS FOR 106 EN, PS AND ES SAMPLES

	SOURCED SPECIES AS / Number of samples		IDENTIFIED SPECIES AS / Number of samples			UNIDENTIFIED Number of samples
			EN	***PS***	***ES***	
EN	61		35	15	6	5
PS	20		0	16	4	0
ES	25		2	2	16	5
Total	*106*		*37*	*33*	*26*	*10*
% Authentic per specie			**57.4**	**80.0**	**64.0**	
% Authentic all species				**63.2**		

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*

When these results are considered proportionately. EN was the least authentic of the three species tested, at 57.4% authentic, one-quarter was substituted with PS, 24.6%, and a further six samples, 9.8% with ES. Five EN samples, 8.2%, could not be identified as EN, ES or PS.

ES resulted as the second most authentic species collected, with 16 of the 25 samples (64%), identified and equal amounts of EN and PS substitution with two samples, at 8% each. A relatively high proportion of ES could not be identified (five samples, 20%), which may be due to the limitations of the HPLTC method in identifying ES, unknown chemical adulteration or unknown species adulteration. The fingerprints visualised in the HPTLC analysis plates for EN and PS are distinct with multiple bands, whereas the ES fingerprints are

comparatively indistinct with fewer bands. It was observed both in this analysis and in the reference HPTLC monograph method documentation (Association, 2015). Further analytical method development through greater extraction times to increase the ES concentration could perhaps improve resolution of ES in this analysis. Additionally, silica gel with higher theoretical plate resolution to effect wider separation and / or visualisation could help. Alternative derivatisation media for ES could be further explored, as seen in the Hong Kong Ci Wu Jia Monograph, which is optimised for eleutheroside B and E (HKCMMS, 2013). However, the method used here is that most suitable of currently available standard HPTLC methods for this investigation, as it was optimised specifically for resolving EN and PS samples solutions and their identities.

PS samples resulted as the most authentic of the three samples sets, 16 of the 20 samples (80.0%) positively identified. A further four non-authentic PS samples amounting to 20% identified as ES. Though approximately one-quarter of EN tested was substituted with PS, none of the PS was found substituted with EN in any of the three, mainland China, Taiwan or UK, regions, suggesting that there is a complete positive bias in the substitution of PS for EN. Some PS substitution with EN would be expected if unintended substitution arose from confusion of the similar Chinese names, WJP and XJP for EN and PS respectively, as reported by previous authors described in the background section 4.2 of this chapter. However, it was not observed in any of the 106 samples analysed in this study.

4.4.4 Geographical trends in EN authenticity

The regional distribution of samples collected were 71 (66.9%) from mainland China, 22 (20.8%) from the UK and 13 (12.3%) from Taiwan. A concentration of approximately 80% of samples were sourced from seven of the 18 cities; Anguo, London, Hefei, Bozhou, Taichung, Nanjing, and Taipei.

4.4.4.1 EN authenticity examined by distance from Bozhou

Locations from where less than three samples were sourced were excluded in drawing conclusions relating to trends to minimise small sample number bias in examining the geographic distribution of authentic samples. The location, co-ordinates and distance from Bozhou market is shown in (*Table 4.9*).

TABLE 4.9 SAMPLING LOCATIONS, CO-ORDINATES, AND DISTANCE FROM BOZHOU CHINESE MEDICINE MARKET

Location	Latitude ° North	Longitude ° West	Distance from Bozhou market (in kilometres)
Bozhou	33.85	115.78	0
Hefei	31.82	117.23	263
Nanjing	32.06	118.76	342
Qizhou	30.23	115.44	404
Anguo	38.42	115.33	510
Shanghai	31.23	121.49	609
Kunyang	27.67	120.57	825
Dazhou	31.21	107.47	832
Baiyin	36.55	104.14	1099
Shenyang	41.80	123.43	1110
Taipei	25.04	121.56	1128
Taichung	24.16	120.65	1176
Guangzhou	23.13	113.26	1217
Dongguan	23.03	113.75	1218
Foshan	23.02	113.12	1231
Kunming	25.07	102.68	1598
London	51.50	-0.13	8660

In general, more authentic samples were found nearer the two major Chinese herbal market sources in mainland China. All sampling locations with more than 71% authentic EN were found within 510 km of the largest international CMP market in Bozhou, including Nanjing, that borders Bozhou's Anhui province. The second highest level of authenticity, 88%, for EN was found in Anguo, the second largest Chinese herbal market. Progressively lower authenticity levels for EN were observed in samples sourced further from these markets, where in Taichung, Taiwan half were found authentic (50%) and less than one-third, 29%, authentic in London (*Table 4.10*).

TABLE 4.10 PERCENTAGE OF AUTHENTIC EN SAMPLES IN ORDER OF DISTANCE FROM BOZHOU MARKET, FOR LOCATIONS WHERE MORE THAN 3 SAMPLES WERE SOURCED

City Sourced	**Region**	**Distance from Bozhou Market** *in Kilometres*	**% AUTHENTIC**
61 EN samples sourced			*35 EN* samples identified
Bozhou	***Mainland China***	0	100
Nanjing		342	100
Qizhou		404	100
Anguo		510	88
Hefei		263	71
Guangzhou		1217	33
Dazhou		832	0
Taichung	***Taiwan***	1176	50
Taipei		1128	25
London	***UK***	8660	29

Dashed line indicates 70% threshold of authentic samples

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*

This trend is also apparent for the 106 samples of the three species in aggregate. More than 75% of the three species were found to be authentic within the Bozhou and surrounding 510 km area (*Table 4.11).*

TABLE 4.11 RESULTS OF THE PERCENTAGE OF EN, PS AND ES SAMPLES FOUND AUTHENTIC RANKED IN ORDER OF DISTANCE FROM BOZHOU MARKET, FOR LOCATIONS WHERE MORE THAN 3 SAMPLES WERE SOURCED

City Sourced	**Region**	**Distance from Bozhou** *in Kilometres*	**% AUTHENTIC**
61 EN, 20 PS, 25 ES samples sourced			*35 EN, 16 PS, 16 ES* samples identified
Qizhou	***Mainland China***	404	100
Anguo		510	91
Nanjing		342	86
Hefei		263	83
Bozhou		0	75
Guangzhou		1217	33
Dazhou		832	0
Taichung	***Taiwan***	1176	38
Taipei		1128	20
London	***UK***	8660	36

"--------" Dashed line indicates 75% threshold of authentic samples

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*

Although no other directly comparable studies for adulteration of EN were previously completed, a large sample number market survey of different CMP was previously published (Han et al., 2016). Han et al. (2016) determined the authenticity of 1,436 samples comprising 295 different types of CHM using DNA analysis, which included seven ES, eight PS and four ES samples. Four of the seven EN samples, 29%, resulted as non-authentic, three of the four ES samples, 75%, non-authentic, all eight of the XJP resulted as authentic. Although this study showed some variation in findings for the level of EN authenticity, that is, 57% in this study versus 70% for Han et al. (2016), agreement was found in the complete bias of PS substitution for EN, and none apparent for PS with EN. Marked differences between the two studies were observed in the levels of authenticity for ES, however the HPTLC analysis used in this study did not identify 20% of the ES samples in comparison to the higher identification rate with their use of DNA analysis.

Systematic geographical sampling at greater sample numbers and at regular distances from the markets is recommended for further investigation, perhaps in conjunction with more detailed spatial analysis, such as that demonstrated by other authors researching herbal supply chains and using techniques combined with statistical principle component analysis (Yao et al., 2018; Booker et al., 2014; Bi et al., 2020).

Furthermore, although the authenticity of EN is assessed here relative to the distance between the sampling locations at supply outlets in addition to the Bozhou and Anguo markets, consideration of the original cultivation sources is

also recommended in future studies to determine the relevance, if any, of the distance between sampling locations and the original growing areas.

4.4.4.2 Sample authenticity examined by cultivation locations

The focus of this study was to investigate the extent of adulteration for EN in context of where it was supplied, therefore the original cultivation locations of the samples were not sought at the time of sampling. However, in retrospective consideration, 12 samples out of the 106 sourced indicated original cultivation locations on packaging. Notably, all of these resulted as authentic (*Table 4.12*). The 12 samples were cultivated in seven diverse regions and represented the three types of species: five EN, one PS and six ES. Most of these, 10 samples, were sourced from markets and two samples from modern (non-traditional style) pharmacies. A limitation here is that the stated cultivation sources on packaging were assumed accurate and were not further verified.

TABLE 4.12 SUMMARY OF SAMPLES WITH ORIGINAL CULTIVATION REGION INDICATED ON PACKAGING. SAMPLE IDENTIFICATION, CULTIVATION AND SAMPLED REGION, AS SPECIES WERE SOURCED AND IDENTIFIED ARE SHOWN

Sample No.	Stated Cultivation Region	Sampling Region	Sourced as	Identified as
S6	Shanxi	Gansu	EN	EN
S12	Guangxi	Guangdong	EN	EN
S61	Shanxi	Hebei	PS	PS
S65	Hubei	Hebei	EN	EN
S66	Jilin	Hebei	ES	ES
S70	Jilin	Hebei	ES	ES
S71	Hunan	Hebei	EN	EN
S72	Heilongjiang	Hebei	ES	ES
S73	Heilongjiang	Hebei	ES	ES
S74	Henan	Hebei	EN	EN
S75	Heilongjiang	Hebei	ES	ES
S76	Heilongjiang	Hebei	ES	ES

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*

4.4.4.3 Sources of unidentified samples

The identity and therefore authenticity of some samples in this study was not established. Ten samples could not be identified, representing 9.4% of the total 106 samples. It is undetermined whether this resulted from unknown species or other chemical adulterants interfering with the HPTLC analysis method. The unidentified sample proportion in this study is comparable with that found by Han et al. (2016), who observed that 176 of 1,436 (12%) of the CMP samples collected from mainland China could not be identified due to adulteration with sulphur, polysaccharides and other pigments, which prevented successful DNA amplification and analysis (Han et al., 2016). In this HPTLC-based analysis most unidentified samples were provided by suppliers, markets and traditional Chinese medicine pharmacy points of supply. One unidentified sample was provided by a botanical research facility. All PS was identified. The authenticity results were tabulated in order from farm to clinic based on a simplified Booker-Heinrich supply chain (Booker et al., 2012), for clearer comparison with sampling locations (*Table 4.13*).

TABLE 4.13 NUMBER OF UNIDENTIFIED SAMPLES AND THEIR SOURCES AT DIFFERENT SUPPLY STAGES

	SUPPLY STAGE									
					OUTLET					
SPECIES SOURCED	FARM	MANUFACTURER	MARKET	SUPPLIER	Modern Pharmacy	Traditional Chinese Pharmacy	Hospital	University	Botanical Research Facility	Clinic
EN	1	0	1	2	0	1	0	0	0	0
PS	-	-	0	0	0	0	-	-	-	-
ES	-	-	1	1	1	1	-	-	1	-

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*, " - " = no samples collected

4.4.5 Variability of sample authenticity along the supply chain

When the authenticity of the samples were examined from a supply chain perspective, in sequence from the cultivation stage through processing, manufacturing and onwards, there is an apparent general reduction in authenticity towards the consumer. This is likely due to samples presented with an increasing number of cumulative possibilities for substitution as they are handled during collection, storage, transport, unpacking, and shelving among others, along a supply chain (Sturm et al., 2021; Neureuther and Kenyon, 2009; Maister, 1976). When all 106 samples of the three species are considered in aggregate there is a notable reduction from 67% found at the markets to 50% authenticity at the supplier stage. Modern pharmacies dispensed more authentic, 71%, samples compared with 59% in traditional Chinese herbal pharmacies at the patient dispensing stage (*Table 4.14*).

TABLE 4.14 PERCENTAGE (%) OF SAMPLES IDENTIFIED AS AUTHENTIC AT DIFFERENT SUPPLY STAGES

	SUPPLY CHAIN STAGE										
					OUTLET						
SPECIES SOURCED	FARM	MANUFACTURER	MARKET	SUPPLIER	Modern Pharmacy	Traditional Chinese Pharmacy	Hospital	University	Botanical Research Facility	Clinic	**% AUTHENTIC**
EN	*50*	*100*	**55**	**50**	**82**	**44**	*100*	*100*	*50*	*0*	**57**
PS	-	-	**100**	*100*	*0*	**63**	-	-	-	-	**80**
ES	-	-	**64**	*0*	*50*	**80**	-	-	*0*	-	**64**
All	*50*	*100*	**67**	**50**	**71**	**59**	*100*	*100*	*33*		**63**

Percentages in **bold** type are calculated from three or more sample numbers, those in *italic* from two or less samples. " - " = no samples collected

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*

This trend of reduced authenticity towards the consumer along the supply chain is most marked for the 61 EN samples. It resulted in the lowest average authenticity of the three species analysed in this study, at 57% authentic. Although most substitution appears to have occurred at the pre-pharmacy supply stages, there is an observed divergence in the CMP quality supplied by modern and traditional pharmacies, at almost twice the proportion of authentic samples, 82%, compared with 44% at traditional Chinese pharmacies.

In classical Chinese medicine practice there is a tradition of modifying herbal prescriptions by intentionally substituting one CMP for another, often to personalise standard reference formulas to the patient's conditioner stage of their disease. Given the observed divergence in authentic samples found at modern and traditional pharmacies, the possibility of intentional substitution of EN, PS and ES is examined further.

4.4.6 Examining intentional substitution of EN

Is the substitution of EN, PS and ES observed in this study due to intentional substitution of one CMP for another with similar therapeutic effects by herbal practitioner prescriptions?

Intentional substitution of one CHM for another is a practice inherent in classical Chinese medicine when composing Chinese herbal formulas, in which practitioners customise prescriptions to match the health condition, lifestyle and personal requirements of different patients, and for the same patients seen at

various stages of a disease (Yeung et al., 2015). In some cases alternative species are substituted for clinical reasons, such as *Codonopsis pilosula* Nannf., (C.P., Dang shen, 黨參), in place of *Panax ginseng* C.A.Mey. (C.P., Ren shen, 人參), where patients present with more lung related health problems, to reduce financial cost of the prescription or due to scarce herbal resources. (Chen et al., 2018; Cheung et al., 2021). In other cases species of the same genus are substituted such as *Panax quinquefolius* L., and *Panax notoginseng* (Burkill) F.H.Chen ex C.Y.Wu & K.M.Feng with *Panax japonicus* (T.Nees) C.A.Mey. (C.P., Zhu jie shen, 竹節參), (Yang et al., 2018). Those with less botanically related sharing similar common names such as *Withania somnifera* (L.) Dunal, are also substituted. In addition to ES, these are commonly referred to as American, Japanese, Chinese, Indian and Siberian ginsengs, respectively. These “ginsengs” are often found substituted in the nutraceutical-supplement market (Ichim and de Boer, 2021). Clinical substitution can also occur where there are general or regionally variable descriptions given in pharmacopeias, such as that documented for *Chrysanthemum* spp., where *C. morifolium* and *C. indicum* L., and others are interchangeably describes as Ju hua, (Gu et al., 2022; Hao et al., 2022).

EN, PS and ES are composed of plant root parts, which comprise the majority of CMP listed in the ChP. Roots are found most commonly substituted, perhaps partially due to their similar forms and shapes which render them more difficult to recognise visually. Cultivation area references such as North, South and others, are used colloquially to aid their description, so-called “Dao di”, or geolocation-specific terms which informs the meaning of both the herb source and clinical

effect (Lei et al., 2018, p273). This practice is not particular to Chinese medicine and is observed in other ethnopharmacy systems globally (Jia, Wang and van Andel, 2021; Ouarghidi et al., 2012). Therefore, justification exists for both intentional clinic substitution together with what could occur from unintentional misidentification of one CMP for another.

The justification for intentional interspecies substitution, more specifically, EN with PS or ES by traditional Chinese medicine practitioners, was considered by comparing the medicinal properties from a classical Chinese medicine perspective, namely, their nature, functions and indications (*Table 4.15*).

TABLE 4.15 COMPARISON OF THE NATURE, FUNCTIONS, AND INDICATIONS OF *ELEUTHEROCOCCUS NODIFLORUS*, *PERIPLOCA SEPIUM* AND *ELEUTHEROCOCCUS SENTICOSUS* SAMPLES

Medicinal Plant	Nature	Functions and Indications *
Eleutherococcus nodiflorus	Acrid, bitter, warm	*Clears **wind-damp**, warms **Kidney** and Liver, stops pain and strengthens the sinews.*
Periploca sepium	Bitter, warm, toxic	*Dispels **wind-damp**, **promotes urination**, and reduces oedema toxic.*
Eleutherococcus senticosus	Acrid, slightly bitter, warm	*Tonifies Spleen and **Kidneys**, augments heart, calm spirit invigorates, blood and unblocks the channels*

* Descriptions From (Bensky, Clavey, & Stõger, 2004)

All three species are commonly described as "bitter" and "warm", with EN and ES sharing an "acrid" quality. These similarities predispose their use for similar clinic indications known collectively as "Bi Syndrome", that are referred to as arthritic-type conditions in biomedicine (Xia et al., 2020). Differences in the nature, function and indications for the species are still apparent, however both EN and PS indications are more closely related for use in "wind-damp" conditions such as joint pain. Whereas ES is more appropriate for a tendon and muscle pain condition that "invigorates blood and unblocks the channels". This supports more likely and frequent inter-substitution between EN and PS, less likely and more occasional ES, in agreement with this study's results.

Although a review of the ten editions of the Chinese pharmacopeia described later in this study shows that clinical substitution of EN with either PS or ES is neither described nor allowed, the tradition of undeclared clinical substitution by Chinese herbal practitioners still remains widespread (Kum et al., 2016; Leon and Lin, 2017; Yao et al., 2022). The significantly lower level of authenticity in EN samples is found when sourced from traditional Chinese pharmacies, 44%, compared with modern pharmacies, 82%, together in consideration with all EN, PS and ES samples combined, 71% and 59% respectively. This strongly supports the practice of intentional clinical substitution in traditional pharmacies. Local practitioners more often diagnose and make up formulas on site, in contrast to modern herbal pharmacies that dispense prescriptions from registered clinicians, hospital doctors and pre-manufactured patent formulas. Deliberate and undeclared substitution appears more probable in the traditional local clinics, which are often omitted in research surveys due to the less stringent recording and prescription practices (Lai, Wu and Wang, 2012; Wang et al., 2021), they are subject to less attention and where included they have been described as “sunset” industries relying on antecedent knowledge that is somewhat more variable and opaque, which continues to be lost over time. (Su et al., 2021). Although most, 85.6%, of Chinese medicine doctors in a sample of 4,503 surveyed from 28 provinces across China were familiar with clinical regulatory guidelines, only half, 50.4%, said they complied (Liu et al., 2017). Variable attitudes, practices, levels of training, recording and compliance practices still exist among pharmacists in larger commercial chain pharmacies than those in more traditional environments, together with challenges for their integration (Yao et al., 2020).

It is therefore possible that due to the differences in accepted clinical practices at traditional clinics and those with a more dispensing focused role in modern herbal pharmacies, that intentional clinical substitution plays a part in the recurrent substitution of EN with PS and ES. This may arise from local acceptance of some non-standard practices, as indicated by reports that substitution with other related species such as *Eleutherococcus henryi* Oliv., still occurs in provincial areas such as Hunan, even though the ChP and provincial standard texts list EN as the official species (Li et al., 2021; Hunan Food Drug Administration, 2009).

However, there are limitations with these findings. An exception is observed for ES when considered independently of other species, where one sample showed a higher authenticity sourced in traditional pharmacies, 80%, compared with traditional pharmacies, 50%, contrary to other findings. As this was representative of a single sample, compared with at least three and more for the other results, it was not considered further. Additionally, no PS samples were sourced from modern pharmacies due to the introduction of COVID-19 restrictions at the time of collection, therefore the findings can only be reasonably interpreted for EN substitution with PS, based on observations with a higher sample number. However, as PS substitution of EN was the focus of this study, sufficient sample numbers were collected and the study findings are considered valid. Further study with larger sample numbers from supply chain sources is recommended for more detailed study of these preliminary findings.

Even though intentional clinical substitution appears to be a significant contributor to reducing the authenticity of the samples, it cannot account for most of the EN adulteration, as relatively low and progressively lower levels of authenticity were observed in earlier in commercial market and supplier stages of the supply chain in pre- and non-clinical settings. This prompted further investigation of non-clinical and commercial reasons, such as unintentional misidentification of species, and that of value based substitution for intentional profit gain.

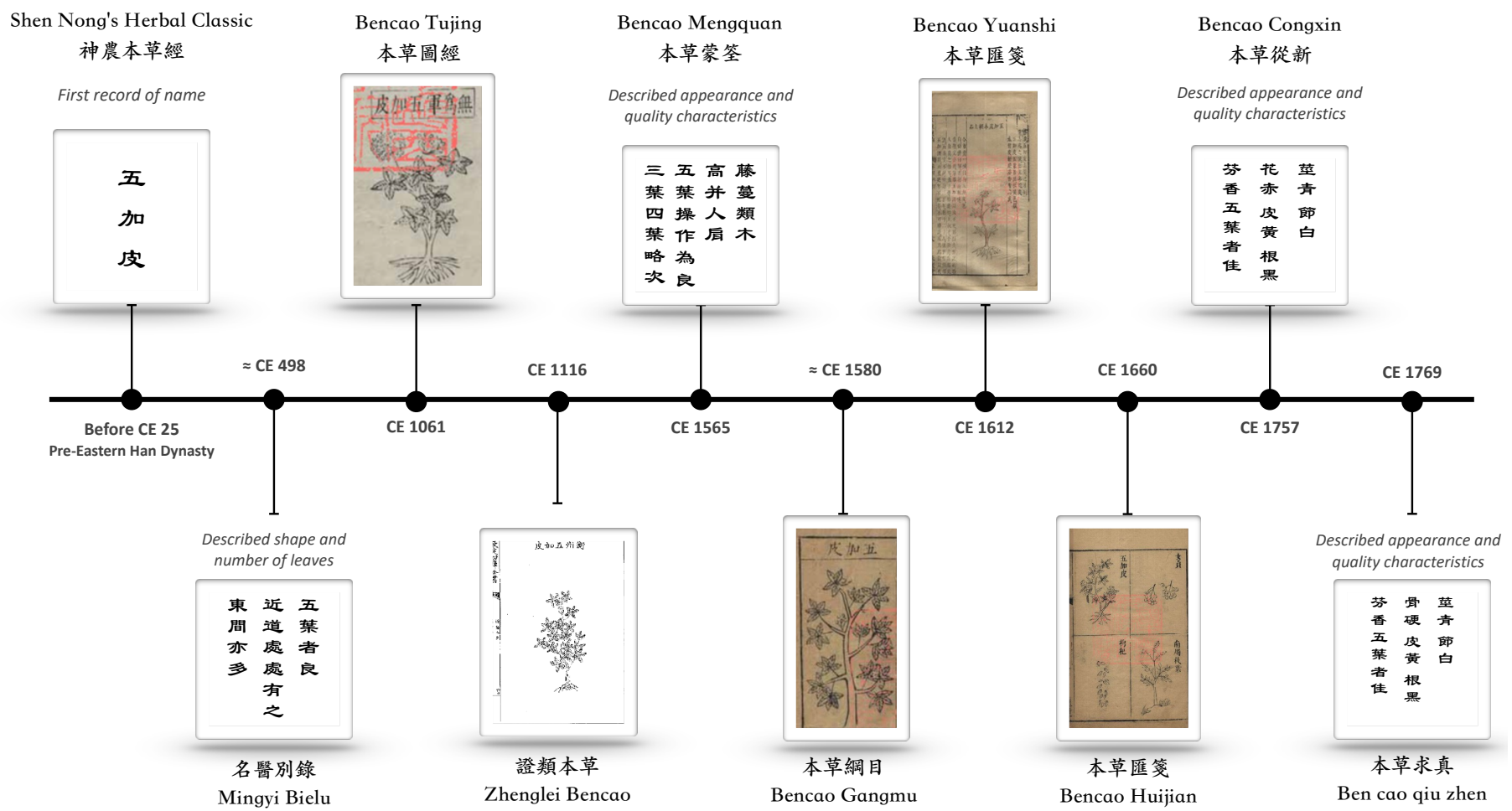
4.4.7 Examining misidentification of EN

Misidentification is a common source of adulteration. It can occur unintentionally though human error when identifying CMP visually or selecting plants with similar names. However, it can also provide a means by which intentional substitution is obscured where macroscopically similar plants and plant parts are used in place of others (van der Valk et al., 2017; Ye et al., 2021). To examine if the substitution of EN from either of the two unintentional and intentional scenarios, primary reference texts commonly used to identify and authenticate EN were reviewed to consider if the descriptions recorded were sufficiently detailed to discriminate EN from other CMP. These texts were drawn from two sources, the first classical and the second contemporary.

Ten classical texts were reviewed, half of which were found to contain illustrations, and the other half, written descriptions only (*Figure 4.7*). The first basic description of EN was recorded in “Shen Nong's Herbal Classic", a pre-Han dynasty text, before CE 25. A more extended description of the physical form and

medicinal characteristics of EN were documented later during the Nanbei Dynasty at the end of the 5th century in the Mingyi Bielu (名醫別錄). A visual depiction sufficiently detailed to compare EN with other CMP species appeared in the Song dynasty, mid-11th century, within the Bencao Tujing (本草圖經), and later during the 12th century, in a more comprehensive description of EN's physical form in Zhenglei Bencao (證類本草).

FIGURE 4.7. CLASSICAL REFERENCE TEXTS USED TO IDENTIFY *ELEUTHEROCOCCUS NODIFLORUS* (WU JIA PI, 五加皮)



Three further significant references appeared throughout the Ming dynasty period, in the mid-16th century without an illustration in the Bencao Mengquan (本草蒙筌) and within two decades in the Bencao Gangmu (本草綱目) containing one of most complete and referenced illustrations recorded historically. The mid-17th century Bencao Yuanshi (本草原始) contained a drawing of EN and noted significantly in Chinese, "生南方者類草，故小；生北方者類木，故大", that differentiated northern woody forms of the plant from those in the south, which were more grass-like forms, both referred to as Wu jia pi, that were both identified as the species EN. This is significant as references in the 20th century sometimes differentiate EN and PS by the prefixes, north (CP; nan, 南) and south (bei,北) Wu jia pi, respectively (Foster, 2016; Committee, 1995, 2007).

Three sources during the Qing Dynasty showed more refined and detailed depictions and descriptions. The Bencao Huijian (本草匯箋), in the mid-17th century, described that the plant parts and the reason for naming Wu jia pi is due to its five leaves, (CP: Wu, 五), meaning five. Later in the 18th century, the Bencao Congxin (本草從新), without illustration, expanded the description and its identification by fragrance. The Bencao Qiu Zhen (本草求真) followed within a decade with a short but similarly highly detailed description of the physical characteristics of EN.

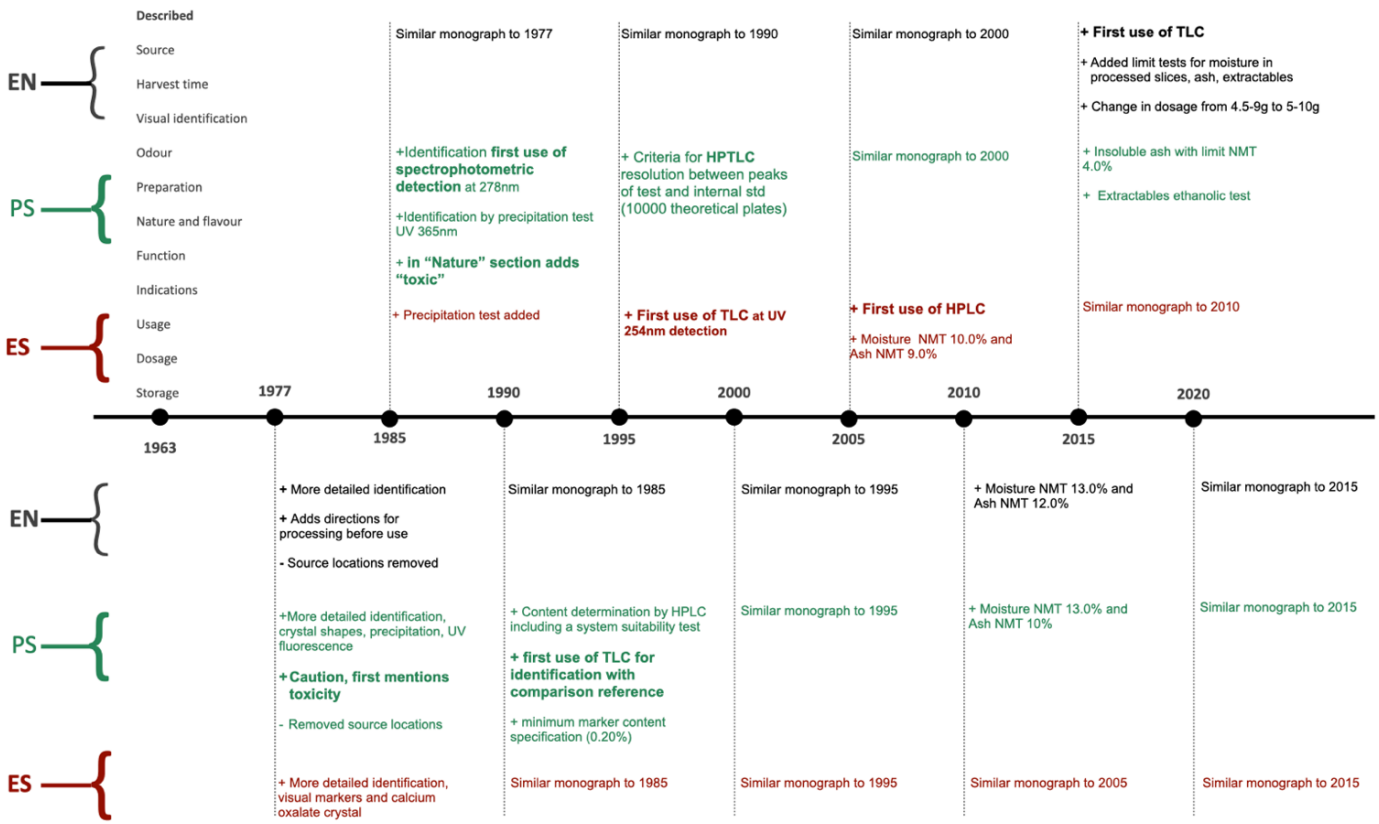
In summary, the ten classical texts describe and show detailed depictions and descriptions of the distinct macroscopic characteristics of EN, suggesting that it was known as a distinct and separate herbal entity for at least one millennia.

Although EN and PS herb species have similar sounding names in Chinese, their Chinese characters are distinctive, and therefore not likely confused when the names of the two CMP are written as 五加皮, Wu jia pi and 香加皮, Xiang jia pi.

However, confusion could arise when referring to references of the 17th century and previous texts describing “northern” and “southern” forms of Wu jia pi, which are likely two different species, those of PS and EN, respectively.

On reviewing contemporary sources, the Chinese pharmacopeias show clear entries for each all three EN, PS and ES species, which are described in separate monographs since the introduction of first substantive modern Chinese pharmacopeia in 1963 and in every subsequent edition to the present day (*Figure 4.8*). An earlier, 1953 first edition of the ChP was published as a forerunner to subsequent pharmacopeia series that did not contain herbal monographs, describing only 65 medicaments, oils and fats, and therefore was not included in this review (Shen et al., 2021, p155).

FIGURE 4.8 SUMMARY OF THE SUCCESSIVE ALTERATIONS TO CHINESE PHARMACOPEIA MONOGRAPHS FOR EN, PS AND ES OVER THE TEN EDITIONS FROM 1963 TO 2020, THAT REFER TO IDENTIFYING AND AUTHENTICATING THE THREE SPECIES



" **+** " = an entry was added, " **–** " = an entry was removed.

Progressive changes occurred in the descriptions used to identify and authenticate EN throughout the series of pharmacopeias. The ChP 1963 edition monographs for both EN and PS describe a preference for herbal material supplied without a “wood heart” form, whereas from 1977 onwards this reference is removed. A knowledge of PS toxicity is apparent and was first indicated since the 1977 second ChP edition in a particularly advanced monograph that remained so in subsequent updates up to 2020. Including the 1985 monograph, which was the first monograph of the three species to describe the use of a spectrophotometric analytical instrument method, in 1990 thin-layer chromatography with a comparative reference for identification of PS was introduced, followed by a relatively early appearance of HPTLC in the 1995 fifth edition. In contrast it was five years after that of PS when TLC was described in the ES monograph and 15 years later in 2015 for EN. Tests for moisture to ensure that CMP are dry to inhibit bacterial growth together with the ashing methods for detection of adulteration was introduced in the 2010 edition for both EN and PS.

It is clear that the three species were known, described, and readily identifiable throughout the 70 years of ChP publication. Further, testing was available during this time that could determine their identity and quality characteristics. Descriptions of PS toxicity, means of identification and detecting adulteration have been available for the three species for at least the last half century. It is therefore less likely that in contemporary times, the three species could be mistakenly confused, particularly in whole-plant form during the cultivation and collection stages of the herbal supply chain, where more visual basic testing occurs and where in unprocessed form they are more easily recognised.

Identification errors appear more likely after the CMP root barks are stripped and processed into similarly looking cut slices after processing into less identifiable cut pieces, and later in the supply (*Figure 4.9*). This is in general agreement with the results of the study findings, where more than 90% of samples could be identified, and generally less authenticity was found both further along the supply chain. A limitation of this study is that the majority of samples were sourced at market and post-market supply stage sources, which restricts comparability with the farm and cultivation stages. However, for most samples the general trend is apparent of reduced authenticity in progression with supply stages and distance from the largest markets.

FIGURE 4.9 PROCESSED (CUT) FORMS OF ELEUTHEROCOCCUS NODIFLORUS (LEFT) AND PERIPLOCA SEPIUM (RIGHT)

On consideration of the findings, the differences in authenticity found at traditional and modern style pharmacies might arise from the difference in descriptions found between classical and modern text sources. Identification of EN based on classical texts and modern pharmacopeia references could lead to differences in authentication and consequently the prescription of EN. Those in traditional practice rely more on classical texts, whereas those in laboratory environments and academic university related environment reference more to pharmacopeias (Luo et al., 2021; Eigenschink et al., 2020; Xue and Lyu, 2019). This is marked by a divergence in Chinese medicine soon after the formation of the People's Republic of China in 1949, when a newly-formed government committee agreed on the contents of university training courses for future Chinese medicine doctors, which adopted many of the western biomedical concepts and teaching structures. This influenced how Chinese medicine was taught and practiced (Chen et al., 2022). Those inheriting knowledge from family and apprenticeship knowledge-lines maintained a more wholistic conceptual approach to practice based on older classical texts, such as those the Jing Fang tradition that has seen a recent resurgence (Huang and Michael, 2009).

The classical texts, from CE 1612 the Bencao Yuanshi (本草原始) referred to woody northern and grass-like southern types of Wu jia pi as the same species. However, these are two distinctly separate species, most likely PS and EN respectively. This reference continued from the classical texts and into the 1963 ChP, however it was removed in the 1977 and later editions. Therefore, those relying on more historical text are more likely to confound the two, whereas those referring to the 1977 ChP and later are less likely to do so.

The northern “woody” form likely refers to the remaining EN that survived colder temperatures in northern China, with more secondary growth of the vascular cambium layer that protects it from lower temperatures, in a similarly “woody” form to ES, which is also resistant to cold environments such as those in northern regions of China and Russia (Li, 1944; Weiser, 1970). Although the classical sources identify the three species as distinctly separate, those relying on historical texts could more easily and intentionally choose to inter-substitute these CMP in the regions locally where both species grow, based on similar clinical and physical attributes. However, modern pharmacopeia sources do not provide a basis for this choice, including pharmacists dispensing in modern pharmacies.

Although the aromas of EN and PS are quite distinctive it is not emphasised as a differentiating characteristic in the ChP. While EN could be described as subtle but “heavy” and “musky”, the latter is significantly “fragrant” and “light” in nature. The ChP monographs do not refer to the fragrance in detail. The EN monographs from the first to the present describe a nondescript, “slight aroma”, in 1963, adding “fragrant” in 1977, which remained similar up to the present 2020 edition. PS monographs from the earliest to the present form simply refer to a “peculiar smell”, perhaps noting its distinctive aroma. The researcher’s experience of these aromas is that they are highly variable and somewhat unreliable for the purposes of identification. Following extended storage time of a year or more, it was difficult to differentiate between EN and PS by fragrance. Some samples did not have any noticeable aroma at the point of sampling. EN odour emanating from the volatile content was previously found to contain mainly approximately 19% α-pinene, 7% farnesol and 7% α-campholenal (Zaluski and Smolarz, 2016). PS

fragrance arises mainly from the presence of approximately 79% 4-2-hydroxy-4-methoxy-benzaldehyde, 3% linalool (3%) and 3% α-terpineol (Chu et al., 2012). As the ChP is considered an official and primary reference for ensuring the identity and quality of CMP, it is more likely used by pharmacists trained after the 1970s within more formal and official environments, such as national universities and hospitals in which CMP are prescribed and dispensed. They receive training in integrated biomedicine and CMP, however often the Classical Chinese medicine component of training is basic and of an introductory nature (Yao et al., 2020, p10). Chinese medicine practitioners from a classical tradition often experience a different training route, refer to more classical texts and hold different views about classical medicine (Hinrichs, 1998; Moorhouse et al., 2021, p5; Hua et al., 2017). The divergence in views between how Chinese medicine is prescribed when following classical traditional and modern practice is well documented (Marié, 2011; Scheid, 2002; Lihong, 2019). Therefore, those who refer mainly to either classical texts or more modern ChP-related references texts are likely to prescribe differently, and may account in part for the difference in levels of authenticity observed between modern and traditional pharmacies in this study's findings.

Although Chinese classical texts and the ChP are primary and important sources of CMP knowledge, other pharmacopeias are used in different geographic and legislative regions. Differences or omissions in regional monographs could potentially lead to misidentification of EN, PS and ES extending across the multi-regional supply chain sampled in this research. A review of five other Asian and Anglo-European regional pharmacopeias found that EN monographs were

included that indicated a general international awareness of EN, its use and a wider-need to monitor its quality, including post-export stage in the supply (*Table 4.16).*

TABLE 4.16 A SURVEY OF SIX CONTEMPORARY REGIONAL PHARMACOPEIAS FOR INCLUSION OF *ELEUTHEROCOCCUS NODIFLORUS, PERIPLOCA SEPIUM* AND *ELEUTHEROCOCCUS SENTICOSUS* MONOGRAPHS

Year	Regional Pharmacopeia	Medicinal Plant Monograph Included?		
		EN	***PS***	***ES***
2020	Chinese	✓	✓	✓
2019	European	✓	✕	✓
2020	British	✓	✕	✓
2019	Taiwan	✓	✕	✕
2016	Hong Kong	✓	✓	✓
2016	Korean	✕	✕	✕
2016	Japanese	✕	✕	✓
		✓ = Yes, ✕ = No		

EN = *Eleutherococcus nodiflorus*, PS= *Periploca sepium,* ES = *Eleutherococcus senticosus*,

In addition to the ChP, four of the six regional contemporary pharmacopeias contained monographs for WJP, including the European Union (EP 2019), Hong Kong (HKP 2016), Taiwan (TP 2019), and the United Kingdom (BP 2020). The

Korean pharmacopeia (KP 2016) did not include monographs specifically for EN, PS, or ES, however it listed a related species used more locally, *Acanthopanax sessilifolium* Seeman (Kim et al., 2014), and the monograph states that the tests *for A. sessilifolium* can be used for “other species of the same genus”, namely, *Araliaceae,* which does include those of Eleutherococcus, both EN and ES. The Japanese (JP, 2016) pharmacopeia did not contain a EN monograph, however it did list ES, as did three others, in the EP 2019, BP 2020 and HK 2016. The HK 2016 was only one of the six reviewed that included all three EN, PS and ES species, and was unique in containing a PS monograph, perhaps due its more central location to mainland China, the source of the three CMP species, and its historically relative higher exposure to a variety global herbal export markets in advance of its return to China mainland control in 1997 (Chiu and Sze, 2021; Xiang et al., 2022).

Although an awareness of EN use and quality testing is apparent internationally indicated by the inclusion of the three monographs in various regional pharmacopeias, only three of the six reviewed pharmacopeias specifically included tests for WJP adulteration with PS, namely, the HKP, EP, and BP through adoption of the EP monograph. Regional variability in testing presents gaps through which PS and other adulteration could potentially recur, particularly at the post-export stage.

If CMP fail authentication or quality tests, there is potential that they could be legitimately exported to another region without detection or legal consequence. Given the absence of PS testing in many regions, including Taiwan where

samples were collected, and the significant EN adulteration found in this research, an update of the other regional pharmacopeias is warranted. The HK pharmacopeia monograph demonstrates the most complete and detailed testing of WJP adulteration for both PS and ES of the six pharmacopeias reviewed and is suggested for consideration by the other regional pharmacopeia commissions to raise the standard of WJP quality internationally. Comparison of three pharmacopeias from regions where the samples in this study were sourced, ChP, EP, (the primary source of the BP monograph) and THP highlights both the regional differences in assessing and detecting the authenticity and adulteration of EN, and consequently where CMP are more likely to circumvent detection in supply, that is, outside the mainland China-Hong Kong regions further along the supply chain.

Following the review of classical and contemporary pharmacopeia methods used to identify and authenticate EN, it appears that adulteration is less likely to recur due to misidentification in whole-plant form at the cultivation and collection stages of supply, as the descriptions were distinctly known and readily identified for centuries. It is possible that intentional substitution, particularly by those referring to classical texts in traditional-style pharmacies, are more likely sources of recurrent EN adulteration.

However, misidentification does also appear more likely after processing into cut slices, where it is more easily confused with the PS and ES species, and outside continuously controlled supply chains where testing is neither completed nor required, such as after exportation to regions relying on both different

pharmacopeias and regulation. This is in agreement with the findings of this study where progressively less authenticity is observed for EN, PS and ES along the supply chain, except where the identity of the samples was preserved from cultivation to source, resulting in 100% authenticity. Furthermore, a 100% positive bias in PS substitution for EN was found where no EN was substituted for PS supporting the argument that misidentification is likely not the prime reason for adulteration. If error occurred, even at the post-processing stage due to misidentification, some PS would be expected to be mistaken for EN by random chance.

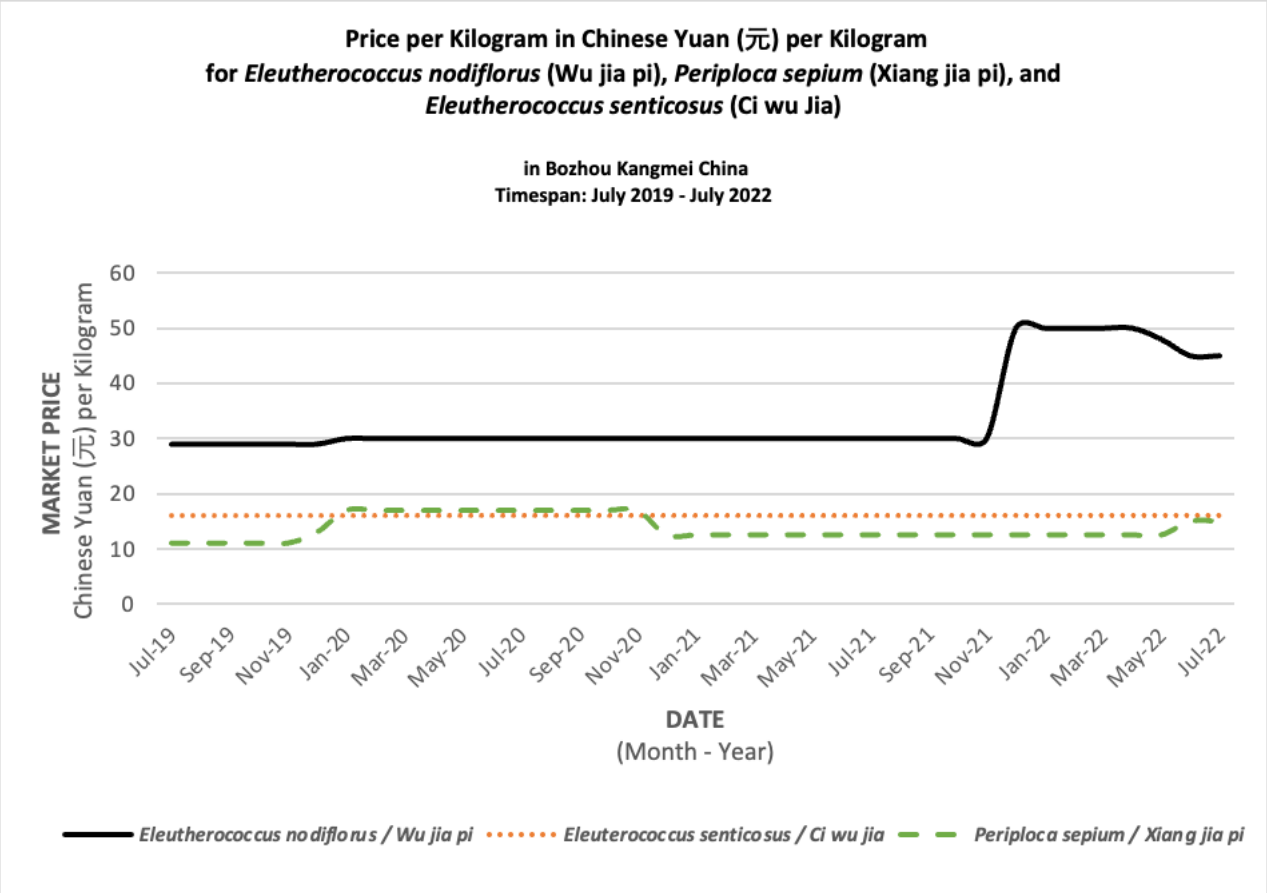
Therefore further investigation around the intentional substitution related to financial value of the three species was completed to determine if profit gain could be a motivation for the observed complete bias in herbal substitution.

4.4.8 Examining economically motivated adulteration of EN

Profit-motivated adulteration occurs throughout the CHM supply and directly affects the chemical composition and quality of medicinal plants, often by the addition of cheaper non-authentic materials (Ichim and Booker, 2021; Booker, Zhai, et al., 2016; Scotti et al., 2019a; Chatzinasiou et al., 2019; Govindaraghavan, 2017; Liu et al., 2015). In this study a low proportion, 57.4%, of EN samples resulted as authentic, with 24.6% identifying as PS and 9.8% ES, and there was a 100% positive bias for PS substitution of EN. Surveying the trade prices of the three species in the largest international CMP market in Bozhou over the last three-year period between July 2019 to July 2022 shows that EN

consistently sold at more than double the price of PS and triple that of ES. Recently, the price of EN has substantially risen from about 30 元 to 45 元 per kilogram, approximately £3.70 to £5.60 (*Figure 4.10).*

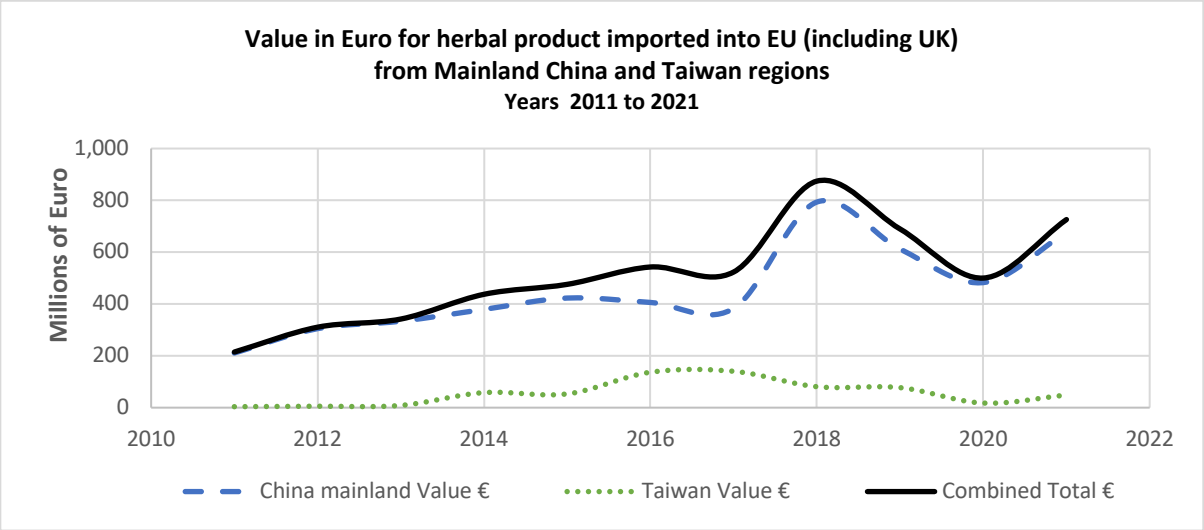
FIGURE 4.10 MARKET SURVEY OF PRICES AT BOZHOU, CHINA FOR (CUT) FORMS OF *ELEUTHEROCOCCUS NODIFLORUS* (WU JIA PI), *PERIPLOCA SEPIUM* (XIANG JIA PI) AND *ELEUTHEROCOCCUS SENTICOSUS* (CI WU JIA), FROM JULY 2019 TO JULY 2022



The Bozhou market, run by the Kangmei company group, that issues communal bulletins and herbal prices to traders reported the reason for the latest price rise was related to harvesting of EN which was more difficult over the January 2021 to May 2022 period due to a combination of reasons. EN resources become scarcer and sparser, particularly in the Sichuan region where much EN is harvested. It reported that EN in particular has become more difficult to collect by an increasingly elderly local demographic, a potential issue flagged in the last decade by the WHO in a review of Chinese medicinal policy and worker demographics (Kangmei, 2022a; Mossialos et al., 2016). By May 2022 the supply was still relatively scarce. The effect of the 2019 COVID-19 pandemic, if any, is not noted in bulletins. These factors pose further motivation for value substitution of PS in place of the increasingly scarce, more difficult to collect and relatively expensive EN, warranting further vigilance and testing.

Though information on individual CMP species were not provided by the European customs office, a review of data they provided for the aggregate quantity and value of herbal imports from mainland China and Taiwan regions to the 28 European countries (including UK pre- and post-Brexit), shows over the last ten full fiscal year periods, 2011 to 2021, there was a cumulative value of €5,636,089,726 for 104,551,748 kilograms of herbal material (*Figure 4.11).* This represents a significantly large market and motivation for profit-based substitution (Commission, 2022).

FIGURE 4.11 SURVEY OF VALUE OF IMPORTED HERBAL PRODUCT IMPORTED INTO THE EU (INCLUDING UK) FROM MAINLAND CHINA AND TAIWAN REGIONS, OVER THE DECADE, DECEMBER 2011 TO DECEMBER 2021



It is therefore apparent that value-based substitution could play a part in the substitution of relatively expensive EN with less expensive PS and ES. This is in agreement with this study as most of the more expensive EN herbal material was substituted by cheaper PS. Exceptions were found for two samples of EN and two PS samples that identified as ES, both with higher market prices than ES. However as this represented less than 4% of the total samples collected, the predominant finding was the substitution of higher value herbal material with that of lower cost.

A limitation in these findings is that 9.4% of samples analysed could not be identified. This could arise from the material either being species other than EN, PS or ES. It could also result from interference of the HPTLC analysis with other unknown adulterants affecting the analysis results due to the aforementioned

limitations of the HPTLC method. Both scenarios where adulterants could not be detected would result in a potentially higher rate of adulteration than conservatively reported in this study, and therefore the findings hold. A further limitation is that the laboratory analysis using HPTLC in this study focused on one type of adulteration, substitution of EN with PS and ES, and other types of unseen and untested adulteration may be present in the samples collected, as found in other CMP described in Chapter Two of this thesis. Future analysis of these samples and other similar studies using alternative analytical techniques such as High Performance Liquid Chromatography, (HPLC) as distinct from HPTLC, to further ascertain potential adulterants, and DNA methods is recommended, such as completed by Bhamra (2016) to produce further insights into the identity and origins of these and other traditional herbal materials. Further interpretation of existing data collected relating to the identity of CMP along supply chains when resolved into spatial and timeline patterns could produce further insights into the transmission of CMP herbal practice into Europe and other regions.

Although the relatively lower cost of PS and ES could motivate value-based substitution of EN, this type of adulteration is known and detectable, and therefore should be captured by testing. Further examination of the gaps in testing and requirements for adulteration in the supply chain was completed. The issue of non-detection due to analytical method limitations, as seen in this study, raises the question if adulteration of EN, and indeed other similar CMP, recurs as a result of gaps in their detection along the supply chain due to limitations of the analytical methods used. Methods in pharmacopeia monographs for EN in the

three regions where the samples were collected were examined in detail, to investigate:

1. What adulteration do the Pharmacopeia tests detect?
2. Do these tests detect adulteration of EN with PS or ES?
3. Is testing conducted where ES adulteration with PS or ES is likely to occur in the supply?

4.4.9 Examining testing of EN with the Chinese, Taiwanese and European pharmacopeias

This study determined the adulteration of EN with PS and ES using HPTLC analysis, however, known limitations of HPTLC including the interference of adulterants that can affect identification of these species raises questions. Specifically, around what adulteration can and cannot be detected, both for this method and the other analytical methods that are in place in the EN supply chain.

Further, are these methods appropriate for known recurrent adulterants? Are they applied to detected adulteration where it most likely occurs? Gaps arising from non-detection is relevant for both interpretation of this study's results and in appraising other reports. They are applicable to other CMP that are commonly adulterated, as the general testing principles rely on common analytical methods and testing approaches.

The pharmacopeia monographs for EN in the ChP, EP and THP are examined in detail to explore:

1. What adulteration do the tests detect?

2. Do these tests detect adulteration of EN with PS or ES?

Finally, section 4.4.10 examines if testing conducted where ES adulteration with PS or ES is likely to recur in the supply.

Examining these questions produced insights around the limitations of analytical testing that is currently in place, and demonstrated that there are gaps that could allow recurrent adulteration of EN and other CMP. It showed what types of adulteration are most likely to recur in context of the testing currently in place.

Improvements were then identified and proposed to reduce both the recurrence of adulteration of EN and other CMP, with PS and ES, in addition to other types of adulteration.

On a review of the Chinese, Taiwan and European pharmacopeias, adulteration of EN with PS and ES is most likely detected by the initial “description” and “identification” sections of the pharmacopeia that involve macro- and microscopic visual testing, and TLC analysis respectively (*Table 4.17).*

TABLE 4.17 A REVIEW OF PHARMACOPEIA TESTING REQUIRED FOR *ELEUTHEROCOCCUS NODIFLORUS* IN THE CHINESE, TAIWANESE, AND EUROPEAN MONOGRAPHS IN REGIONAL PHARMACOPEIAS

PHARMACOPEIA SECTION	DESCRIPTION	IDENTIFICATION		CHECK			EXTRACT		PROCESSING	Nature, flavour and channels	Functions and indications	Usage and Dosage	Storage
		Visual	Thin Layer Chromatography	Moisture maximum	Total ash maximum	Acid insoluble ash maximum	Extracts minimum	Assay minimum					
Chinese Pharmacopeia (2020)	✓	✓	✓	✓ (11.0**, 12.0%*)	✓ (12.0%)	✓ (3.5%)	✓ (10.5%*E)	✕	✓	✓	✓	✓ (5-10g)	✓
Taiwan Pharmacopeia (2019)	✓	✓	✓	✓ (12.0%*)	✓ (12.0%)	✓ (4.0%)	✓ (12.0%*E, 9.0%*A)	✓ (0.04% *S)	✕	✓	✓	✓ (5-12 g)	✓
European Pharmacopeia (2019)	✓	✓	✓ (*PS)	✓ (12.0%*)	✓ (12.0%)	✓ (2.0%)	✓ (16.0%*E)	✕	✕	✕	✕	✕	✕
What is detected?	*Authenticates EN* *Can sometimes detect high concentration of other herb and chemical adulterants*	*Authenticates EN* *Can sometimes detect high concentration (multiple %'s) of other herbs and chemical adulterants*		*Water content / bulk herb weight content* *Limits potential for microbial growth*	*Detects EN ash and non-plant inorganic matter e.g., silt on plant from cultivation or dust from storage*	*Detects hardier silica and siliceous earth content from cultivation or dust from storage*	*Physiochemically active content of EN that can be extracted with solvents to indicate a general minimum content of expected herb can exert potential efficacy*		*Instructions for processors*	*Information for clinical reference for composing prescriptions and deciding substitutions*	*Information for clinical reference for composing prescriptions and deciding substitutions. matching patient presentations with herbal properties*	*Information for clinical reference on typical dosage ranges in prescriptions*	*Instructions for all in the supply chain for storage conditions*
Do methods detect EN adulteration with PS and ES? **Y** = *Yes,* **N** = *No*, **P** = *possibly in limited circumstances*	**P**	**Y**		**Y**			**P**		**N**	**N**	**N**	**N**	**N**

The first sections of the ChP, EP and THP, EN monographs describe the authentication of EN root bark, the second sections detecting adulteration, and the third sections determining additional finer phytochemical quality attributes. The three sections appear progressively most relevant as CMP pass along a supply chain, in selecting the correct herb at cultivation and harvesting, then ensuring purity during preparation and processing, to establishing sufficient efficacy before consuming. The three monograph sections in common represent assessing the authenticity, safety and efficacy of EN, respectively. The earlier "description" and "identification" are the only tests that authenticate EN. Although the "extract" test can indicate if there is a low concentration and therefore possibly less EN present than expected, it tests for a EN bioactive content marker, but does not test for other species present. Therefore, the earlier, cultivation and collection stages of the supply are when the pharmacopeia testing is most effective for identifying EN adulteration with PS or ES, however, after these stages the checks are not unlikely to capture such adulteration. Full EN substituted or adulteration with PS and ES is most likely to pass undetected from the processing step and later stages in the supply chain. This is in agreement with the findings of the study, which finds increasing adulteration towards the consumer supply stages generally in aggregate for all samples.

The three sections of the ChP, TP and EP pharmacopeias are examined in greater detail for the authentication, adulteration and finer chemical attributes of EN. Although it is clear from examining the pharmacopeia methods in overview that EN adulteration or substitution with PS or ES is not likely captured in the later stages of the supply, there are regional variations in how the testing is conducted

which affect the transmission of adulterated samples further along the supply. Further, some improvements could be implemented to better address some regional gaps identified.

4.4.9.1 Authenticating EN using Chinese, Taiwanese and European pharmacopeias

Authenticating EN with all three ChP, TP and EP monographs requires the use of similar methods. A macroscopic visual check for the correct plant and medicinal plant part, the root bark, followed by microscopic examination of a ground sample should match the specific and detailed text based descriptions given. A reference illustration is included in the EP. All three pharmacopeias use a TLC test where the residue patterns on a silica plate remaining after sample solutions of EN separated with solvents. Although there are differences in the monographs of how the EN is visualised, all three monographs similarly require both the position and visual patterns should correspond to those of an authenticated EN reference sample. The THP favours direct drying of the test plate and viewing under UV at a 254 nm wavelength, whereas the EP and ChP use colour-enhancing solutions, anisaldehyde and sulphuric acid respectively, before viewing both in daylight and under 365nm light. TLC is a simple and robust technique, however variability when visualising the sample results could present discrepancies between regions which use different approaches and therefore, slightly different interpretations. Particularly, as seen in the HPTLC analysis results in this study, there are marked differences in chromatographic patterns and colour tones of the TLC plates, even when viewed under the same

wavelength of light. This presents potential for EN and its adulterants to be in some instances identified and others not, moreover when using other methods or visualisation techniques.

Although the general macroscopic check is intended primarily to authenticate CMP, it also can incidentally capture gross adulteration. Though the visual check based on text descriptions or hand-drawn illustrations in the monographs is a useful academic reference, its use is liable to human error as plants and their parts can look similar (Ahmed et al., 2005; Han et al., 2016). However in practice, at the early critical stages in the supply where CMP are selected cultivators and collectors may neither refer to nor rely on a pharmacopeia reference in outdoor, wild, or farm settings, where they rely on personal experience and discernment aided by the bounds of a known limited growing area of a farm or region to select correct species when they are apparent (Silva, Silva and Ramos, 2018; Lei et al., 2018). Furthermore, although some details of harvest times are noted in the ChP, accurate collection times and standards have generally not been established (Jiang et al., 2022). It is impractical to visually check every EN root bark in larger scale harvests, and it is possible that extraneous non-medicinal parts or matter can go undetected and enter the supply at this stage, which is particularly important as more than 80% of CMP are wild harvested (Li et al., 2015). Pharmacopeias are more conveniently referenced indoors, later in the supply, alongside equipment for the microscopic check of powdered EN samples and the TLC test in controlled environments, such as a laboratory housed within commercial manufacturing facilities. This is where herbal prescription decoction pieces are created at the processing stage of the supply under the directions of

the ChP monograph to remove impurities, wash, soak, cut into thick slices, and dry EN. Although pharmacopeias provide guidance on representatively sampling large amounts of herbs it is feasible to test only a small portion of the processed bulk CMP in a laboratory, which if not homogeneously mixed can allow adulteration to pass undetected, a limitation of pharmacopeia-laboratory based testing (WHO, 2007a). However, as much washing and slicing is done manually by operators who handle all of the bulk CMP material, if vigilant, can detect unusual, non-authentic material based on experience and prevent it from entering further into the supply.

The final identification test, TLC, in the ChP and THP is effectively an additional authentication tool for EN within mainland China and Taiwan regional monographs, respectively. However these TLC tests do not include a check for PS. In incidences where levels of adulteration are high, as found in this study where complete substitution of EN was observed, the TLC can detect some adulteration, as the samples were wholly non-authentic, however lower levels could go undetected. The exception is the EP monograph which does include an initial macroscopic visual check for another commonly known adulterant species, *Acanthopanax giraldii*, and tests for PS with the TLC method. As the ChP monograph is that most commonly used in mainland China, where most of the tested EN samples were sourced and originated, it presents a gap in testing within mainland China and Taiwan regions where PS adulteration could occur undetected in the earlier stages of supply before supply to other local regions and when exported globally.

4.4.9.2 Adulteration of EN with other species detection using Chinese, Taiwanese and European pharmacopeias

The second “examination” section of the three regional EN monographs relate more to the detection of adulterants than identification. They include tests for excess water in EN after drying, extraneous adulteration material detected by incineration or “ashing”, and minimum herb content after “extraction” into a solution. The water test ensures both that the EN bulk herb, purchased by weight, does not contain excessive water and additionally does not provide moist conditions that make it susceptible to microbial spoilage or mycotoxins, which can develop post-cultivation while awaiting collection, or any other points in the supply chain when stored. Though all three pharmacopeias describe differences in their methods of up to three hours in their drying times, they impose similar maximum limits on moisture, the ChP and THP, 11.0% and the EP 12.0%, where the longer drying times used require lower moisture results. The three regional pharmacopeias vary where testing is specified at different points in the supply chain. The THP and EP both describe testing on the post-processed decoction material ready for prescription, whereas the ChP directs checking both pre- and post- processing, with limits of 12.0% moisture on the bulk raw CMP material and 11.0% on the washed, cut and dried decoction pieces. This difference is presumably due to most of the EN already being processed before it is exported to Taiwan and Europe, and therefore pre-processed testing is most relevant at source in mainland China and post-processing in the EU. Though testing moisture is a relatively simple procedure it requires the use of sensitive, highly accurate analytical balances in a vibration and air-current controlled environment,

such as previously mentioned in manufacturing companies where on the arrival of material and after processing, before sale or distribution, the moisture checks are completed. Although dry samples inhibit bacterial-mycotoxin growth, once left processing facilities water-moisture levels are unlikely to be checked again. This presents subsequent possibilities for medicinal herb spoilage and undetected toxicity throughout the network of many potential in-transit, static storage distribution, and export points globally (Jeyaraj et al., 2022). Moisture was not tested in this study, however it's effects are relevant to both EN, its potential adulterants, and CMP in general. Some CMP, especially seeds and those with fibrous exteriors are more susceptible to microbial contamination than others (Chien et al., 2018; Tumukunde et al., 2020; Jallow et al., 2021).

The "ashing" test in this examination section describes three steps. First, in detecting silt or dust accumulated from cultivation or storage stages of the supply. The second step, for silica or siliceous earths that could accumulated during cultivation, or afterwards before collection, or later added as bulking adulterants pre-sale. In the third and final step, the water soluble portion of EN that is extracted by decoction at the pharmacy or consumer patient step in the supply. A characteristic minimum weight is defined in each monographs for each herb that ensures consumers both receive a minimum intended medical dose, and financial value for the weight of herb purchased at the market, pharmacy or clinic setting. The ChP, EP and THP monographs approximately agree that there should be greater than 88.5%, 88.0% and 86% organic matter present in the bulk herbs purchased, based on the 11.5%, 12.0%, 14.0% maximum total insoluble ash limits in the three pharmacopeias, respectively. Silicon is the second most

abundant element in soil after oxygen, mostly in the form of silica, SiO_2. Silica has been long supplemented to crops to enhance harvest yields, as it enhances the absorption of nutrients resulting in increased crop height, strength, robustness and contributes to crop weight. (Ligaba-Osena et al., 2020; Tripathi et al., 2021), including producing more stress-resistant CMP (Zhang et al., 2018; Shen et al., 2022). If undetected, the content of active phytochemicals in final herbal material weight could be lower due to increased bulk mass, and its effects on heath remain debated (Roney, Faroon and Williams, 2019; Guo, Liu and Li, 2021).

These total-ash tests confirm the presence of a limited amount of non-organic herb matter in EN samples by exposure to extreme temperature conditions. The subsequent “extractable matter” test in the “examination” section of the monograph ensures a minimum amount of phytochemical content in EN can be extracted under less extreme conditions more typically conducted as decoctions by consumers. Using water or alcohol extraction solutions following maceration and shaking, more similarly to that occurring in a human stomach. Variation from typical result values can indicate poor quality and therefore low value for herbs purchased, such as older, less fresh or degraded herbs stored for unusually long periods of time or where adulterants or undetected substitutes that have been added between earlier cultivation to supplier supply chain stages, which cannot be easily detected in the previous “identification” section or by ashing.

Though the three regional pharmacopeias use slightly different conditions for their respective “extractable” tests, they approximately agree on its minimum

requirements of 10.5%, 16% and 12.0%, in the ChP, EP and THP respectively. The ChP and EP require extracts in concentrated ethanol solutions only, whereas the THP has an additional water extract limit of 9.0%. This is of relevance when calculating concentrations of herbs for formulation of prescriptions in alcoholic tinctures, powdered / granules forms, and for the whole decoction pieces.

The HPTLC analysis is more definitive when determining the identity of EN, however PS or ES and many other types of adulteration can be present but not detected if not at relatively high concentration due to limits of detection inherent in the method (Kowalska and Sajewicz, 2022). Although the ChP and THP does include a TLC test, it does not include a specific PS check and therefore it is more likely to pass undetected before export to the EU region, where the EP does check for PS. Therefore, much of the material may not be tested pre-export and it is recommended that TLC testing for PS could be added to the ChP within the source area, mainland China, where it would capture such adulteration earlier in the supply chain. Even the more advanced assays have limitations which may not capture substitution.

The THP includes a HPTLC assay for not less than 0.04% of syringoside to assure minimum content of EN. Syringoside, more commonly named Eleutheroside B which is abundant throughout the bark and pulp together with other Eleutherosides, are responsible for the crystalline needles sought in the microscopic examination tests (Huang, Hu and Yu, 2013). Analysis shows that multiple *Eleutherococcus* species, including ES, an adulterant of EN, also contain equivalent or higher levels of Eleutherococcus B compared with EN: 0.05% in *E. sessiliflorus*, 0.08% in *E. senticosus*, 0.13% in *E. gracilistylus*, 0.16% in *E.*

divaricatus, 0.18% in *E. setchuensis* and 0.34% in *E. henryi* (Ciesla et al., 2011). This presents the possibility that other species including ES could be added as a bulking agent, or replace EN for the purposes of passing pharmacopeia assays as seen with other CMP (Mudge et al., 2016; Fong, 2002). Particularly as syringoside-eleutheroside B can be easily sourced commercially, and presents potential for addition directly to substituted, or poor quality EN (Sigma-Aldrich, 2022).

However, as the ChP does not include a HPLC assay, such adulteration is most likely captured either by a manufacturing company following importation, for example in the Taiwan or Hong Kong regions that require a HPLC assay, or a vigilant supplier pre-sale that tests beyond the minimum requirements of pharmacopeias, such as those in Switzerland (Complemedis, 2023; Widmer et al., 2006).

The other pharmacopeia tests for moisture, ashing and extractable material would not easily differentiate or capture EN adulteration with PS and ES as it determines in a relatively non-specific manner the minimum content of bulk root bark material, all with similar test limits. These tests neither differentiate EN from other herbs with similar bulk content, nor added synthetic adulterants. The other specific contaminant tests, for sulphur dioxide, heavy metals, bacterial / aflatoxin microbes and pesticides, similarly, were not designed to, and cannot differentiate PS or ES in EN.

Therefore, substitution of EN with PS or ES following the cultivation, harvest and processing stages is likely to remain undetected where the initial identification tests are completed.

Adulteration that occurs after testing in the supply irrespective of well-designed analytical tests renders them ineffective. Where quality systems direct testing to be conducted directly determines the likelihood of whether or not adulteration is detected.

4.4.9.3 Contamination detection in EN using Chinese, Taiwanese and European pharmacopeias

Progressing through the pharmacopeia monograph sections from “identification” to “examination”, from macroscopic to microscopic visual checks through to TLC, and more specific water, ashing, extracts and assays, they approximately and sequentially capture course adulterants likely occurring at the initial cultivation steps to those of a sequentially finer, to those less visually apparent later in the supply up to distribution and consumer stages. The exception is in the final section of the monographs, which uses the most advanced techniques to capture often the lowest concentration adulterants, more often referred to as contaminants, which can occur at any stage of the supply. Although these tests for contaminants do not capture species adulteration, they are examined in this study as their presence can affect analytical testing results, including HPTLC. An examination of the contaminant tests illustrate further the gas in testing due to regional variations between pharmacopeias that apply to both EN and CMP in general (*Table 4.18*).

The THP monograph includes further specific limits for heavy metals and sulphur dioxide in EN samples, whereas in the ChP general limits of CMP apply to EN under section 0212 General principle for inspection of crude drugs and decoction pieces and a general monograph called “Herbal drugs” in the EP

In particular pesticides and heavy metals can directly affect HPTLC analysis. The pesticidal fumigants added to CMP at the cultivation and collection stages that

were previously detailed in Chapter One, section 1.10, contain potassium or sodium sulphite, bisulphite or metabisulphites forms, which from a basic chemistry perspective are reducing agents. These interfere by competition with the p-anisaldehyde, which is also a reducing agent and which made up in a sulfuric acid solution (Sherma, 2000). Heavy metals are often used for pigments due to the strong colours their solutions and complexes form and be observed in the visible spectrum (Puthran and Patil, 2023). These have the potential to interfere with the production of coloured bands during the development and derivatisation steps in HPTLC analysis (Reich and Schibli, 2007).

In reviewing contamination tests in the ChP, TP and EP monographs for EN, regional variations are apparent. In particular, sulfur dioxide used for fumigation of the CMP in addition to copper and arsenic heavy metals tests are lacking in the EP, which could allow toxic contaminants to enter the EU market.

TABLE 4.18 A REVIEW OF PHARMACOPEIA TESTING REQUIRED FOR *ELEUTHEROCOCCUS NODIFLORUS* IN THE CHINESE, TAIWAN, AND EUROPEAN MONOGRAPHS IN REGIONAL PHARMACOPEIAS

PHARMACOPEIA SECTION	Sulfur Dioxide	Heavy Metals					Microbial		Aflatoxins		Pesticides
		Cadmium	Copper	Arsenic	Mercury	Lead	TAMC	TYMC	B1	Sum of G2, G1, B2 and B1	
Chinese Pharmacopeia (2020)	✓ (150ppm)	✓ (1 ppm)	✓ (20 ppm)	✓ (2 ppm)	✓ (0.2 ppm)	✓ (5.0%)	✓ (10^2 CFU/ml)*E)	✓ (10^1 CFU/ml)*E)	✓ (≤ 5 μg/kg)	✓ (≤ 10 μg/kg)	✓ (33 specified pesticide limits)
Taiwan Pharmacopeia (2019)	✓ (150ppm)	✓ (1 ppm)	×	✓ (3 ppm)	✓ (0.2 ppm)	✓ (15.0%)	✓ (10^2 CFU/ml)*E)	✓ (10^1 CFU/ml)*E)	✓ (≤ 5 μg/kg)	✓ (≤ 10 μg/kg)	✓ (DDT, 0.9 ppm, BHC 1 ppm, PCNB,1 ppm)
European Pharmacopeia (2019)	×	✓ (1 ppm)	×	×	✓ (0.1 ppm)	✓ (5.0%)	✓ (10^2 CFU/ml)*E)	✓ (10^1 CFU/ml)*E)	✓ (≤ 2 μg/kg)	✓ (≤ 4 μg/kg)	✓ (69 specified pesticides limits)
Do methods detect EN adulteration with PS and ES? **Y** = *Yes,* **N** = *No,*	**N**	**N**					**N**		**N**	**N**	**N**

Examining pharmacopeia tests for authentication, adulteration and contamination detection revealed gaps in the testing methods, and shows that where testing occurs in the supply chain is critical to detecting quality issues. The legislation that directs where the pharmacopeias' analytical tests should be conducted is guided by the GxP framework. This is examined to assess if gaps are apparent across the supply chain. More specifically, does testing occur where adulteration of EN is likely to occur in the supply?

4.4.10 Examining where EN substitution with another CMP is likely to occur in the supply

CMP as medicinal products are subject to GxP guidance at different stages of the herbal supply chain, GAP at cultivation, GCP at collection, GMP at manufacturing stages, as previously described (Xiong et al., 2022). Testing for potential adulterants is applied based on the "risk of deliberate contamination", as full testing for all known adulterants at every stage in supply chains may not be feasible or viable (COE, 2019, p5). Test results are accepted where validated methods, such as those described in pharmacopeias, are used appropriately as directed by the regulatory guidelines in the regions where the supply chain operates within the "framework of a suitable quality system" (COE, 2019, p3). "Good Practice" guidelines are those most widely used globally for CMP, and all medicines irrespective of source or production location must comply with GxP if imported into the EU (Cuddy, 2017).

Specific types of pharmacopeia testing is required and appropriate at various stages of herbal supply chains. These include the visual identity checks during collection,

tests for adulteration before processing and content-quality checks at the manufacturing stage. These types of testing, as directed by GxP requirements, when viewed together with their relevant herbal supply chain steps facilitate the analysis of where adulteration in a CMP herbal supply chain is most likely to recur. It can be further ranked as more, less or relatively unlikely using a simple scoring system, as shown in *Table 4.19.*

TABLE 4.19 SCORING SYSTEM FOR RANKING LIKELIHOOD OF ADULTERATION RECURRING IN AN HERBAL SUPPLY CHAIN

Ranked Likelihood of adulteration recurring	**Adulteration likely?**	**Testing required?**	**Score**
More Likely	✓	×	★★★
Less likely	✓	✓	★★
Unlikely	×	✓	★
✓ = Yes, × = No			

The scoring system was applied to a Booker-Heinrich model supply chain with nine stages, in context of the Chinese pharmacopeia 2020 testing requirements. It illustrates the relative likelihood of where substitution of EN with other CMP could occur (*Table 4.20).*

TABLE 4.20 RANKED LIKELIHOOD OF ADULTERATION RECURRING ACROSS AN HERBAL SUPPLY CHAIN

SUPPLY CHAIN STAGE	CULTIVATION →	COLLECTION →	PROCESSING / MANUFACTURING →	MARKET →	TRADING →	CONSUMER OUTLETS
Key GxP guidelines	GAP	GCP	GMP	GDP	GDP	GDP
Chinese Pharmacopeia Testing Required	Visual inspection and contsminants	Visual inspection and weighing	Full pharmacopeia testing	Visual inspection or none	Visual inspection or none	Visual inspection or none
Identification	✓	✓	✓	×	×	×
Check	×	✓	✓	×	×	×
Extract	×	×	✓	×	×	×
Processing	×	×	✓	×	×	×
Specific contaminants	✓	×	✓	×	×	×
Key Pharmacopeia Testing	Visual inspection	Visual inspection	Full pharmacopeia testing	Visual inspection and weighing	Visual inspection	Visual inspection OR none
Testing (for subsitution) required?	✓	✓	✓	×	×	×
Adulteration (substitution) likely?	×	✓	✓	✓	✓	✓

✓ = Yes, × = No

★★★ More likely = Adulteration likely and Testing not required, ★★ Less likely = Adulteation likely and Testing required, ★ Unlikelty = Adulteration unlikely and Testing required

SCORE: Ranked Likelihood of adulteration (substitution) recurring	★	★★	★★	★★★	★★★	★★★

Market, trading and consumer outlets presented the greatest likelihood of EN substitution with PS and ES. These are where only basic visual checks and weighing is conducted. This concurs with the HPTLC analysis findings in this study where the greatest reduction to 50% in authenticity both for all 106 samples combined and EN individually was found at the market trading and supplier outlets. The exception was for the one PS sample sourced from a supplier that resulted as authentic, however one instance constituted quite a low sample number to be considered generally indicative.

Although a somewhat low 50% proportion of EN samples was found authentic, post-trading and post-supplier stages a higher, 82%, was found in modern pharmacies and less, 44%, in traditional Chinese pharmacies. The practitioner stage ranked as the next most likely stage for adulteration to occur. As discussed, reliance on more classical texts sources and the accepted traditional practices of substituting one CMP for another contributes to more likely substitution by herbal practitioners in more traditional settings. Generally, modern pharmacies in China herbal medicine are dispensed by sales assistants when a patient presents a prescription from a hospital-based practitioner or those resident in-store, whereas many traditional pharmacies combine diagnosis, treatment and dispensing. An observation while collecting samples was that modern pharmacies tended to remove herb samples from packaging with some identification and batch number details, whereas traditional pharmacies mostly wrapped prescriptions taken from labelled drawers containing loose herbs. Potentially, this leaves more opportunity for herbal substitution to occur.

Substitution of EN with PS also could occur at other stages of the supply chain, from cultivation where seed of one herb could be grown in place of EN, a wild source of PS could be collected in place of EN, and processors could swap PS of in place of ES. These scenarios seem unlikely, as the plants are easily observed and inspected during cultivation and collection as directed by GAP and GCP, and GMP and GLP in controlled manufacturing environments that would detect any substitution, even at low levels.

Substitution of EN is ranked as improbable during the import / export process, distribution and at the consumer stages, where items are packed and labelled in transit. Further, it seems improbable that consumers could somehow swap EN for PS, ES, or other herbs.

Therefore, substitution most likely occurs where middlemen handle and traders sell EN to customer outlets, which would not be detected at the later stages in the herbal supply chain where only basic visual checks, if any, are generally conducted.

Considering the complete bias of PS substituted for EN and no EN found substituted for PS, together with the particular financial focus of middlemen, general trading and consumer outlet stakeholders, this supports the recurrence of value-based substitution of EN. This is in alignment with where gaps in testing were found, at the middlemen, trading and consumer outlets in the herbal supply chain.

Given the following observations in this study, a suggested solution is warranted and proposed.

Observations:

- The described limitations of macroscopic and microscopic visual testing that are central to detecting EN adulteration / substitution with PS, ES and other CMP.

- The gaps in detecting species adulteration / substitution particularly after the cultivation stages, particularly at and post traditional Chinese medicine pharmacies.

- The highly controlled laboratory type conditions required for the more sophisticated testing, including HPTLC, to reliably detect EN species adulteration / substitution.

Proposal:

It is therefore recommended that more robust analytical test methods that can be used in-situ at field locations such as cultivation sites, markets and at pharmacies are further considered and developed. Although the current and proposed future analytical methods are highly sensitive and capable in pharmaceutical biomedical type manufacturing processes and laboratory environments, their application in herbal supply chains with more variable practical considerations is limited and unlikely to contribute to the reduction in persistent quality problems such as misidentification, substitution and adulteration of EN with other species.

The common development and validation of current pharmacopeia analytical methods in laboratory-type environments, in which their development is generally considered complete, could perhaps be considered as a pilot stage or prototype for the environments in which they are expected to perform when detecting CMP quality issues in a timely manner and relevant supply chain location.

4.4.11 Examining the applicability of monograph pharmacopeia tests for in-field use in the EN supply-chain

To examine how relevant and applicable the current ChP pharmacopeia monograph tests are for in-situ use a simple three score analysis was conducted and shown in *Table 4.21.*

TABLE 4.21 ANALYSIS OF THE APPLICABILITY OF EN CHINESE PHARMACOPEIA MONOGRAPH TESTING FOR IN-SITU USE IN THE HERBAL SUPPLY CHAIN

Low = + Medium = ++ High = +++

DESCRIPTION	TESTS	Comment	Advantages	Disadvantages	Equipment complexity	Expertise required	Speed	Sensitivity	Specificity	In-field applicability
Identification	**macroscopic and microscopic**	Authenticates EN and can detect gross adulteration	Relatively simple method requiring little or no equipment. Can be conducted in-field. Quickly conducted. Can detect a wide scope of adulterant if visually apparent, eg., wires, string, non-medicinal plant parts.	Requires some expertise. Highly subjective. Prone to misidentification with similar plants	+	+	+++	+	+	+++
	TLC	Authenticates EN Can sometimes detect high concentration of other herb and chemical adulterants	Relatively simple method. Can be conducted in-field. Relatively quickly conducted	Requires expertise and some equipment. Subjective. Specificity of test may not detect common adulterants unless sought	++	++	++	++	++	++
Check	**moisture**	Water content / bulk herb weight content Limits potential for microbial growth	Relatively simple method requiring little equipment and expertise. Could be conducted in-field.	Requires some equipment. Non-specific.	+	+	++	++	+	++

TABLE 4.21 ANALYSIS OF THE APPLICABILITY OF EN CHINESE PHARMACOPEIA MONOGRAPH TESTING FOR IN-SITU USE IN THE HERBAL SUPPLY CHAIN

Low = + Medium = ++ High = +++

DESCRIPTION	TESTS	Comment	Advantages	Disadvantages	Equipment complexity	Expertise required	Speed	Sensitivity	Specificity	In-field applicability
			Relatively quickly conducted. Low specificity of method can detect a wide range of contaminants	Only some adulterants at high concentrations (multiple %'s) can be detected.						
	total ash	Detects EN ash and non-plant inorganic matter e.g., silt on plant from cultivation or dust from storage	Relatively simple method. Could be conducted in-field.	Requires some expertise. Only some adulterants at high concentrations (multiple %'s) can be detected. Non-specific and some common adulterants such as pesticides, heavy metal contaminants are not detected.	++	++	++	++	+	++
	acid insoluble ash	Detects silica and siliceous earth content	Relatively simple method requiring basic equipment. Can sometimes be conducted in-field. Relatively quickly conducted. Low specificity of method can detect a wide range of contaminants.	Requires some expertise. Only insoluble adulterants at high concentrations (multiple %'s) can be detected.	++	++	++	++	+	++

TABLE 4.21 ANALYSIS OF THE APPLICABILITY OF EN CHINESE PHARMACOPEIA MONOGRAPH TESTING FOR IN-SITU USE IN THE HERBAL SUPPLY CHAIN

Low = + Medium = ++ High = +++

DESCRIPTION	TESTS	Comment	Advantages	Disadvantages	Equipment complexity	Expertise required	Speed	Sensitivity	Specificity	In-field applicability
extract		Physiochemically active content of EN that can be extracted with solvents to indicate a general minimum content of expected herb and potential efficacy	Somewhat simple method requiring equipment. Can sometimes be conducted in-field. Somewhat quickly conducted. Low specificity of method can detect a wide range of contaminants	Low specificity does not identify contaminants.	++	++	++	++	+	+
Sulfur dioxide		Detects fumigant residues	High specificity of method can detect a narrow range of contaminants	More complex and relatively slower method requiring mainly laboratory-based equipment. Not quickly conducted. Not suited for in-field use.	+++	+++	+	+++	+++	+
Heavy metals		Detects accumulated heavy metals from soil, airborne particles and in some bulking agents	Very high specificity of method can detect and identify a very narrow range of contaminants	Quite complex method requiring laboratory-only based equipment. Not suited for in-field use. Not conducted quickly.	+++	+++	+	+++	+++	+
Microbial		Detects microbial contamination from supply and storge. Can detect spoilage of product.	Somewhat simple method requiring simple equipment. Can sometimes be conducted in-field. Medium specificity of method can detect a moderately wide range of microbial contaminants	Incubations time impart long analysis times.	++	++	++	++	+++	++

TABLE 4.21 ANALYSIS OF THE APPLICABILITY OF EN CHINESE PHARMACOPEIA MONOGRAPH TESTING FOR IN-SITU USE IN THE HERBAL SUPPLY CHAIN

Low = + Medium = ++ High = +++

DESCRIPTION	TESTS	Comment	Advantages	Disadvantages	Equipment complexity	Expertise required	Speed	Sensitivity	Specificity	In-field applicability
Pesticides		Detects allowed pesticide residues and those restricted by regulation.	Very highly specificity method that can detect and identify a very narrow range contaminant	Quite complex method requiring laboratory-only based equipment. Not suited for in-field use. Not quickly conducted	+++	+++	+	+++	+++	+
Processing		Instructs processing	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Nature, flavour, and channels		Informs classical practice use	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Functions and indications		Informs clinical use	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Usage and Dosage		Informs usage dosage ranges in herbal formulas	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

In particular, the relatively simple macroscopic tests which scored highly for in-situ use in the EN herbal supply should be noted, however in general, the current testing pharmacopeia testing requirements appear at best medium and mainly low in their suitability for in-field use.

Alternative approaches to analysis could perhaps be considered. Some instrumentation has already demonstrated usefulness in “real-world”, non-laboratory conditions, which are generally referred as patented, process, or portable analytical technology (PAT). PAT instruments based on liquid chromatography and spectroscopic analytical techniques have been developed to work in more non-controlled laboratory environments such as industrial production areas and challenging in-field environments (*Table 4.22*).

TABLE 4.22 TYPES OF PATENTED (PORTABLE) ANALYTICAL TECHNOLOGY

Patented Analytical Technology (PAT)	Analytical Principle	Reference
Mass Spectrometry	Ionization and Mass-to-Charge Ratio	Wang et al., 2022
Polymerase Chain Reaction (PCR)	DNA Amplification	Zhu et al., 2020
Liquid Chromatography	Separation based on Retention Time	Hemida et al., 2023
Spectroscopy	Interaction with Light	Cruz et al., 2023
Nuclear Magnetic Resonance (NMR)	Interaction with Magnetic Field	Saviano, Paris and Iorizzi, 2023
Flow Cytometry	Cell Analysis and Sorting	Loureiro et al., 2023
Gas Chromatography	Volatile Compound Separation and Identification	Sharma, 2023
X-ray Crystallography	Crystal Structure Determination	Kashyap et al., 2023

PAT has shown capability in conditions exceeding those required for CMP quality monitoring, such as in extreme climatic conditions (Kramer et al., 2023) and in exploration of planetary surfaces (Lehner, 2023). With these PAT developments already being demonstrated and in combination with the apparent advanced

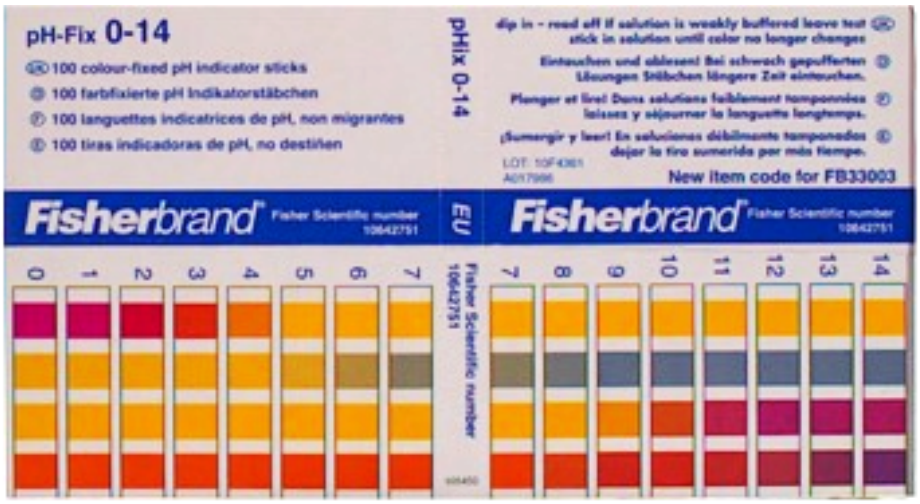
computing power of consumer mobile phone technology, it could perhaps form a focus on which to base future research for advancing the reduction of persistent CMP quality issues (Tan et al., 2020). Further, with the relatively recent emergence of Blockchain technology as a means to capture data in multiple locations, in immutable storage that is distributed to facilitate data entry and access globally, it is plausible that Blockchain could provide an accessible and transparent GxP and analytical test data repository for CMP which, in principle, has been previously demonstrated (Ming-Yi et al.,2020; Heinrich et al., 2019).

4.4.12 Example of how simpler in-field methods for use in the EN supply-chain could be developed

A simple experiment not warranting a full section or extended description was completed to explore in principle if simpler, inexpensive and effective in-field methods could be developed for differentiating EN and its substitutes PS and ES in the herbal supply chain.

The following investigation was completed using pH test strips shown in *Figure 4.12.*

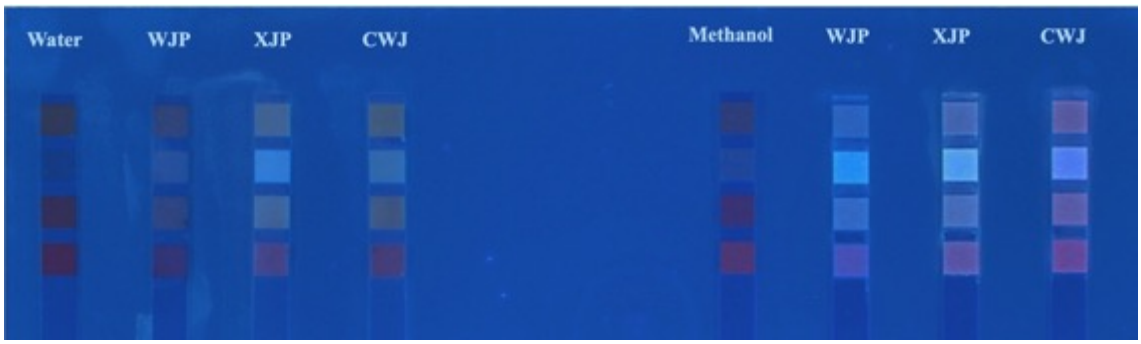
FIGURE 4.12 PH TEST STRIPS



180 mg of ground EN, PS and ES was incubated at 80°C in 10 ml of water for 30 minutes, A second set of ground of EN, PS and ES samples was similarly incubated at 80°C in 10 ml of 30% Ethanol: water for 30 minutes.

A pH test strip was then dipped into each of the solutions, which were then photographed under 366nm UV light, shown in *Figure 4.13.*

FIGURE 4.13 VISUALISING PH STRIPS UNDER 366 NANOMETRE LIGHT THAT WERE DIPPED IN EN, PS AND ES SAMPLES IN WATER AND ETHANOL INCUBATED AT 80 DEGREES CELSIUS FOR 30 MIN.



EN = *WJP = Wu Jia Pi,* ***PS*** *= XJP=Xiang Jia Pi, ES = CWJ = Ci Wu Jia*

"Water" and "**Methanol"** are controls with no herb samples

Indication of any differentiation of EN (WJP), PS (XJP) and ES (CWJ) was evident for both groups in water (group of four strips on left in picture) and even more pronounced in the alcohol solution (group of four strips on the right). This test was completed without any chromatography or any pre-treatment of herbs except sample grinding following simple dissolution, dipping and observation under UV light without any additions.

Total preparation and analysis time was less than 45 minutes. Active analyst time during this period about 15 minutes. The additional 30 minutes was waiting time for the incubation of samples.

Chromatography-free test strips that could produce unique colour patterns for different herbs is a prospect that could simplify, reduce cost and accelerate analysis for many herbal identification issues in a practical manner. Here, simple

pH test strips have been used to demonstrate the principle, however specific “panels” on strips could be developed to indicate different levels of target constitutes, such as alkaloids / flavonoids, terpenes etc., which could then be used not only to compare reference and sample herbs but also give information about the chemical composition and colour / chemical “fingerprint” to aid unknown discrimination. This is practical, inexpensive and without requiring expertise. A reference book or card of colour patterns could be easily carried around for field work or conveniently stored in herbalists’ clinics.

Smartphone / tablet apps could be developed to measure and analyse such results, potentially building up a database as herbalists use it.

Alternatively, a tube containing water or alcohol containing similar materials to the test strips could be developed simply requiring breaking off the top and “dipping” into samples to compare standard and suspect test herbs. Coloured rings could indicate various chemical constituents in the tube, simply, safely and inexpensively.

Tubes or test strips could be further developed which react to known adulterants or toxins enabling simple field or in-clinic analysis. Again, without any expertise or specialist training required.

Further work on materials and different light spectrum regions (or combinations thereof) could produce more versatile, sensitive and informative strategies to detect and alert forgeries, adulterations and toxins. Or simply to test freshness or suitably for prescription of raw, powered / granulated herbs.

In practice further simplification rather than adding more complex developed test methodologies could be an equally valuable and viable route to making this type of analysis cheaper and more widely practiced.

The work here is merely supporting evidence of the problem that exists with the use of PS in place of EN and demonstration of proof of principle for new method ideas for the differentiation in a simple, practical, cost effective way. Though a UV illumination chamber as part of the HPTLC equipment was used here, simple blacklight torches are commonly available (UV-A. Region, 250-400 nm range) such as the one in shown in *Figure 4.14*. This was purchased for £5 in a London high-street hardware store.

FIGURE 4.14 BLACKLIGHT TORCH

4.5 Limitations of the EN study

4.5.1. Limitations in sampling

The Collection of CMP samples was planned from the four major markets in China, which are some the largest globally, located Bozhou, in Anhui province, Anguo, in Hebei, Yuzhou in Henan, and Chengdu market in the Sichuan province. Further, a relatively general distribution of samples was planned for collection across the EN supply chain. However, due to the outbreak of the COVID-19 pandemic, access to the markets and supply point locations was prohibited. As described in this EN study, the analysis was progressed with samples that were already collected from Bozhou and Anguo, rather than all four markets as originally intended. Furthermore, there were relatively low number of samples collected from farm and cultivation sites. Most samples were collected at markets. This produced an uneven sample distribution across the complete supply chain and reduced comparability, particular to the earlier stages of the supply. To offset bias when comparing results, locations where three or more samples were collected were compared in assessing trends. It is acknowledged that this limitation is present in the study, which was completed under the circumstances and is presented. However, the general trends observed and discussed are well-represented within the 106 samples collected from two of the world's largest Chinese medicine markets, and the findings presented are considered valid. It is suggested that a follow-up project could complete the planned sample collection, which may lead to further valuable observations.

4.5.2. Limitations in verifying sample identities

Only one method, HPTLC, was used to authenticate the identity of the samples analysed in this study. DNA analysis-based techniques are considered foremost in the identification of plant species (Zhu et al., 2022).

The HPTLC method was chosen due to previous successes demonstrated by researchers (Frommenwiler et al., 2020; Upadhye, Rajopadhye and Dias, 2018), and in combination with key informants (Yao et al., 2017; Booker et al., 2012), and DNA techniques (Raclariu et al., 2018).

This research followed their approach and DNA analysis was planned as a secondary verification method. Firstly, by collaboration by the Natural History Museum in Oslo, Norway and, later, to conduct a second verification by HPTLC at another laboratory, that of the HPTLC Association in Rheinfelden near Basel, Switzerland.

Due to logistics and staff disruptions during the COVID-19 pandemic some postal services were affected, the samples sent to Oslo were lost in transit, and could not be tracked and traced by the courier company, therefore the analysis could not be completed. A further attempt was made to conduct a second verification, by the HPTLC Association whose method was used in this study who kindly offered to replicate the analysis at a second laboratory to produce data that could potentially support revision of the European Pharmacopeia monograph. Even though the samples did arrive, a cleaner at the facility disposed of the samples

executing a COVID-19 cleaning protocol in the correct course of their instructed duties. Therefore, the analysis was not progressed.

Although limitations from practical considerations arose, the research was completed with considerable rich and detailed contributions from 18 expert key informants and 106 CMP samples analysed from three global regions. It is on this data and interpretations thereof, that the findings are founded and presented in this doctoral thesis.

4.6 Conclusion of the EN study

The analysis of 106 samples for the three species EN, PS and ES using HPTLC has shown that EN is significantly adulterated across three regions, mainland China, Taiwan and the UK. The adulteration is mainly with PS and sufficient to present a health concern globally.

The recurrence of the adulteration due to misidentification of whole plant species suggested by previous authors appears unlikely. However, intentional substitution in traditional Chinese medicine pharmacies appears to play a part in EN substitution with PS and ES. Most adulteration recurs in the market and supplies stages of the herbal supply, most likely due to value-based substitution of less expensive PS and ES for more costly EN

The recurrence of such previously known and detectable adulteration is facilitated by gaps in pharmacopeia testing requirements as directed by GxP, together with variability in regulations between regions.

Introducing more simple distributed in-field testing for adulteration outside complex laboratory environments with overly sophisticated analytical instrumentation, together with a visible and immutable quality recording system such as Blockchain, could lead to improvements to the recurrent problem of EN adulteration with PS and ES, in addition to other such known and detectable adulterants. Further research in this area is suggested.

Emergent quality issues in the supply of Chinese medicinal plants

中草藥供應中發生的品質問題

A mixed methods investigation
of their contemporary occurrence
and historical persistence

當代發生和歷史延續混合調查法

VOLUME II of III

A

Doctoral Thesis

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2023

Chapter Five Gathering the Investigation Findings

5.1 Overview of the research findings

This research set out to investigate why similar and well-documented Chinese medicinal plant quality issues that emerged centuries ago still recur in this Contemporary Era of advanced analytical testing and extensive regulation, so that a solution to the problem of their persistence may be proposed. The results of this investigation have clarified the identity of CMP quality issues and generated insights into why they recurred. These insights informed a solution to their persistence.

Reviewing the literature gathered existing knowledge in Chapter Two. Consulting with key informants generated new perspectives from synthesising the opinions of experts in multiple occupations within the field of CHM in Chapter Three. New insights were generated around a case example of toxic adulteration in the global supply chain and contributed to understanding its unexplained persistence in Chapter Four. The gathered insights combined informed a solution that is proposed in this Chapter Five.

The proposed solution provides an alternative approach to strategies currently planned by authorities that are based on those previously in place that did not prevent the persistence of well-known and detectable CMP quality issues.

5.2 Objective One Exploring knowledge of key informants – the KI study

Completing the first research objective was described in Chapter Three during the KI Study. To explore the knowledge of expert key informants in the field of Chinese medicine with questionnaire and interview tools then using thematic analysis to identify what similar and well-documented Chinese medicinal plant quality issues occurred. Furthermore, to generate insights into why they recurred, so that solutions to the problem of their persistence could be proposed.

5.3 Objective Two: Investigating the unexplained case example – the EN study

Completing the second research objective was described in Chapter Four during the EN Study. To collect Chinese medicinal plant samples; *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu*, Periploca sepium* Bunge and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim from the global supply chain across the Chinese mainland, Taiwan, and the United Kingdom, so that they could be analysed using high-performance thin-layer chromatography to determine their authenticity and investigate why this unexplained case example of adulteration recurs. This was done so that a solution to the problem of its persistence may be proposed.

5.4 Objective Three: Gathering the study findings to describe the identity of CMP quality issues, why they persisted, and a solution.

The third and final research objective is described in this Chapter Five, gathering the findings to concisely describe:

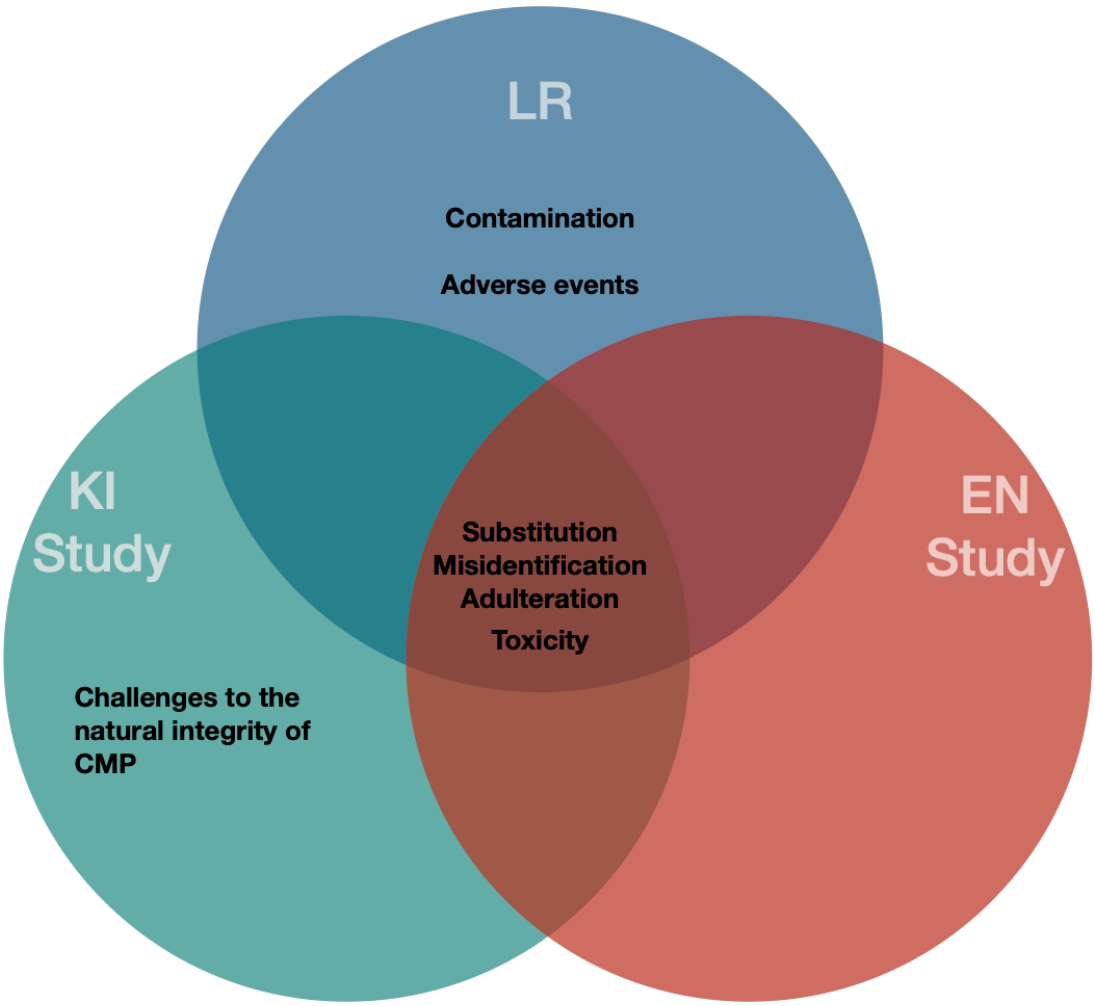
- The identity of the main CMP quality issues,
- insights into why they persisted, and,
- a proposed solution to the problem of their persistence.

The insights gained from the KI and EN studies are visually summarised in context of what was previously reported in the literature as shown in the Venn diagrams, *Figures 5.1* to *5.3* inclusive, in the following section.

5.4.1 Identity of the main CMP quality issues

Figure 5.1 illustrates visually how existing knowledge in the literature-base and the two studies contributed to clarifying the identity CMP quality issues, *Figure 5.2*, the insights into why they persisted, and *Figure 5.3*, arriving at a proposed solution.

FIGURE 5.1 VISUAL ILLUSTRATION OF HOW EXISTING KNOWLEDGE IN THE LITERATURE-BASE AND THE TWO STUDIES CONTRIBUTED TO INSIGHTS INTO THE IDENTITY OF CMP QUALITY ISSUES



LR = Literature Review**, KI** = Key Informant study**, EN** = *Eleutherococcus nodiflorus* study case example

The identity of the main quality issues found were substitution, misidentification, adulteration, and toxicity.

The literature base extensively recorded the occurrences of CMP quality issues substitution, misidentification, and adulteration, many of which were found through reports of adverse events. In total 190 examples of quality issues were noted during the literature review, as recorded in the supplementary data in *Appendix to the literature review* (ALR), Tables ALR 1, 2, 3, 4, 5 and 6, inclusive, summarised in *Table 5.1*.

TABLE 5.1 SUMMARY OF CMP QUALITY ISSUES AND NUMBER OF EXAMPLES IDENTIFIED FROM LITERATURE REVIEW

CMP quality issues identified during the literature review In both reviews and primary research articles	**Number of examples**
Substitution	81
Adulteration	53
Misidentification	18
Toxicity	14
Adverse Events	12
Synthetic Drugs Addition	6
Variable quality	3
Incorrect prescriptions	1
Contamination	1
Traceability	1

CMP quality issues were identified by key informants during the KI study. In total 95 examples were noted from KI responses as recorded in supplementary data attached in *Appendix to the KI study* (AKI), section AKI 12, and summarised in the *Table 5.2.*

TABLE 5.2 SUMMARY OF CMP QUALITY ISSUES AND NUMBER OF EXAMPLES IDENTIFIED DURING THE KI STUDY

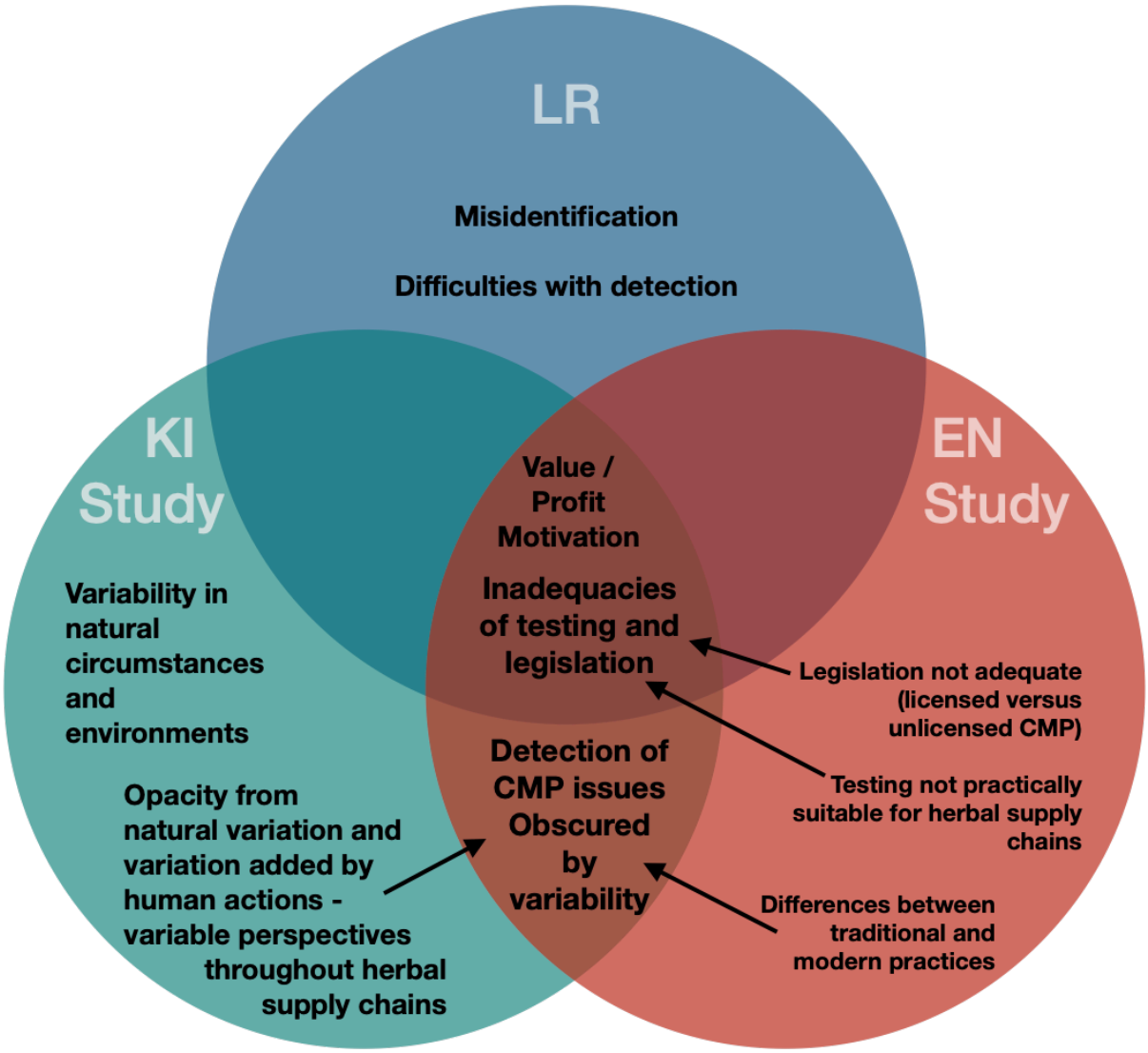
CMP quality issues identified during the KI study	Number of examples
Toxicity	43
Adulteration	23
Substitution	23
Scarcity	4
Variable quality	1
Rejected material resold	1

The literature reviewed placed more emphasis on contamination, whereas in the KI study there were collectively considered as challenges to the original natural integrity and their potential toxic effects.

The EN study, in agreement with both the literature base and KI study showed adulteration and, in some cases, full substitution with cardiotoxic PS as the main quality issues.

5.4.2 Why did CMP quality issues persist?

FIGURE 5.2. VISUAL ILLUSTRATION OF HOW EXISTING KNOWLEDGE IN THE LITERATURE-BASE AND THE TWO STUDIES CONTRIBUTED TO INSIGHTS INTO WHY CMP QUALITY PROBLEMS PERSISTED



LR = Literature Review**, KI** = Key Informant study**, EN** = *Eleutherococcus nodiflorus* study case example

CMP issues were found to persist historically due to a combination of reasons. The recurrence of similar quality problems was driven by the motivation for economic gain combined with difficulties in detection. Many were obscured from detection by the natural phytochemical variability of plants and were not sought by those handling CMP who had varied and siloed perspectives, concerns, and knowledge at different stages of the supply chain. Detection was further obscured by the absence of adequate in-field testing. Quality issues could occur undetected between the gaps in testing evident along the supply chain. The by-design, highly specific and repeatable nature of analytical testing in locations prescribed by regulation renders them highly predictable, and therefore relatively easily evaded by those motivated to circumvent such detection.

The findings from the literature-base in particular emphasised difficulties with detecting CMP quality issues, together with the economic motivation that perpetuated their occurrence. In total 173 examples from the literature review contributed to informing why CMP quality issues persisted as recorded in the supplementary data in *Appendix to the literature review* (ALR), Table ALR 6, and summarised in *Table 5.3.*

TABLE 5.3. NUMBER QUALITY ISSUE EXAMPLES IDENTIFIED FROM LITERATURE REVIEW

Interpreted reasons why CMP quality issues could persist during the literature review of primary research articles	**Number of Examples**
Difficult to detect	117
Value Profit Motivation	29
Variable perception	6
Error	3
Toxicity	6
Incorrect Herb Usage	4
Accepted practice	2
Not investigated sufficiently	2
Variability of botanicals	1
Multiple reasons - complex	1
Unlicensed herbs not tested	1
Analytical fraud	1

The KI study findings agreed on the point of detection difficulties, and further found that CMP quality issues were obscured from detection by the natural phytochemical variability of CMP and the variation contributed from those with different views on how CMP should be handled in the supply chain. In total 95 examples in the KI study contributed to informing why CMP quality issues persisted, as recorded in the supplementary data in *Appendix to the KI study* (AKI), Table AKI 12, and summarised in *Table 5.4.*

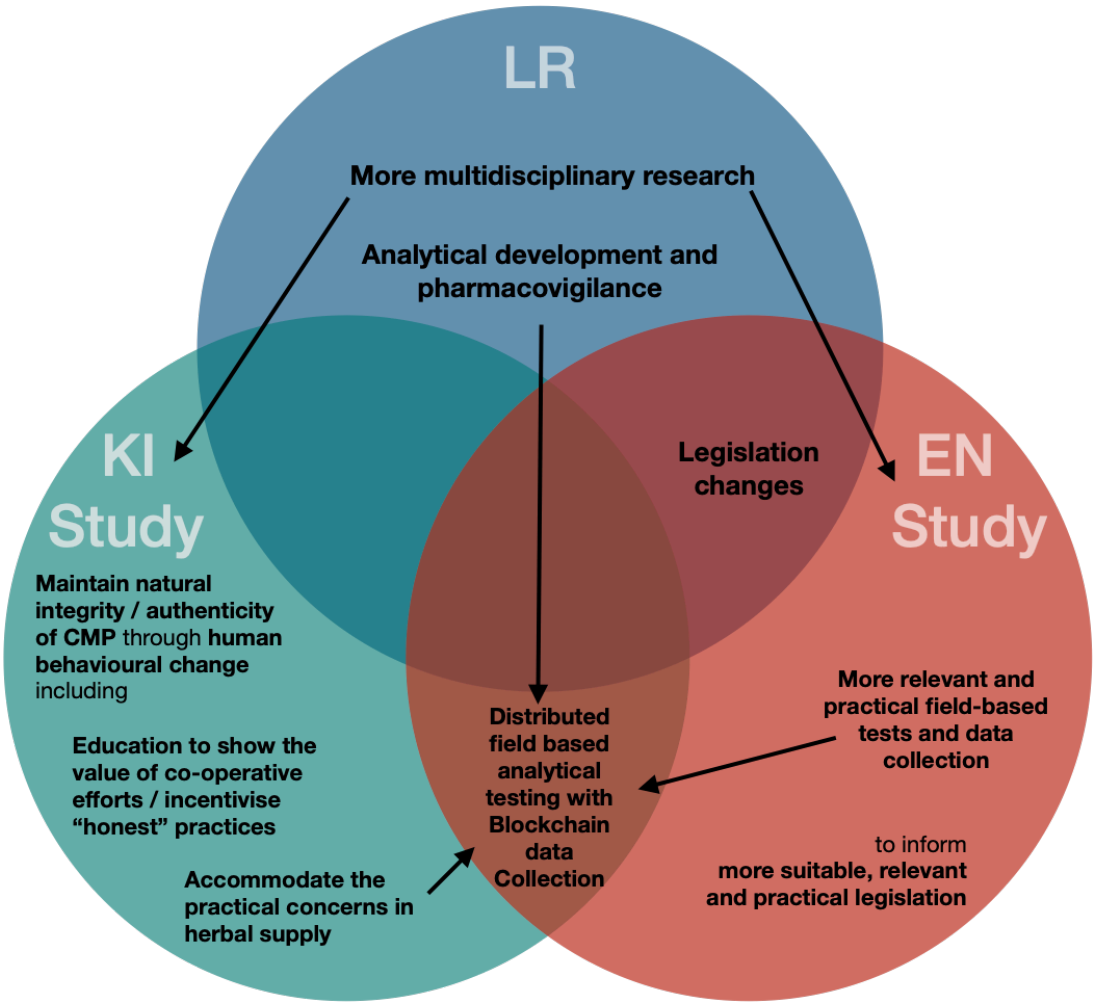
TABLE 5.4. NUMBER EXAMPLES IDENTIFIED IN THE KI STUDY INFORMING WHY QUALITY ISSUES PERSIST

Reasons why CMP quality issues could persist identified during the KI study	**Number of examples**
Difficult to detect, not detected, not known	48
Value	31
Acceptable practice	7
Intrinsic nature	3
Divergence from traditional practice	3
Supply and demand	3

The EN study further supported this point on variable perspectives by those handling CMP in the supply chain, finding different levels of substitution in modern pharmacies compared with that in traditional pharmacy settings. Comparatively, CMP sealed in packages and with cultivation sources declared were found 100% authentic. The EN study further highlighted the gaps and inadequacies of current testing, as mandated by legislation, that directs what and where testing should occur.

5.4.3 Solution to common persist CMP quality issues

FIGURE 5.3 VISUAL ILLUSTRATION OF HOW EXISTING KNOWLEDGE IN THE LITERATURE-BASE AND THE TWO STUDIES CONTRIBUTED TO ARRIVING AT A PROPOSED SOLUTION.



LR = Literature Review**, KI** = Key Informant study**, EN** = *Eleutherococcus nodiflorus* study case example

The proposed solution to reduce the persistence of CMP quality issues is to, firstly, shift reliance on sophisticated laboratory-bound testing towards simpler and more robust field-base testing where CMP quality issues most likely go undetected. That is, in-situ in along the supply chain where gaps are apparent in current testing. Data from more distributed in-situ testing could be collected and accessed across the supply chain in conjunction with systems such as Blockchain and currently advanced hand-held mobile phone-based technology.

Secondly, introducing educational initiatives that demonstrate the benefits of providing medicinal plants without problematic issues to consumers that could perhaps incentivise those motivated to perpetrate substitution and adulteration of CMP for short-term economic gain to consider the value of ongoing, sustainable supply of CMP. This could also encourage stakeholders to perhaps consider the longer-term value of more equitable profit sharing and more transparently highlight the efforts expended communally by those within the herbal supply who produce CMP with less quality issues.

The findings from the literature-base particularly emphasised developing more sensitive and increasingly sophisticated analytical methods as solution in line with the strategy of previous decades. Improved pharmacovigilance was also highlighted together with tighter legislation on the supply of medicinal plants. The literature underscored the need for further research and prompted the investigation approaches completed in the KI and EN study. In total 213 examples from the literature review contributed to informing a solution to the persistence of CMP quality issues as in the supplementary data, *Appendix to the literature review* (ALR), Tables ALR 5 and 6, inclusive, and summarised in *Table 5.5.*

TABLE 5.5 SUMMARY OF SOLUTIONS TO THE PERSISTENCE OF CMP QUALITY ISSUES AND THE NUMBER OF EXAMPLES IDENTIFIED FROM LITERATURE REVIEW

Solutions to the persistence of CMP quality issues identified during the literature review In both reviews and primary research articles	**Number of examples**
Analytical development	132
Pharmacovigilance	22
Legislation	19
Not proposed	14
Education	9
More Research	5
Standardisation / harmonisation	4
Mixed solutions	4
Predictive toxicology and omics	1
Selective sourcing and regulation	1
Study quality issues in context of whole supply chain (value chain)	1
Supervised prescriptions by TCM Practitioner	1

The KI study findings supported using analytical testing as a solution, but more so from novel approaches, and in combination with altered legislation that support more practical means of detecting CMP quality issues. The KI study found education as a proposed solution in contrast to more research suggested by the literature review. Education to reduce the siloed nature of knowledge and

associated variable perspectives of those who handle CMP and influence its quality should be conducted. Education to incentivise practices and actions communally aligned towards producing less problematic quality issues in the herbal supply could also be considered. In total 95 examples in the KI study contributed to informing a solution to the persistence of CMP quality issues as recorded in the supplementary data, *Appendix to the KI study* (AKI), tables AKI 12, and summarised in *Table 5.6*.

The EN study also supported the literature review and KI study findings suggesting that further analytical testing is required. However, more alike that of the KI study in seeking alternative testing approaches to those currently in place. The EN study proposed specifically more field-based, distributed, and in-situ testing to improve collection of data in gaps where currently testing is not conducted. This new data could inform more suitable and relevant legislation to herbal supply chains and the GxP good practices regulators recommend.

TABLE 5.6 SUMMARY OF SOLUTIONS TO THE PERSISTENCE OF CMP QUALITY ISSUES AND THE NUMBER OF EXAMPLES IDENTIFIED DURING THE KI STUDY

Solutions to CMP quality issues identified during the KI study	Number of examples
Analytical surveillance and altered regulation	*77*
Education (including regulators and practitioners)	*5*
None recommended / Unknown	*6*
Regulation and harmonisation	*2*
Regulation and increased practitioner surveillance	*1*
Reducing vulnerability in the supply chain	*1*
Use traditional Chinese medicine directed preparation	*1*
Not considered a problem by manufacturer	*1*
Conservation	*1*

5.4.4 Summary of the gathered findings

In summary, the common persistent CMP problematic issues are misidentification, substitution, and adulteration, are similar to those that have been well known and recurred for centuries. The predominant response to these has been to control the quality of CMP by detecting the occurrence of quality problems using increasingly sophisticated analytical methods often developed in highly controlled laboratory environments. Combined with legislation to highly restrict their use together in the context of the “good practice” regulatory frameworks that directed where the methods should be used in the herbal supply chain. The main reason why well-known and detectable CMP quality issues recur is due to actions that are economically motivated.

The reason why CMP quality issues can persist in an era of sophisticated testing technology and well-developed legislation is that CMP issues are difficult to detect using methods that were neither fully implemented nor were fully suitable for where the quality issues likely occur, in variable field-based conditions outside laboratory environments. Further, the legislation in place is not yet developed to deal with common use of unlicensed herbs. These insights informed a solution, as suggested.

Rather than continuing to invest predominantly in the development of increasingly sensitive and sophisticated laboratory-based technology, it is suggested that development of simpler, more robust, and distributed field-based sensor technology to capture real-time quality information in conjunction with a data system such as Blockchain which could allow transparent access to CMP quality information globally. Hand-held mobile phone type technology has advanced sufficiently to support such a solution. This new data could better inform more practical, relevant, and effective legislation.

Education outlining the communal benefits of co-operation and “honest” practices while handling medicinal plants in the herbal supply chain could perhaps contribute to reducing the prime motivation for persistence CMP quality issues, that of value-profit gain. More equitable profit sharing and transparency around those who do produce, and supply CMP less problematic quality issues may further contribute to preventing historical CMP quality issues that persisted in contemporary times from persisting into the decades ahead.

5.5 Implications of the research and contributions to the field of CMP Quality

Considering that more than 85% of the world's population are estimated to consume medicinal plants and CMP are the most populous with 3 million tonnes exported globally every year, which is predicted to rise, improving the ongoing problem of persistent CMP quality issues has the potential to influence a substantial proportion of the global population (Pešić & Stanković, 2015; NSBC, 2018; FAO, 2020, p7).

Insights gained during this research by considering recurrent CMP quality issues more collectively and as a unified problem of persistence for the first time, in contrast to previously researching the area may prompt others to similarly explore quality issues from such a perspective and yield further new insights in the field of CMP, and plant medicines from other traditions.

It is hoped that presenting the findings of this study as planned through online publication of this thesis, journal publications, and at GP-TCM, BAPP, ABC and ISE conferences could encourage those investing efforts only towards developing similar and more sophisticated analytical testing solutions for CMP quality issues, to perhaps consider divesting efforts into simpler and potentially more effective testing solutions.

The findings of this research highlight the importance of education in altering the behaviour of those who are motivated to purposefully adulterate medicinal plants. This is central to improving the quality of CMP. Although training is mandated by

GxP for those handling medicinal herbal materials from their cultivation to supply stages, it mainly focuses on basic hygiene and how to complete documentation, in particular checklists accurately. Furthermore, the training is specific to each stage of the supply, such as GCP for collection and GMP for manufacturing (May, 2023; WHO, 2007b; Committee, 2006). If GxP training could be revised to include as standard a broader overview of the importance every CMP handler's influence at each stage has on that in the whole supply, this could at least begin to reduce the siloed nature of information in the supply.

Furthermore, if the value of producing CMP with less problematic quality issues was highlighted in this training, together with the value each person's contribution to the well-being of the herb-handlers and their families who consume medicinal plants, then perhaps some may be motivated to avoid more nefarious practices. Similarly, this highlights the value that herb-handlers contribute to final herbal products and the financial renumeration that is appropriate for their efforts. During this research others have shown the potential benefits of fair trading had within the craft industry in China, which could be mirrored in the herbal supply (Zhang, Liu and Wang, 2020).

The KI study showed that even though large groups with hundreds of experts in the field of CHM made a significant contribution to the knowledgebase, still new and important insights can be gained from a single researchers with a limited number of KI experts and resources (GPTCM, 2023). This study demonstrates to those considering future research that smaller scale research can make a valuable contribution.

The EN study demonstrated that even complex and unexplained cases of CMP quality issues can be informed by taking a multidisciplinary approach, rather than the predominant research route relying on laboratory analysis or social sciences studies in isolation. Exploring problems in the context of knowledge accrued historically from classical texts sources in addition to more modern electronic literature based sources can contribute to previously researched but unexplained sources of CMP quality issues. Combining expert consultation with laboratory analysis could yield new insights into the many other cases of CMP unexplained CMP quality issues for future researchers.

Researchers studying the EN case example further could consider collecting additional samples along the herbal supply chain completed in the EN study, and include DNA testing to further validate and expand the findings of this study. It is hoped that future collaboration with the HPTLC association can help improve the current HPTLC monograph in the EP to capture additional cases of herbal substitution and improve the general CMP quality situation.

This research proposes the use of newly developing technology such as Blockchain and hand-held mobile technology, which is hoped to inspire researchers in this area to consider new applications for their research in the CMP herbal supply chain. During the course of the research described in this doctoral thesis, both collaborating researchers and others independently have already started exploring the application of Blockchain in the herbal supply to increase traceability and reduce much obscured information in herbal supply (Heinrich et al., 2019; Ming-Yi et al., 2020). This includes the real-time traceability of herbal quality in the herbal supply (Yik et al., 2021), and the use of mobile

phone software applications in combination with blockchain to help small scale spice producers to comply with official quality requirements (CBI, 2023). Although these concepts have yet to be combined with comprehensive in-field network of analytical testing in the CMP herbal supply, together with Blockchain and mobile phone type applications, it is hoped that the publication of this research can perhaps prompt those already in this field to take the next step towards combining their progressing research and towards such new applications.

This research identified gaps in the literature, shortcomings in quality testing, legislation, and difference in practices within CMP in supply chains. It is intended that these limitations highlighted together with those noted and inherent this study, as detailed in the next section, can provide a starting point for other researchers beginning out on their research journey.

5.6 Conclusion of the investigation

This research, to the best of the doctoral researcher's knowledge, has demonstrated a novel approach, findings, and alternative solution to investigating problematic quality issues in the field of Chinese herbal medicine.

Taking an alternative and broader approach by considering CMP quality issues collectively as a unified problem that has persisted historically to contemporary times has successfully generated new insights. Using a mixture of methods to consult with key informants and examine a case example of CMP produced a unique, rich, and diverse array of expert opinions, and furthermore illuminated a

previously unexplained case of substitution for EN. It determined the extent of toxic adulteration in the EN herbal supply chain with PS. These insights have clarified the most concerning CMP quality issues, contributed to the general understanding of why they persist, and informed an alternative and practical solution to those in place current and proposed for the future.

Focusing more specifically on reducing misidentification, substitution, and adulteration can meaningfully contribute to the quality of CMP and potentially to the well-being of much of the world's population who consume medicinal plants.

Shifting the current focus from using more sophisticated, sensitive laboratory-bound analytical technology to simpler, more robust field-based testing where CMP quality issues occur is likely to unveil much obscured information about CMP quality. Legislation and recommended good practices informed by such information is likely to be more suitable and relevant to the specific and practical concerns of CMP herbal supply chains. However, any such solutions are not likely to be as successful in isolation, and educational initiatives addressing economic motivation underpinning many of the actions that contribute to CMP quality issues are central to resolving the recurrent, age-old problem of persistent CMP quality issues.

The aim and objectives of this investigation have been completed and the doctoral research is concluded.

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Appendix

Contents of the Appendix

Appendix to the Literature review (ALR)

ALR 1: 207 journal articles excluded from the first phase general literature review

ALR 2: 152 journal articles excluded from the second phase specific literature review

ALR 3: 37 review articles included in the first phase general literature review

ALR 4: 122 journal articles included in the first phase general literature review

ALR 5: 40 review articles included in the second phase specific literature review

ALR 6: 173 journal articles included in the second phase specific literature review

Appendix to the literature review 1: 207 journal articles excluded from the first phase general literature review

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Social media not quality related	2021	Evaluation of the quality of YouTube videos on traditional Chinese medicine and inflammatory arthritis Quality of TCM videos for inflammatory arthritis	(Woon, Chia, Kwan, Phang, & Fong, 2021)
Methodological review	2022	Methodological quality of systematic reviews on Chinese herbal medicine: a methodological survey	(A. K. L. Cheung et al., 2022)
Methodological review	2021	Systematic Review and Quality Evaluation of Pharmacoeconomic Studies on Traditional Chinese Medicines	(N. Yang, Zhang, Deng, Guo, & Hu, 2021)
Methodological review	2019	Critical quality evaluation and application value of network Meta-analyses in traditional Chinese medicine	(Y. Chen et al., 2019)
Methodological review	2021	Effect of traditional Chinese medicine (TCM) on survival, quality of life, and immune function in patients with ovarian carcinoma: A protocol for systematic review and meta-analysis	(S. Ge, Q. Xing, A. Zhang, & Y. Wang, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Methodological review	2017	Epidemiology characteristics, reporting characteristics, and methodological quality of systematic reviews and meta-analyses on traditional Chinese medicine nursing interventions published in Chinese journals	(M. Yang, Jiang, Wang, & Xu, 2017)
Methodological review	2011	Epidemiology, Quality and Reporting Characteristics of Systematic Reviews of Traditional Chinese Medicine Interventions Published in Chinese Journals	(B. Ma et al., 2011)
Methodological review	2011	Methodological quality assessment of systematic reviews correlated to traditional Chinese medicine published in China	(D. Hu, Kang, & Wu, 2011)
Methodological review	2007	Methodology and reporting quality of systematic review/meta-analysis of traditional Chinese medicine	(Junhua et al., 2007)
Methodological review	2011	Overview of the quality standard research of traditional Chinese medicine	(H. Gao, Wang, Li, & Qian, 2011)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Methodological review	2015	Overview of traditional Chinese medicine quality evaluation method based on overall research	(H. Jiang, Gao, Yang, & Meng, 2015)
Methodological review	2011	Quality assessment of reporting of randomization, allocation concealment, and blinding in traditional Chinese medicine RCTs: a review of 3159 RCTs identified from 260 systematic reviews	(Jia He et al., 2011)
Methodological review	2004	Recommendations for enhancing the quality of traditional Chinese medicine clinical research reporting	(Lao, 2004)
Methodological review	2019	Reporting quality of Cochrane systematic reviews with Chinese herbal medicines	(X. Zhang, Q. Y. Aixinjueluo, et al., 2019)
Methodological review	2015	The quality analysis of literature retrievals of systematic reviews for traditional Chinese medicine	(M. Chen et al., 2015)
Methodological review	2010	Quality of reporting of trial abstracts needs to be improved: using the CONSORT for abstracts to	(L. Wang et al., 2010)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		assess the four leading Chinese medical journals of traditional Chinese medicine	
Methodological	2012	Advice of improving systematic review--meta analysis quality for traditional Chinese medicine	(Zhan & Hu, 2012)
Methodological	2022	Cochrane systematic reviews on traditional Chinese medicine: What matters-the quantity or quality of evidence?	(Dai et al., 2022)
Injections not CMP prescriptions	2021	Advances in analytical techniques and quality control of traditional Chinese medicine injections	(Tu, Li, Wang, & Yang, 2021)
Injections not CMP prescriptions	2014	Analyse causes of adverse reactions induced by traditional Chinese medicine injections from its quality standards	(H. Y. Cui & Liang, 2014)
Injections not CMP prescriptions	2022	Development of a comprehensive method based on quantitative 1H NMR for quality evaluation of Traditional Chinese Medicine injection: a case study of Danshen Injection	(W. Li, F. Zhao, J. Yang, J. Pan, & H. Qu, 2022)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Injections not CMP prescriptions	2013	Qualitative and quantitative analysis of cinobufacini injection using rapid separation liquid chromatography coupled with quadrupole-time-of-flight mass spectrometry and HPLC-photodiode array detection, a feasible strategy for the quality control of Chinese medicine injections	(H. Y. Zhao et al., 2013)
Financial and legal related	2019	Research on patent quality of Chinese listed traditional Chinese medicine enterprises from R&D investment perspective	(Y. D. Cao, Gong, Chen, & Liu, 2019)
Editorial commentary	2019	Facing the Challenge for Quality Control of Chinese Medicines	(J. Zhao, Ma, & Li, 2019)
Editorial commentary	2009	QUALITY CONTROL OF TRADITIONAL CHINESE MEDICINES Foreword	(P. Xie & van Beek, 2009)
Editorial commentary	2017	Determination of Quality Markers is Basis for Establishing Quality Standard and Control of Chinese Herbal Medicines	(C. X. Liu, 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Editorial commentary	2017	Quality Marker Concept Inspires the Quality Research of Traditional Chinese Medicines	(D. A. Guo, 2017)
Editorial commentary	2015	A holistic approach to the quality control of traditional Chinese medicines	(D. A. Guo, W. Y. Wu, M. Ye, X. Liu, & G. A. Cordell, 2015)
Editorial commentary	2017	On traditional Chinese medicine regulation in China: How quality and safety of use are insured	(Q. L. Hu & Calduch, 2017)
Editorial commentary	2008	Survey and practice of reporting quality of randomized controlled clinical trials on traditional Chinese medicine	(李廷谦, 毛兵, 王刚, 常静, & 王蕾, 2008)
Editorial commentary	2017	Determination of Quality Markers is Basis for Establishing Quality Standard and Control of Chinese Herbal Medicines	(C. X. Liu, 2017)
Editorial commentary	2017	Quality Marker Concept Inspires the Quality Research of Traditional Chinese Medicines	(D. A. Guo, 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Editorial commentary	2015	A holistic approach to the quality control of traditional Chinese medicines	(D. A. Guo et al., 2015)
Editorial commentary	2017	On traditional Chinese medicine regulation in China: How quality and safety of use are insured	(Q. L. Hu & Calduch, 2017)
Editorial commentary	2008	Survey and practice of reporting quality of randomized controlled clinical trials on traditional Chinese medicine	(李廷谦 et al., 2008)
Clinical trial	2007	Administration and quality control of large-scale clinical trials of traditional Chinese medicine	(H. Shang et al., 2007)
Clinical trial	2021	Comparison of the effect of traditional Chinese medicine injection combined with chemotherapy and chemotherapy alone on the prognosis, quality of life and immune function in patients with ovarian carcinoma: A protocol for systematic review and network meta-analysis	(X. Xu, L. Zhu, & L. Long, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical review of registrations	2021	Calling for improved quality in the registration of traditional Chinese medicine during the public health emergency: a survey of trial registries for COVID-19, H1N1, and SARS	(Kuang et al., 2021)
Clinical not quality related	2021	Association of Traditional Chinese Medicine Body Constitution and Health-Related Quality of Life in Female Patients with Systemic Lupus Erythematosus: A Cross-Sectional Study	(N. S. Lai et al., 2021)
Clinical not quality related	2021	Dietary supplementation with daidzein and Chinese herbs, independently and combined, improves laying performance, egg quality and plasma hormone levels of post-peak laying hens	(L. Zhang et al., 2021)
Clinical not quality related	2022	Effect of Combining Traditional Chinese Medicine with Hormonal Therapy on Quality of Life and Tumour Markers of Prostate Cancer Patients	(Gai, Li, & Liu, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2022	Effect of probiotics and Chinese medicine polysaccharides on meat quality, muscle fibre type and intramuscular fat deposition in lambs	(C. T. Nie et al., 2022)
Clinical not quality related	2021	Effects of Chinese herbal medicines on the productive performance, nutrient retention, egg quality, immune function of laying hens	(J. Bai & Li, 2022)
Clinical not quality related	2021	Effects of Psychological Intervention on Perioperative Quality of Life and Serum PSA and FPSA Levels of Patients with Prostate Cancer Treated with Integrated Traditional Chinese and Western Medicine	(X. F. Sun et al., 2021)
Clinical not quality related	2021	Improving the quality of clinical research for the prevention and treatment of COVID-19 with Traditional Chinese Medicine	(Z. Bian, 2021)
Clinical not quality related	2022	Influence of Integrated Traditional Chinese and Western Medicine Nursing on the Living Quality of	(F. Li, Ji, Du, Zheng, & Wang, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
		Patients with Angina Pectoris under the Concept of Evidence Based Nursing	
Clinical not quality related	2021	Molecular quantification, a new strategy for quality control of Chinese patent medicine containing animal-derived crude drug: Qi She in Jinlong capsule as an example	(C. Li et al., 2022)
Clinical not quality related	2021	Perceived service quality's effect on patient loyalty through patient attitude within the context of traditional Chinese medicine	(H. B. Li, Wang, Xia, & Liu, 2021)
Clinical not quality related	2021	Chinese Herbal Medicine for Chemotherapy-Induced Leukopenia: A Systematic Review and Meta-Analysis of High-Quality Randomized Controlled Trials	(Qing Wang et al., 2021)
Clinical not quality related	2021	Comparison of the effect of traditional Chinese medicine injection combined with chemotherapy and chemotherapy alone on the prognosis, quality of life	(X. N. Xu, L. Zhu, & L. Long, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		and immune function in patients with ovarian carcinoma A protocol for systematic review and network meta-analysis	
Clinical not quality related	2021	Current trends of Chinese herbal medicines on meat quality of pigs. A review	(Y. Cui, Lu, Tian, Deng, & Ma, 2021)
Clinical not quality related	2021	Effect of traditional Chinese medicine (TCM) on survival, quality of life, and immune function in patients with ovarian carcinoma A protocol for systematic review and meta-analysis	(S. X. Ge, Q. Q. Xing, A. Q. Zhang, & Y. C. Wang, 2021)
Clinical not quality related	2022	Effects of Integrated Chinese Traditional Medicine and Conventional Western Medicine on the Quality of Life of Breast Cancer Patients: A Systematic Review and Meta-Analysis	(X. Bai et al., 2022)
Clinical not quality related	2021	Effects of traditional Chinese medicine exercise therapy on cancer-related fatigue, anxiety and sleep	(L. H. Jiang, J. Ouyang, & X. F. Du, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		quality in cancer patients A protocol for systematic review and network meta-analysis	
Clinical not quality related	2022	Efficacy and safety of Chinese herbal medicine for atopic dermatitis: Evidence from eight high-quality randomized placebo-controlled trials	(X. Cai et al., 2022)
Clinical not quality related	2022	Quality of evidence supporting the role of Chinese herbal medicine for the treatment of poststroke depression A protocol for systematic review and meta-analysis	(H. S. Shi et al., 2022)
Clinical not quality related	2022	Health-Related Quality of Life and Utility Scores of Lung Cancer Patients Treated with Traditional Chinese Medicine in China	(L. Liu et al., 2022)
Clinical not quality related	2012	Psychometric properties of the Chinese quality of life instrument (HK version) in Chinese and Western medicine primary care settings	(W. Wong, Lam, Leung, & Zhao, 2012)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2008	Quality of life assessment in clinical research on Chinese medicine: Early experience and outlook	(L. Y. E. Wong & Leung, 2008)
Clinical not quality related	2005	Discussion on design and quality control of clinical trials of traditional Chinese medicine on the basis of Fuhuang Tablets clinical study	(J.-G. Lu, Pan, Cao, Yang, & Zhang, 2005)
Clinical not quality related	1993	EFFECT OF SOME CHINESE TRADITIONAL MEDICINE ON SCAVENGING FREE-RADICAL RETARDING AGING AND IMPROVING QUALITY-OF-LIFE IN THE LIFE ELDERLY	Hanmin et al., 1993
Clinical not quality related	2006	Effect of traditional Chinese medicine in improving quality of life of patients with non-small cell lung cancer in late stage	(LZ Lin, Zhou, & Zheng, 2006)
Clinical not quality related	2021	Effect of traditional Chinese medicine nursing on postoperative patients with gastric cancer and its impact on quality of life	(Yi Zhang, Wang, & Yang, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2006	Effect of traditional Chinese medicine on survival and quality of life in patients with oesophageal carcinoma after esophagectomy	(L. Ping et al., 2006)
Clinical not quality related	2022	Effect of traditional Chinese medicine-based rehabilitation nursing combined with scalp acupuncture on negative emotions and quality of life of patients with stroke: A randomized controlled trial	(J. Xie, Li, Sun, & Cai, 2022)
Clinical not quality related	2021	Effects of traditional Chinese medicine exercise therapy on cancer-related fatigue, anxiety, and sleep quality in cancer patients: A protocol for systematic review and network meta-analysis	(L. Jiang, J. Ouyang, & X. Du, 2021)
Clinical not quality related	2010	Elderly quality of life impacted by traditional Chinese medicine techniques	(Figueira et al., 2010)
Clinical not quality related	2015	Follow-up study in traditional Chinese medicine of reinforcing kidney and resolving stasis and thinking	(K. Ma & Li, 2015)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		of improving women's ability of high-quality fertility and pregnancy	
Clinical not quality related	2022	High-quality trials and pharmacological studies needed as translational evidence for the application of traditional Chinese medicine Lianhua Qingwen against COVID-19	(N. Huang & Li, 2022)
Clinical not quality related	2011	Impact of Chinese herb on quality of life of stable chronic obstructive pulmonary disease: a randomized controlled study	(F. Jiang, Yan, Yang, Song, & Li, 2011)
Clinical not quality related	2013	Influence of Chinese medicine on weight loss and quality of life during radiotherapy in head and neck cancer	(Y.-H. Huang et al., 2013)
Clinical not quality related	2015	Influence of traditional Chinese medicine syndrome groups on quality of life in women with metabolic syndrome	(L. W. Huang, Chen, & Hsu, 2016)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2009	Is the content of the Chinese Quality of Life Instrument (ChQOL) really valid in the context of traditional Chinese medicine in Hong Kong?	(W. Wong, Lam, Leung, & Zhao, 2009)
Clinical not quality related	2022	Levonorgestrel intrauterine devices improve body constitution deviations in the perspective of traditional Chinese medicine and quality of life in patients with chronic pelvic pain and heavy menstrual bleeding	(C.-M. Chen et al., 2022)
Clinical not quality related	2006	Methodological quality assessment of clinical trials in traditional Chinese medicine: the principles of evidence-based medicine	(J.-P. Liu, 2006)
Clinical not quality related	2009	Perceived quality of communication amongst outpatients in western and traditional Chinese medicine clinics in a Chinese population	(Chung, Lau, Wong, Yeoh, & Griffiths, 2009)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2022	Perceived Quality of Traditional Chinese Medicine Care in Community Health Services: A Cross-Sectional Survey in Hangzhou of China	(X. Y. Zhang, Ren, Sun, & Liu, 2022)
Clinical not quality related	2022	Progress in the design and quality control of placebos for clinical trials of traditional Chinese medicine	(Ning Guo et al., 2022)
Clinical not quality related	2020	Quality evaluation recommendation list and interpretation of traditional Chinese medicine clinical practice guidelines	(Xue Bai et al., 2020)
Clinical not quality related	2012	Relationship between Obesity-related Hormone Peptides and Quality of Life in Obese Women among Different Traditional Chinese Medicine Syndrome Groups	(Y.-L. Song et al., 2012)
Clinical not quality related	2021	Sequential therapy for kidney-tonifying via traditional Chinese medicine effectively improves the reproductive potential and quality of life of women	(W. Duan & Cheng, 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		with decreased ovarian reserve: a randomized controlled study	
Clinical not quality related	2013	Study on quality of life of asymptomatic HIV infected persons with traditional Chinese medicine	(L. R. Xu et al., 2013)
Clinical not quality related	2013	The correlation of lab data, hormone peptides, quality of life, and different traditional Chinese medicine syndrome groups in type 2 diabetes patients	(C.-M. Luo et al., 2013)
Clinical not quality related	2012	The correlation of traditional Chinese medicine deficiency syndromes, cancer related fatigue, and quality of life in breast cancer patients	(T.-J. Chien, Song, Lin, & Hsu, 2012)
Clinical not quality related	2014	Therapeutic efficacy and quality of life investigation of traditional Chinese medicine-based therapy of chronic hepatitis B-related liver fibrosis	(J. An, Ni, & Qiao, 2014)
Clinical not quality related	2022	Traditional Chinese medicine formula 01 for nasopharyngeal carcinoma (NPC01) for head &	(Y. W. Li, He, Wang, & Pan, 2022)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		neck cancer and health-related quality of life: a retrospective study	
Clinical not quality related	2021	Use of Traditional Chinese Medicine in Malaysia: A Knowledge and Practice Study among General Population toward Complementary and Alternative Medicine in Relation to Health and Quality of Life in Malaysia	(Mohiuddin et al., 2021)
Clinical not quality related	2021	Quality Appraisal of the Pharmacoeconomic Research Literature about Antivirals: A Comparison between Chinese Medicine and Non-Chinese Medicine	(J. L. Zhang, Bai, & Bian, 2021)
Clinical not quality related	2022	An integrated strategy for anti-inflammatory quality markers screening of traditional Chinese herbal medicine Mume Fructus based on phytochemical analysis and anti-colitis activity	(Z. H. Liu et al., 2022)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2021	Chinese Herbal Medicine for Psoriasis: Evidence From 11 High-Quality Randomized Controlled Trials	(Y. Luo et al., 2021)
Clinical not quality related	2021	HPLC-MS and Network Pharmacology Analysis to Reveal Quality Markers of Huo-Xue-Jiang-Tang Yin, a Chinese Herbal Medicine for Type 2 Diabetes Mellitus	(Q. G. Chen et al., 2021)
Clinical not quality related	2021	Observation on the Improvement of Quality of Life in Patients with Advanced Non-small Cell Lung Cancer by DC-CIK Maintenance Therapy Combined with Traditional Chinese Medicine Therapy	(J. Huang, Zhang, & Zhou, 2021)
Clinical not quality related	2017	Quality of life and self-care in elderly patients with cardiovascular diseases: The effect of a Traditional Chinese Medicine health educational intervention	(Y.-Q. Sun et al., 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Clinical not quality related	2021	The Tongmai Tiaoshen abdominal massage therapy of traditional Chinese medicine improves sleep quality of chronic insomnia patients: A case report	(S. Qi, Lou, & Tan, 2021)
Clinical not quality related	2005	CHANGES OF QUALITY OF LIFE FOR XIAO (ASTHMA) PATIENTS WHO WERE TREATED BY CHINESE MEDICINE	Liu, H. 2005
Chinese article with English abstract	2006	Significance and necessity of developing quality of life questionnaire for cancer patients adapting to traditional Chinese medicine	(J. You, 2006)
Chinese article with English abstract	2007	A fast method for identifying the quality of Chinese medicine injections based on self-organizing maps neural network	(Xue-Song, Chao-Sheng, Yi-Yu, & Hai-Bin, 2007)
Chinese article with English abstract	2017	A strategy of constructing the technological system for quality control of Chinese medicine based on process control and management	(Y. Y. Cheng, Qian, & Zhang, 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2012	Advance in hepatic protective formulations of traditional Chinese medicine and their quality control methods	(Ju, Tong, Wang, Yu, & Xu, 2012)
Chinese article with English abstract	2017	Analysis and countermeasure for quality risk in process of traditional Chinese medicine preparations	(M. Yang, Y. Z. Yang, et al., 2017)
Chinese article with English abstract	2014	Analysis and design of signalling transfer mechanism based on third-party certification: quality prestige index of traditional Chinese medicine enterprises	(G. Yang, Wang, Guo, & Huang, 2014)
Chinese article with English abstract	2012	Analysis and study on quality control methods and modes of traditional Chinese medicine preparations	(Z. Wu et al., 2012)
Chinese article with English abstract	2004	Analysis of bio membrane permeable compounds and quality control in combined prescription of traditional Chinese medicine by immobilized liposome chromatography	(Sheng, Li, Li, Zou, & Kong, 2004)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2010	Analysis of Chinese medicine tablets on coating quality based on support vector machine	(Zai, Shi, & Qiao, 2010)
Chinese article with English abstract	2021	Analysis of innovative drug category 1.2 in traditional Chinese medicine and considerations on quality control of extracts	(X. X. Zhao, 2021)
Chinese article with English abstract	2020	Analysis on quality evaluation and control methods of Chinese medicine polysaccharide	(W.-J. Zhang, Wang, Huang, & Guo, 2020)
Chinese article with English abstract	2019	Application of Chinese medicine quality constant in grades evaluation of Moutan Cortex	(M. Yan et al., 2019)
Chinese article with English abstract	2008	Application of chromatography and related techniques in quality evaluation of traditional Chinese medicine	(Yong Wang, Liang, Hu, & Luo, 2008)
Chinese article with English abstract	2018	Application of fingerprint technology in quality evaluation and process control of traditional Chinese medicine formula granules	(H. Zhang et al., 2018)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2014	Application of multivariate statistical analysis and thinking in quality control of Chinese medicine	(N. Liu, Li, & Li, 2014)
Chinese article with English abstract	2009	Application of near infrared spectroscopy in quality control of excipients of traditional Chinese medicine	(L. Nie, Wang, Li, & Lin, 2009)
Chinese article with English abstract	2021	Application of oscillating chemical fingerprint technology combined with mathematical analysis method in quality control analysis of traditional Chinese medicine and food	(Z.-S. Zhang, Wang, Ye, Pei, & Li, 2021)
Chinese article with English abstract	2002	Application of pattern recognition to quality assessment of the traditional Chinese medicine	(Y.-x. Zhao & Li, 2002)
Chinese article with English abstract	2014	Application of traditional Chinese medicine reference standards in quality control of Chinese herbal pieces	(T. L. Lu, Li, et al., 2014)
Chinese article with English abstract	2020	Application of traditional Chinese medicine (TCM) traceability system based on TCM quality characteristics and HACCP system	(An-Qi et al., 2020)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2017	Application progress on near infrared spectroscopy in quality control and process monitoring of traditional Chinese medicine	(W. Li & Qu, 2017)
Chinese article with English abstract	2005	Application solid phase extraction-ultrasonication with water bath heating in the quality control of traditional Chinese herb Forsythia suspense	(C. Zheng, Zu, Li, & Zhang, 2005)
Chinese article with English abstract	2011	Assessment of therapeutic efficacy on treating advanced non-small cell lung cancer in the aged by Chinese medicine adopting the international questionnaire of quality of life	(M. J. Shan, Han, & You, 2011)
Chinese article with English abstract	2020	Biological research of color and quality evaluation in "quality discrimination by character" of Chinese medicine	(Tian-Rui et al., 2020)
Chinese article with English abstract	2003	Cause and measure of short of quality control on Chinese medicine herbs	(Jiyan Chen, Chen, An, Yu, & Zhan, 2003)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2015	Construction and implementation of quality control index for clinical safety of Chinese medicine injection	(J. Jiang & Xie, 2015)
Chinese article with English abstract	2022	Construction of quality evaluation strategy for Chinese medicine based on ambient mass spectrometry	(C. J. Lai, Qiu, Wei, & Chen, 2022)
Chinese article with English abstract	2012	Correlation between physical characteristics of sticks and quality of traditional Chinese medicine pills prepared by plastic moulded method	(Ling Wang, Xian, Hong, Lin, & Feng, 2012)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: modular identification of Tongren Niuhuang Qingxin Pills based on efficacy with chemical properties	(Lei et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: online NIR quality control research on boiling time during extraction process	(J. Q. Zeng et al., 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: process quality control method of Suhuang Zhike Capsules intermediate based on physical properties of powder and granules	(M.-L. Zhu et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: quality control method of ginkgo leaves extract material based on powder physical properties	(J. Zhang et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: quality control method of Huangjing Zanyu Capsules based on chemical properties of characteristic components	(J. Y. Zhu et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: quality control of	(J.-Q. Zeng et al., 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		Tongren Niuhuang Qingxin Pills in texture and sensory attributes	
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: study on NIR field detection method of chemical properties of moisture in Tongren Niuhuang Qingxin Pills	(Y. N. Wei et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: visualization of blending process for rare medicines in Tongren Niuhuang Qingxin Pills based on spatial distribution uniformity	(F. Y. Zhang et al., 2021)
Chinese article with English abstract	2021	Critical quality attribute assessment of big brand traditional Chinese medicine: visualization method for quality control of Ginkgo Leaves Tablets based on spatial distribution uniformity	(L. Lin et al., 2021)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2018	Current situations and problem analysis of influencing factors of traditional Chinese medicine tablets on forming quality	(Y.-N. Li et al., 2018)
Chinese article with English abstract	2021	Data collection, quality and evidence formation for human use experience of traditional Chinese medicine	(Z. Q. Yang et al., 2021)
Chinese article with English abstract	2019	Design and development of sustained and controlled release preparations in traditional Chinese medicine based on quality by design(QbD)	(Y. F. Wang, Zhu, Wu, & Li, 2019)
Chinese article with English abstract	2016	Development and Quality Evaluation of Evidence-based Clinical Practice Guidelines of Chinese Medicine	(YR Jiang & Chen, 2016)
Chinese article with English abstract	2018	Development of bioassay method in quality control of traditional Chinese medicine	(Y. You, Liao, & Huang, 2018)
Chinese article with English abstract	2013	Development of quality traceability system of traditional Chinese medicine	(Y. Cai, Hu, Ni, & Wang, 2013)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2017	Development of whole process quality control and management system of traditional Chinese medicine decoction pieces based on traditional Chinese medicine quality tree	(W. K. Yu et al., 2017)
Chinese article with English abstract	2005	Discussion of relationship between quality of life and clinical effect assessment of malignant tumour treated with traditional Chinese medicine	(Que et al., 2005)
Chinese article with English abstract	2012	Discussion on establishment of quality control system for intensive hospital monitoring on traditional Chinese medicine injections	(J. J. Jiang & Xie, 2012)
Chinese article with English abstract	2017	Discussion on research thinking of traditional Chinese medicine standardization system based on whole process quality control	(L. Dong et al., 2017)
Chinese article with English abstract	2017	Effect and regulation of drying on quality of traditional Chinese medicine pills	(Y. R. Qi et al., 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2011	Effect of Chinese medicine comprehensive regimen as the maintenance therapy on time to progression and quality of life of patients with advanced non-small-cell lung cancer	(Yi Jiang, Liu, & Li, 2011)
Chinese article with English abstract	2008	Effect of traditional Chinese medicine on quality of life and survival period in patients with progressive gastric cancer	(X. Liu & Hua, 2008)
Chinese article with English abstract	2012	Establishing quality assurance system of processed Chinese medicine to ensure clinical effect of traditional Chinese medicine	(Y. Xiao et al., 2012)
Chinese article with English abstract	2013	Establishment and application of "multi-dimensional structure and process dynamic quality control system" in preparation products of traditional Chinese medicine (II)	(J. F. Gu, Zhang, Feng, Wu, & Jia, 2013)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2013	Establishment and application of "multi-dimensional structure and process dynamic quality control technology system" in preparation products of traditional Chinese medicine (I)	(J. F. Gu, Feng, Zhang, Wu, & Jia, 2013)
Chinese article with English abstract	2012	Establishment of Dao-Di index and its significance in quality control and rational usage of Chinese medicine	(X. Xiao, Wang, Yan, & Lv, 2012)
Chinese article with English abstract	2021	Evaluation on review quality management and progress and suggestions of reform in traditional Chinese medicine review	(N. An & Han, 2021)
Chinese article with English abstract	2021	Expert consensus on key issues of quality control in clinical trials of new drugs of traditional Chinese medicine	(W. A. Yuan et al., 2021)
Chinese article with English abstract	2007	Exploration of quality control of inorganic elements in Chinese herbal medicines for stimulating blood	(Mang, Fan, Wang, Tu, & Wang, 2007)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		circulation and relaxing muscles and joints by atomic absorption spectrophotometry	
Chinese article with English abstract	2017	Explore and analyse influence factors of quality control on traditional Chinese medicine preparation	(Y. Liu, Feng, & Jia, 2017)
Chinese article with English abstract	2021	Formulation of technical guidelines in line with characteristics and principles of traditional Chinese medicine changes to improve quality of such preparations--interpretation of technical guidelines for the study of pharmaceutical changes in traditional Chinese medicines	(C. M. Yang, Zhao, Qu, & Zhou, 2021)
Chinese article with English abstract	2005	Fuzzy neural network classifier for fast evaluating the quality of Chinese traditional medicine products using near infrared spectroscopy	(X.-S. LIU & CHENG, 2005)
Chinese article with English abstract	2019	High quality and superior effect of Dachuanxiong Formula based on quality constant grading evaluation technology of Chinese medicine pieces	(J. Shi et al., 2019)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2012	Investigation on production process quality control of traditional Chinese medicine--Banlangen granule as an example	(M. Tan et al., 2012)
Chinese article with English abstract	2021	Management system and development strategy of quality Chinese medicine	(L.-L. Dong et al., 2021)
Chinese article with English abstract	2012	Method for discriminating key quality control indicators of concentrated solution before traditional Chinese medicine ethanol precipitation	(A. Yan, Gong, & Qu, 2012)
Chinese article with English abstract	2012	New idea of traditional Chinese medicine quality control based on "composition structure" theory	(D. Liu, Jia, & Yu, 2012)
Chinese article with English abstract	2011	Novel Approach for Quality Evaluation of Traditional Chinese Medicine Based on Integrated Selected-ion Chromatograms	(Y. F. Zhang, Fan, & Qu, 2011)
Chinese article with English abstract	2015	On Chinese medicine quality precision in expectation	(R. B. Shi, Wang, & Lv, 2015)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2011	On the necessity of developing quality of life instruments in traditional Chinese medicine	(Z. K. Hou et al., 2011)
Chinese article with English abstract	2019	Overview and prospects of traditional Chinese medicine blending technology oriented by quality consistency	(X.-R. Xu et al., 2019)
Chinese article with English abstract	2016	Physical fingerprint for quality control of traditional Chinese medicine extract powders	(Y. Zhang et al., 2016)
Chinese article with English abstract	2021	Preparation of personalized traditional Chinese medicine condensed water pill without excipients based on correlation between concentrate viscosity and moulding quality	(X. Zhang et al., 2021)
Chinese article with English abstract	2004	Pressurized solvent extraction in quality control of Chinese herb	(Peng Li, Li, Fu, Kan, & Wang, 2004)
Chinese article with English abstract	2007	Probe into innovation and development of pattern of quality control and evaluation for Chinese medicine	(X.-H. Xiao, Jin, Zhao, Xiao, & Wang, 2007)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2014	Problems in quality standard research of new traditional Chinese medicine compound	(G. Zhou & He, 2014)
Chinese article with English abstract	2008	Prospects of the development of quality control technologies for traditional Chinese medicine	(X. Liang, Feng, Jin, Guo, & Xu, 2008)
Chinese article with English abstract	2020	Protoplast and its application in molecular mechanism of quality formation of traditional Chinese medicine	(C. Jiang, Jie, Qing-Hua, Yun-Tong, & Jin, 2020)
Chinese article with English abstract	2007	Quality appraisal of systematic reviews or meta-analysis on traditional Chinese medicine published in Chinese journals	(J. Liu & Xia, 2007)
Chinese article with English abstract	2008	Quality assessment of the report of randomized controlled trials on treatment of liver carcinoma with traditional Chinese medicine	(Ying Zhang, Zhang, & Chang, 2008)
Chinese article with English abstract	2017	Quality by design approaches for pharmaceutical development and manufacturing of Chinese medicine	(B. Xu et al., 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2022	Quality control mode based on engineering quality view of Chinese medicine pharmacy	(Z. F. Wu et al., 2022)
Chinese article with English abstract	2003	Quality control of Chinese patent medicine flavonol glycoside in Ginkgo biolba extract with micellar, electrokinetic capillary chromatography	(Y. Deng, Yuan, Jin, & Lin, 2003)
Chinese article with English abstract	2000	Quality control of Chinese traditional medicine aconitum sinomontanum Nakai by capillary electrophoresis	(R. Fan et al., 2000)
Chinese article with English abstract	2016	Quality evaluation method for Chinese medicine based on color grading	(M. F. Xu, Wu, Liu, Shi, & Qiao, 2016)
Chinese article with English abstract	2020	Quality evaluation of angelica broken wall powder based on QbD concept of traditional Chinese medicine	(Z. Luo, Deng, Zhang, Fang, & Cheng, 2020)
Chinese article with English abstract	2014	Quality evaluation of guizhi fuling capsule using self-control method of reference Chinese medicine preparation	(Geng et al., 2014)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2010	Quality evaluation system for the oral sustained- and controlled-release drug delivery systems of traditional Chinese medicine	(Y. F. Wei, Lin, Zhang, & Feng, 2010)
Chinese article with English abstract	2010	Quality inspection of clinical research in traditional Chinese medicine	(R. Li, Weng, Tian, Li, & Lu, 2010)
Chinese article with English abstract	2018	Quality process control system of Chinese medicine preparation based on "holistic view"	(Y. Q. Wang et al., 2018)
Chinese article with English abstract	2013	Rapid screening and quality evaluation for the harmful substance 5-hydroxymethyl furfural in commercially available traditional Chinese medicine injection using LC-MS/MS method	(Zang et al., 2013)
Chinese article with English abstract	2010	Relationship between quality of life and basic syndromes of traditional Chinese medicine in patients with posthepatitic cirrhosis	(Q. Zhang, Wang, & Liu, 2010)
Chinese article with English abstract	2014	Reliability theory based on quality risk network analysis for Chinese medicine injection	(Z. Li, Kang, & Fan, 2014)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2019	Research on grades evaluation of Glycyrrizae Radix et Rhizoma Praeparata Cum Melle based on Chinese medicine quality constant	(Z. Deng et al., 2019)
Chinese article with English abstract	2019	Research progress on quality control methods of traditional Chinese medicine glues	(W. L. Li et al., 2019)
Chinese article with English abstract	2016	Research progress on standardization study of NIR spectroscopy-based method for quality control of traditional Chinese medicine	(W. L. Li & Qu, 2016)
Chinese article with English abstract	2014	Research situation of effects of sulfur fumigation on quality of traditional Chinese medicine	(T. L. Lu, Ning, et al., 2014)
Chinese article with English abstract	2010	Some issues to notice in the research and quality evaluation of external preparations of traditional Chinese medicine	(Jin, 2010)
Chinese article with English abstract	2017	Status, problems, and warranty strategy of quality uniformity for traditional Chinese medicine preparations	(L.-H. Zeng et al., 2017)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2014	Strategies and key technologies for risk control and management in quality of Chinese medicine injections based on integrated pharmacology	(X. P. Zhao, Kang, Tang, & Li, 2014)
Chinese article with English abstract	2014	Strategies for elaboration of comprehensive quality standard system on traditional Chinese medicine	(W. Y. Wu & Guo, 2014)
Chinese article with English abstract	2009	Strategies on the Quality Control and DMPK Studies of Traditional Chinese Medicine	(M. Ye & Guo, 2009)
Chinese article with English abstract	2019	Studies on the methodology for quality control in Chinese medicine manufacturing process based on knowledge graph	(Y. Zhong, Ru, Zhang, & Cheng, 2019)
Chinese article with English abstract	2020	Study of intelligent manufacturing quality digitalization of traditional Chinese medicine and practice on Compound Danshen Dripping Pills	(H.-S. Xiong et al., 2020)
Chinese article with English abstract	2013	Study on quality control of Houttuynia Cordata, a traditional Chinese medicine by fingerprint combined	(B. He, Liu, Tian, Li, & Yang, 2013)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
		with quantitative analysis of multi-components by single marker	
Chinese article with English abstract	2007	Study on quality control of traditional Chinese medicine ginseng injection with Fourier transform infrared spectroscopy	(J.-b. Chen, Zhou, Sun, Yu, & Xu, 2007)
Chinese article with English abstract	2003	The application of Fourier transform infrared spectroscopy on the quality control of traditional Chinese medicine formula particles	(H. Huang, Jing, Qin, Zhou, & Sun, 2003)
Chinese article with English abstract	2013	The development of quality-of-life questionnaire of Chinese medicine for postoperative patients with colorectal cancer and item screening	(X. Fan et al., 2013)
Chinese article with English abstract	2019	The Methodological Quality assessment of Current Traditional Chinese Medicine's Clinical Trials	(Z. Cui, Liu, Cai, & Bian, 2019)
Chinese article with English abstract	2015	The technological innovation strategy for quality control of Chinese medicine based on Big Data	(Z. H. Li, Qian, & Cheng, 2015)

TABLE ALR 1 FIRST PHASE GENERAL LITERATURE REVIEW: 207 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Chinese article with English abstract	2019	Third investigation and analysis of quality control situation of intensive care unit in traditional Chinese medicine hospitals in Sichuan Province	(J. Chen et al., 2019)
Chinese article with English abstract	2022	Three-dimensional multi-component quality evaluation of Chinese medicine based on proportion consistency of active components: a study of Salvia miltiorrhiza	(D. F. Yang & Liang, 2022)
Article not accessible	2006	Quality control of traditional Chinese medicine and natural products	(X. Yao, 2006)
Article not accessible	2002	Study concept of traditional Chinese medicine quality standards	(Jiyan Chen et al., 2002)

Appendix to the literature review 2: 152 journal articles excluded from the second phase specific literature review

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not specific enough - instrument discussion	2007	Applications of capillary electrophoresis to the analysis of drug formulations and natural medicines	(Kuwahara, 2007)
Not relevant clinical not CMP related	1999	Effect of acupuncture in keratoconjunctivitis sicca]	(Nepp et al., 1999)
Not relevant clinical not CMP related	2000	Alternative therapies and medical science: designing clinical trials of alternative/complementary medicines--is evidence-based traditional Chinese medicine attainable?	(J. A. Critchley, Y. Zhang, C. C. Suthisisang, T. Y. Chan, & B. Tomlinson, 2000)
Not relevant clinical not CMP related	2003	Structure-activity relationships in allergic contact dermatitis. Part III. The sensitizing capacity of substituted phenanthrenequinones: a quantum-mechanical approach	(Hausen, Elsässer, Krohn, & Loock, 2003)
Not relevant (seed oil food)	2019	Authentication of Eucommia ulmoides Seed Oil Using Fourier Transform Infrared and Synchronous Fluorescence Spectroscopy Combined with Chemometrics	(K. Hu, Huyan, Sherazi, & Yu, 2019)
Not relevant (seed food)	2020	Comprehensive identification of Vitex trifoliafruit and its five adulterants by comparison of micromorphological, microscopic characteristics, and chemical profiles	(X. X. Li et al., 2020)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (pharmaceutical drug policy)	2020	The Impacts of National Centralized Drug Procurement Policy on Drug Utilization and Drug Expenditures: The Case of Shenzhen, China	(L. Chen et al., 2020)
Not relevant (Not CMP)	2015	Evaluation of kefir as a potential probiotic on growth performance, serum biochemistry and immune responses in broiler chicks	(Toghyani, Mosavi, Modaresi, & Landy, 2015)
Not relevant (Not CMP)	2014	Comparing Medicinal Uses of Eggplant and Related Solanaceae in China, India, and the Philippines Suggests the Independent Development of Uses, Cultural Diffusion, and Recent Species Substitutions	(Meyer, Bamshad, Fuller, & Litt, 2014)
Not relevant (Not CMP)	2009	Detection and characterization of synthetic steroidal and non-steroidal anti-inflammatory drugs in Indian ayurvedic/herbal products using LC-MS/TOF	(Savaliya, Prasad, Raijada, & Singh, 2009)
Not relevant (Not CMP)	2013	Discrimination of the Thai rejuvenating herbs Pueraria candollei (White Kwao Khruea), Butea superba (Red Kwao Khruea), and Mucuna collettii (Black Kwao Khruea) using PCR-RFLP	(Wiriyakarun et al., 2013)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (Not CMP)	2018	Luteolin escape mutants of dengue virus map to prM and NS2B and reveal viral plasticity during maturation	(M. H. Peng et al., 2018)
Not relevant (Not CMP)	2020	Isolation and characterisation of N-benzyl tadalafil as a novel adulterant in a coffee-based dietary supplement	(P. Z. Dong et al., 2020)
Not relevant (Not CMP - minerals)	2019	Rapid Identification of Nine Easily Confused Mineral Traditional Chinese Medicines Using Raman Spectroscopy Based on Support Vector Machine	(Ming et al., 2019)
Not relevant (Not CMP - Korean)	2017	BOKP: A DNA Barcode Reference Library for Monitoring Herbal Drugs in the Korean Pharmacopeia	(J. X. Liu et al., 2017)
Not relevant (Not CMP - Indian)	2019	Evaluation of rapid molecular diagnostics for differentiating medicinal Kaempferia species from its adulterants	(Basak, Moolam, Parida, Mitra, & Rangan, 2019)
Not relevant (Not CMP - Indian)	2016	Internal transcribed spacer guided multiplex PCR for species identification of Convolvulus prostratus and Evolvulus alsinoides	(Sharma & Shrivastava, 2016)
Not relevant (Not CMP - Hallucinogens)	2019	Datura and Brugmansia plants related antimuscarinic toxicity: an analysis of poisoning cases reported to the Taiwan poison control centre	(Doan et al., 2019)
Not relevant (Not CMP - food)	2002	Nostoc flagelliforme and faked items retailed in Hong Kong	(But, Cheng, Chan, Lau, & But, 2002)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (Not CMP - food)	2019	Development of conventional PCR and real-time PCR assays to discriminate the origins of Chinese pepper oil and herbal materials from Zanthoxylum	(W. J. Kim et al., 2019)
Not relevant (Not CMP - food)	2018	Sequencing and Analysis of Chrysanthemum carinatum Schousb and Kalimeris indica. The Complete Chloroplast Genomes Reveal Two Inversions and rbcL as Barcoding of the Vegetable	(X. Liu et al., 2018)
Not relevant (Not CMP - Food)	2004	Adulteration of drugs in food - Glucocorticoids, anorexics and hypnotic-sedatives (I)	(Tsai, Wei, Wu, Chen, & Wen, 2004)
Not relevant (narrative)	2001	Herbal supplements: Considerations for the athletic trainer	(Winterstein & Storrs, 2001)
Not relevant (Marketing discussion)	2011	The importance of safety issues in Traditional Chinese Medicine marketing	(A. K. M. Leung & Fong, 2011)
Not relevant (Legal discussion)	2011	Scope of claim coverage in patents of fufang Chinese herbal drugs: Substitution of ingredients	(X. S. Wang, Tian, & Chan, 2011)
Not relevant (insect study)	2017	Species-level identification of the blowfly Chrysomya megacephala and other Diptera in China by DNA barcoding	(D. Y. Qiu et al., 2017)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (genetic study)	2016	Exome Sequencing and Gene Prioritization Correct Misdiagnosis in a Chinese Kindred with Familial Amyloid Polyneuropathy	(H. Chen et al., 2016)
Not relevant (genetic study)	2013	The KAL1 pVal610Ile mutation is a recessive mutation causing Kallmann syndrome	(S. L. Zhang, Xu, Wang, Liu, & Liu, 2013)
Not relevant (genetic characterisation study)	2020	Comparing chloroplast genomes of traditional Chinese herbs Schisandra sphenanthera and S. chinensis	(X. P. Wei et al., 2020)
Not relevant (genetic characterisation study)	2017	A Comprehensive Quality Evaluation System for Complex Herbal Medicine Using PacBio Sequencing, PCR-Denaturing Gradient Gel Electrophoresis, and Several Chemical Approaches	(X. S. Zheng et al., 2017)
Not relevant (genetic characterisation study)	2011	Feed-forward neural network assisted by discriminant analysis for the spectroscopic discrimination of cracked spores Ganoderma lucidum: A prospective biotechnology production tool	(C. W. Lim, Chan, & Visconti, 2011)
Not relevant (genetic characterisation study)	1996	IgA2 genotyping by polymerase chain reaction (PCR) using allele-specific amplification primers	(Takata, Yamamoto, & Ishizu, 1996)
Not relevant (genetic characterisation study)	2019	Cloning of a novel trypsin inhibitor from the Traditional Chinese medicine decoction pieces, Radix Trichosanthis	(Sang et al., 2019)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (genetic characterisation study)	2017	Genetic analysis of drug metabolizing phase-I enzymes CYP3A4 in Tibetan populations	(L. J. Liu et al., 2017)
Not relevant (genetic characterisation study)	2016	Recurrence pattern and TP53 mutation in upper urinary tract urothelial carcinoma	(C. H. Chen et al., 2016)
Not relevant (genetic characterisation study)	2000	Genetic heterogeneity of ribosomal RNA gene and matK gene in Panax notoginseng	(Fushimi, Komatsu, Namba, & Isobe, 2000)
Not relevant (General historical discussion)	2014	A supplement to Prof. Shoji Shibata's achievements: the history of ShAisAi-in Medicines and the reason why Magnolia obovata (old name: Hoogashiwa) was not given a Chinese herbal name in Japan's oldest anthology Man'yoshu	Kinoshita et al., 2014
Not relevant (general clinical not CMP)	2014	Retention of participants in medication-assisted programs in low- and middle-income countries: an international systematic review	(Feelemyer, Des Jarlais, Arasteh, Abdul-Quader, & Hagan, 2014)
Not relevant (General clinical discussion)	2000	Alternative therapies and medical science: Designing clinical trials of alternative/complementary medicines - Is evidence-based traditional Chinese medicine attainable?	(J. Critchley, Y. Zhang, C. C. Suthisisang, T. Y. K. Chan, & B. Tomlinson, 2000)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (General clinical discussion)	2018	Mutation spectrum analysis of Duchenne/Becker muscular dystrophy in 68 families in Kuwait: The era of personalized medicine	(Mohammed et al., 2018)
Not relevant (General clinical discussion)	2006	Traditional Chinese medicine in the treatment of diabetes	(H. L. Zhao, Tong, & Chan, 2006)
Not relevant (General clinical discussion)	2017	Complementary and Alternative Medicine Use in Rheumatoid Arthritis: Considerations for the Pharmacological Management of Elderly Patients	(S. Z. Zhao, Otieno, Akpan, & Moots, 2017)
Not relevant (General clinical discussion)	2012	The Current Acceptance, Accessibility and Recognition of Chinese and Ayurvedic Medicine in the United States in the Public, Governmental, and Industrial Sectors	(Park, Beckman-Harned, Cho, Kim, & Kim, 2012)
Not relevant (General clinical discussion)	2013	High-throughput genotyping system as a robust and useful tool in oncology: Experience from a single institution	(Henriquez-Hernandez et al., 2013)
Not relevant (General clinical discussion)	2016	Genetic variants and haplotypes of the UGT1A9, 1A7 and 1A1 genes in Chinese Han	(X. Q. Zhang et al., 2012)
Not relevant (General clinical discussion)	2016	How much could be saved in Chinese hospitals in procurement of anti-hypertensives and anti-diabetics?	(J. Sun, Ren, & Wirtz, 2016)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (food supplement related)	2017	The Regulatory Framework Across International Jurisdictions for Risks Associated with Consumption of Botanical Food Supplements	(Low, Wong, Yap, De Haan, & Rietjens, 2017)
Not relevant (DNA characterisation study)	2019	A Comparative Analysis of the Chloroplast Genomes of Four Salvia Medicinal Plants	(C. L. Liang et al., 2019)
Not relevant (DNA characterisation study)	2018	Positive Selection Driving Cytoplasmic Genome Evolution of the Medicinally Important Ginseng Plant Genus Panax	(P. Jiang et al., 2018)
Not relevant (Diversity study)	2018	Genetic diversity and population structure of a protected species: Polygala tenuifolia Willd	(Y. Q. Peng et al., 2018)
Not relevant (Clinical discussion)	2017	Apolipoprotein Al rs5070 A/G polymorphism with stroke subtypes in Taiwan	(Hsu & Lee, 2017)
Not relevant (Clinical discussion)	2009	Overdose beliefs and management practices among ethnic Vietnamese heroin users in Sydney, Australia	(Maher & Ho, 2009)
Not relevant (Clinical discussion)	2020	Provider perspectives on general practice in Henan, China: a mixed-methods study	(J. Zhu & Ariana, 2020)
Not relevant (Clinical discussion)	2020	Premature Stroke Secondary to Severe Hypertension Results from Liddle Syndrome Caused by a Novel SCNN1B Mutation	(P. Fan et al., 2020)
Not relevant (Clinical discussion)	2020	A case of unexplained duodenal ulcer and massive gastrointestinal bleed	(Y. R. Luo et al., 2020)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (Clinical discussion)	2020	A combined study on the skeletal vibration of aminopyrine by terahertz time-domain spectroscopy and DFT simulation	(F. Huang, Liu, Xie, Liu, & Sun, 2020)
Not relevant (Clinical discussion)	2019	The production of penicillin in wartime China and Sino-American definitions of normal microbiology	(Brazelton, 2019)
Not relevant (Clinical discussion)	2017	Targeted next generation sequencing in Chinese colorectal cancer patients guided anti-EGFR treatment and facilitated precision cancer medicine	(H. L. Hou et al., 2017)
Not relevant (Clinical discussion)	2020	Qidong Yixin Oral Liquid for Viral Myocarditis: A Systematic Review and Meta-Analysis	(J. Hu, Tan, Wang, He, & Wang, 2020)
Not relevant (Clinical discussion)	2020	Refractory Hypotension Following Elective Total Hip Replacement Surgery in a Patient Treated With Herbal Medicine: A Case Report	(Goh, Zhang, Chee, & Chan, 2020)
Not relevant (Clinical discussion)	2017	Integrative nutrition in thyreoid diseases	(Siedentopp, 2017)
Not relevant (Clinical discussion)	2015	The Comparison of Different Colloid Applications and Traditional Chinese Medicine Nursing in Plasma Replacement Therapy	(X. J. Hu, Li, & Guo, 2015)
Not relevant (Clinical diagnosis related)	2018	Diagnosis of Cushing's Syndrome in the Modern Era	(Nieman, 2018)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (chemical toxicity study)	2015	In vitro genotoxicity tests point to an unexpected and harmful effect of a Magnolia and Aristolochia association	(Nachtergael, Poivre, Belayew, & Duez, 2015)
Not relevant (chemical characterisation study)	2016	Comparing morphological, chemical and anti-diabetic characteristics of Puerariae Lobatae Radix and Puerariae Thomsonii Radix	(K. H. Wong, Razmovski-Naumovski, Li, Li, & Chan, 2015)
Not relevant (chemical characterisation study)	2016	Natural and synthetic flavonoid modulation of TRPC5 channels	(Naylor et al., 2016)
Not relevant (chemical characterisation study)	1999	HPLC analysis of Juzen-taiho-to and its variant formulations and their antimetastatic efficacies	(Saiki et al., 1999)
Not relevant (chemical characterisation study)	2018	Precise species detection of traditional Chinese patent medicine by shotgun metagenomic sequencing	(T. Y. Xin et al., 2018)
Not relevant (chemical characterisation study)	2006	Catalytic roles of CYP2D6.10 and CYP2D6.36 enzymes in mexiletine metabolism: In vitro functional analysis of recombinant proteins expressed in Saccharomyces cerevisiae	(Hanioka et al., 2006)
Not relevant (chemical characterisation study)	2016	Compound Library Screening Identified Cardiac Glycoside Digitoxin as an Effective Growth Inhibitor of Gefitinib-Resistant Non-Small Cell Lung Cancer via Downregulation of alpha-Tubulin and Inhibition of Microtubule Formation	(Y. Z. Zhang et al., 2016)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (chemical characterisation study)	2018	Mechanism of action of cytotoxic compounds from the seeds of Euphorbia lathyris	(Teng et al., 2018)
Not relevant (chemical characterisation study)	2015	Identification of Novel Compounds against an R294K Substitution of Influenza A (H7N9) Virus Using Ensemble Based Drug Virtual Screening	(Tran, Van, Nguyen, & Le, 2015)
Not relevant (chemical characterisation study)	2018	Evaluation of thyme and ajwain as antibiotic growth promoter substitutions on growth performance, carcass characteristics and serum biochemistry in Japanese quails (Coturnix japonica)	(Kheiri, Faghani, & Landy, 2018)
Not relevant (chemical characterisation study)	2008	Chloroplast DNA variation and phylogeographic patterns in the Chinese endemic marsh herb Sagittaria potamogetifolia	(B. Tan et al., 2008)
Not relevant (chemical characterisation study)	2004	Substitution for natural musk in Pien Tze Huang does not affect its hepatoprotective activities	(W. Y. Chan, Chau, Lee, Kwong, & Yew, 2004)
Not relevant (chemical characterisation study)	2017	New homoisoflavonoid analogues protect cells by regulating autophagy	(Gan, Zeng, Li, Zhou, & Li, 2017)
Not relevant (chemical characterisation study)	2016	Anti-allergic potential of Typhonium blumei : Inhibition of degranulation via suppression of PI3K/PLC gamma 2 phosphorylation and calcium influx	(Korinek et al., 2016)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (chemical characterisation study)	2012	The combination of polyalanine expansion mutation and a novel missense substitution in transcription factor FOXL2 leads to different ovarian phenotypes in blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) patients	(J. Y. Fan et al., 2012)
Not relevant (chemical characterisation study)	1998	Sterol synthesis, synthesis of 3 beta-hydroxy-25,26,26,26,27,27,27-heptafluorocholest-5-en-7-one and its effects on HMG-CoA reductase activity in Chinese hamster ovary cells, on ACAT activity in rat jejunal microsomes, and serum cholesterol levels in rats	(Carroll et al., 1998)
Not relevant (chemical characterisation study)	2018	Genotoxicity Evaluation of an Ethanol Extract Mixture of Astragali Radix and Salviae miltiorrhizae Radix	(J. S. Lee, Cho, Lee, & Son, 2018)
Not relevant (chemical characterisation study)	2016	Bamboo tea: reduction of taxonomic complexity and application of DNA diagnostics based on rbcL and matK sequence data	(Horn & Häser, 2016)
Not relevant (chemical characterisation study)	2019	Antiviral effect of saikosaponin B2 in combination with daclatasvir on NS5A resistance-associated substitutions of hepatitis C virus	(W. P. Lee et al., 2019)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (chemical characterisation study)	2012	Study on the Metabolic Characteristics of Aconite Alkaloids in the Extract of Radix aconiti under Intestinal Bacteria of Rat by UPLC/MSn Technique	(Y. Xin, Pi, Song, Liu, & Liu, 2012)
Not relevant (chemical characterisation study)	2018	Drechmeria panacis sp nov., an endophyte isolated from Panax notoginseng	(Y. Yu et al., 2018)
Not relevant (chemical characterisation study)	2006	Screening for pregnane glycosides with immunological activities from the stems of Stephanotis mucronata by high-performance liquid chromatography/tandem mass spectrometry	(X. J. Cao, Tal, Li, Ye, & Pan, 2006)
Not relevant (chemical characterisation study)	2008	Synthesis, radiosynthesis and anticancer activity of beta-elemene tricarbonyl rhenium complex	(Y. F. Ren, Cheng, Liu, Sun, & Shen, 2008)
Not relevant (chemical characterisation study)	2020	The present and future synthetic strategies of structural modifications of sinomenine	(Ng, Coghi, Law, Liu, & Wong, 2020)
Not relevant (chemical characterisation study)	2018	Investigation of the in vivo metabolism of harpagoside and distribution of its metabolites in rats by HPLC-IT-TOF-MSn	(J. Z. Wang et al., 2018)
Not relevant (chemical characterisation study)	2018	The Prophylactic and Therapeutic Effects of Fermented Cordyceps sinensis Powder, Cs-C-Q80, on Subcortical Ischemic Vascular Dementia in Mice	(Y. Chen et al., 2018)
Not relevant (chemical characterisation study)	2014	Chemistry and Biology of Bakuchiol	(S. H. Huang, Huang, Jia, & Hong, 2014)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (chemical characterisation study)	2020	Neural bases for attenuation of morphine withdrawal by Heantos-4: role of l-tetrahydropalmatine	(Ahn et al., 2020)
Not relevant (chemical characterisation study)	2018	Synthesis and anti-tumor activities of novel 7-O-amino acids chrysin derivatives	(D. Liu et al., 2018)
Not relevant (chemical characterisation study)	1997	A new asymmetric synthesis of (+)-(3R, 4S, 5R, 7S)-Neoclausenamide via intramolecular nucleophilic attack of carbon anion onto cyclic sulfate	(J. Q. Wang, Luo, & Tian, 1997)
Not relevant (chemical characterisation study)	2013	Synthesis, Characterization and Antidiabetic Activities of Novel Genipin Derivatives	(Z. W. Li et al., 2013)
Not relevant (chemcial synthesis)	2003	Synthesis of daidzin analogues as potential agents for alcohol abuse	(G. Y. Gao, Li, & Keung, 2003)
Not relevant (animal study)	2019	Effects of stinging nettle (Urtica dioica) powder on laying performance, egg quality, and serum biochemical parameters of Japanese quails	(Moula, Sadoudi, Touazi, Leroy, & Geda, 2019)
Not relevant (animal study)	2020	Specific, sensitive and rapid authentication of donkey-hide gelatine (Colla corii asini) in processed food using an isothermal nucleic acid amplification assay	(Sheu, Huang, Lien, & Lee, 2020)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (animal study)	2016	Rapid identification of bile acids in snake bile using ultrahigh-performance liquid chromatography with electrospray ionization quadrupole time-of-flight tandem mass spectrometry	(J. Zhang et al., 2016)
Not relevant (animal study)	2017	Identification of the Adulterated Asini Corii Colla with Cytochrome c Oxidase Subunit I Gene-based Polymerase Chain Reaction	(H. L. Zuo et al., 2017)
Not relevant (animal study)	2015	Detection of Gelatin Adulteration in Traditional Chinese Medicine: Analysis of Deer-Horn Glue by Rapid-Resolution Liquid Chromatography-Triple Quadrupole Mass Spectrometry	(J. Chen et al., 2015)
Not relevant (animal study)	2020	Rapid identification of cervus antlers by species-specific PCR assay	(Y. Yang et al., 2020)
Not relevant (animal study)	2020	The experimental research on neuroplasticity in rats' hippocampus subjected to chronic cerebral hypoperfusion and interfered by Modified Dioscorea Pills	(H. B. Li, Liang, & Zhou, 2020)
Not relevant (animal study)	2019	Development of a Species-Specific Polymerase Chain Reaction-Based Technology for Authentication of Asini Corii Colla and Taurus Corii Colla	(L. Q. Chen et al., 2019)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (animal study)	2019	Simultaneous detection of four flavonoids and two alkaloids in rat plasma by LC-MS/MS and its application to a comparative study of the pharmacokinetics between Abri Herba and Abri mollis Herba extract after oral administration	(R. Liu, W. Yan, et al., 2019)
Not relevant (animal study)	2010	Tortoise DNA Detection from Highly Processed Tortoise Shell Using SINE Element	(P. Lv et al., 2010)
Not relevant (animal study)	2020	Harnessing Multiplex Polymerase Chain Reaction Assay for Convenient and Simultaneous Differentiation of Testudinis Carapax et Plastrum from Trionycis Carapax	(Jiao et al., 2020)
Not relevant (animal study)	2016	Molecular identification of antelope horn by melting curve analysis	(Tong et al., 2016)
Not relevant (animal study)	2019	Harnessing multiplex PCR assay targeting specific mitochondrial DNA elements for simultaneous identification of antelope species in Cornu Saigae Tataricae	(Y. F. Chen, Y. Y. Yang, et al., 2019)
Not relevant (animal study)	2019	Identification of the original species of cubilose based on DNA barcode	(S. Wang, Guo, & Hou, 2019)
Not relevant (animal studies)	2012	Metabolomic profiling of the flower bud and rachis of Tussilago farfara with antitussive and expectorant effects on mice	(Z. Y. Li et al., 2012)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Not relevant (animal products)	2016	Perception, Price and Preference: Consumption and Protection of Wild Animals Used in Traditional Medicine	(Z. Liu et al., 2016)
Not relevant (animal products)	2004	An extremely sensitive species-specific ARMS PCR test for the presence of tiger bone DNA	(Wetton, Tsang, Roney, & Spriggs, 2004)
Not relevant (animal products)	2018	DNA Barcoding for the Identification and Authentication of Animal Species in Traditional Medicine	(F. Yang et al., 2018)
Not relevant (animal products)	2017	Species-specific identification of collagen components in Colla corii asini using a nano-liquid chromatography tandem mass spectrometry proteomics approach	(X. Li et al., 2017)
Not relevant (animal products)	2018	DNA barcoding of traded shark fins, meat and mobulid gill plates in Singapore uncovers numerous threatened species	(Wainwright et al., 2018)
Not relevant (animal products)	2009	Geckos in traditional medicine: forensic implications	(A. M. Bauer, 2009)
Not relevant (animal products)	2019	A strategy for identifying species-specific peptide biomarkers in deer-hide gelatin using untargeted and targeted mass spectrometry approaches	(R. Liu, Y. Huang, et al., 2019)
Not relevant (animal products)	2004	An extremely sensitive species-specific ARMs PCR test for the presence of tiger bone DNA (vol 126, pg 137, 2002)	(Wetton et al., 2004)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Not relevant (animal products)	2017	Simultaneous determination of nine kinds of dominating bile acids in various snake bile by ultrahigh-performance liquid chromatography with triple quadrupole linear iontrap mass spectrometry	(J. Zhang et al., 2017)
Not relevant (animal products)	2008	Study on Cornu Bos grunniens from Tibet substituting Cornu Rhinoceri]	(M. Q. Shen, Ye, Ding, & Luo, 2008)
Not relevant (animal products)	2020	DNA fingerprinting identification of bile power(bile)medicines	(N. Tian et al., 2020)
Not relevant	2019	Potentially Cardiotoxic Diterpenoid Alkaloids from the Roots of Aconitum carmichaelii	(Zong et al., 2019)
Not relevant	2003	Adulteration of dietary supplements	(Cole & Fetrow, 2003)
Not relevant	2008	Inhibitory effect on alpha-glucosidase by Adhatoda vasica Nees	(H. Gao, Huang, Gao, Li, et al., 2008)
Not relevant	2016	Mangiferin: A review of sources and interventions for biological activities	(Jyotshna, Khare, & Shanker, 2016)
Not related to quality issue	1996	Pharmacological and biochemical actions of simple coumarins: Natural products with therapeutic potential	(Hoult & Paya, 1996)
Not related to CMP - Indonesian medicine	2016	Analysis of adulterants in a traditional herbal medicinal product using liquid chromatography-mass spectrometry-mass spectrometry	(Melchart et al., 2016)
Non relevant topic	2019	Formononetin: A Review of Its Anticancer Potentials and Mechanisms	(Tay et al., 2019)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Non relevant topic	2014	Testosterone deficiency: a historical perspective	(Nieschlag & Nieschlag, 2014)
Non relevant topic	2010	Microsomal Cytochrome P450-Mediated Metabolism of Protopanaxatriol Ginsenosides: Metabolite Profile, Reaction Phenotyping, and Structure-Metabolism Relationship	(H. P. Hao et al., 2010)
Non relevant topic	2006	Further studies with a cell immortalization assay to investigate the mutation signature of aristolochic acid in human p53 sequences	(Feldmeyer et al., 2006)
Non relevant topic	2006	Mechanism of triptolide-induced apoptosis: effect on caspase activation and Bid cleavage and essentiality of the hydroxyl group of triptolide	(Xianxi et al., 2006)
Non relevant topic	2016	Sulfated modification of the polysaccharide from Sphallerocarpus gracilis and its antioxidant activities	(Y. F. Xu et al., 2016)
Non relevant topic	2004	The interactive effects of hepatic lipase gene promoter polymorphisms with sex and obesity on high-density-lipoprotein cholesterol levels in Taiwanese Chinese	(Ko, Hsu, Hsu, Ko, & Lee, 2004)
Non relevant topic	2012	Comparison of the hepatoprotective activity between cultured Cordyceps militaris and natural Cordyceps sinensis	(B. S. Wang, Lee, Chen, Yu, & Duh, 2012)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Non relevant topic	2001	Irreversible block of human heart (hH1) sodium channels by the plant alkaloid lappaconitine	(Wright, 2001)
Non relevant topic	2017	What risks do herbal products pose to the Australian community?	(Byard, Musgrave, Maker, & Bunce, 2017)
Non relevant topic	2002	Antiplatelet aggregation activity of diterpene alkaloids from Spiraea japonica	(L. Li et al., 2002)
Non relevant topic	2019	A review of the application of near-infrared spectroscopy to rare traditional Chinese medicine	(L. H. Yin et al., 2019)
Non relevant (Historical)	2010	Thinking of current situation about decreasing, abolishing and substitution of Chinese medicine species in Shanghanlun	(Ling & Zhou, 2010)
Non relevant (drug discovery)	2010	Merging traditional Chinese medicine with modern drug discovery technologies to find novel drugs and functional foods	(Graziose, Lila, & Raskin, 2010)
Doesn't describe adulteration only analytical development	2006	Chromatographic fingerprint analysis - a rational approach for quality assessment of traditional Chinese herbal medicine	(P. S. Xie et al., 2006)
Doesn't describe adulteration only analytical development	2020	Strategies to approach high performance in Cr3+-doped phosphors for high-power NIR-LED light sources	(Z. W. Jia et al., 2020)
Doesn't describe adulteration only analytical development	2008	alpha-Glucosidase inhibitory effect by the flower buds of Tussilago farfara L.	(H. Gao, Huang, Gao, Xu, et al., 2008)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED

Exclusion Reason	Publication Year	Article Title	Citation
Doesn't describe adulteration only analytical development	1999	Honokiol and magnolol increase the number of [H-3]muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites	(Squires et al., 1999)
Doesn't describe adulteration only analytical characterisation	2012	New Tricks for an Old Natural Product: Discovery of Highly Potent Evodiamine Derivatives as Novel Antitumor Agents by Systemic Structure-Activity Relationship Analysis and Biological Evaluations	(G. Q. Dong et al., 2012)
Chinese article English abstract only	2014	Development of Chinese herbal pieces and analysis of problems of total quality management	(J. Wang, Qiao, Lin, & Chen, 2014)
Chinese article English abstract only	2019	Rapid chemical profiling of Artemisiae Scopariae Herba using reversed phase liquid chromatography-hydrophilic interaction liquid chromatography-predictive multiple reaction monitoring	(Y. Cao et al., 2019)
Chinese article English abstract only	2020	Permeation mechanism of phenolic acid components from traditional Chinese medicine on PES membrane separation process	(S. S. Huang et al., 2020)
Chinese article English abstract only	2016	Application of microscopic spectroscopy in quality control of Niuhuang Qingxin pills	(L. X. Nie et al., 2016)

TABLE ALR 2 SECOND PHASE SPECIFIC LITERATURE REVIEW: 152 ARTICLES EXCLUDED			
Exclusion Reason	**Publication Year**	**Article Title**	**Citation**
Already included in phase one review	2016	Quality Control and Complication Screening Programme of Chinese Medicinal Drugs at the First German Hospital of Traditional Chinese Medicine - A Retrospective Analysis	(Melchart et al., 2016)
Already included in phase one review	2009	HPTLC for Quality Control of Traditional Chinese Medicines: Identification and Detection of Adulteration	(Z. Li & Reich, 2009)

Appendix to the literature review 3: 37 review articles included in the first phase general literature review

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
Analytical methods	QC	2006	Quality control of Cordyceps sinensis, a valued traditional Chinese medicine	(S. P. Li et al., 2006)
Markers	Improvements	2021	Recent Advances in Molecular Marker-Assisted Breeding for Quality Improvement of Traditional Chinese Medicine	(Z. Q. Song & Li, 2021)
Pharmacovigilance	QC	2016	Quality Control and Complication Screening Programme of Chinese Medicinal Drugs at the First German Hospital of Traditional Chinese Medicine - A Retrospective Analysis	(Melchart et al., 2016)
QAS	Data	2010	The Reporting Quality, Scientific Rigor, and Ethics of Randomized Placebo-Controlled Trials of Traditional Chinese Medicine Compound Formulations and the Differences Between Chinese and Non-Chinese Trials	(Y. Q. Zhong et al., 2010)
QAS	Review	2019	A Chinese medicine formula (Jinqi Jiangtang Tablet): A review on its chemical constituents, quality control, pharmacokinetics studies, pharmacological properties and clinical applications	(Y. Liu et al., 2019)
QAS	Review	2019	Red Yeast Rice: A Systematic Review of the Traditional Uses, Chemistry, Pharmacology, and Quality Control of an Important Chinese Folk Medicine	(B. Zhu et al., 2019)

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
QAS	Strategy	2016	The spectrum-effect relationship-a rational approach to screening effective compounds, reflecting the internal quality of Chinese herbal medicine	(C. S. Zhu et al., 2016)
QA	Data	2018	Assessing the methodological and reporting quality of network meta-analyses in Chinese medicine	(F. W. Yang et al., 2018)
QA	Standards	2020	Quality standard of traditional Chinese medicines: comparison between European Pharmacopoeia and Chinese Pharmacopoeia and recent advances	(F. Leong et al., 2020a)
QA	Strategy	2020	Analytical strategies for the discovery and validation of quality-markers of traditional Chinese medicine	(J. L. Ren et al., 2020)
QA	Strategy	2013	Application of Plant Metabonomics in Quality Assessment for Large-Scale Production of Traditional Chinese Medicine	(Ning et al., 2013)
QA	Strategy	2007	Quality assurance of Chinese Herbal Medicines (CHMs)	(Z. Z. Zhao et al., 2007)
QC	Fingerprinting	2020	Quality evaluation of traditional Chinese medicines based on fingerprinting	(X. Y. Liu, W. W. Jiang, et al., 2020)

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
QC	Marker	2019	Quality Markers of Traditional Chinese Medicine: Concept, Progress, and Perspective	(Y. Z. Li et al., 2019)
QC	Marker	2019	Prediction of quality markers of traditional Chinese medicines based on network pharmacology	(Y. L. Wang et al., 2019)
QC	Markers	2022	Research progress on quality markers of traditional Chinese medicine	(H. B. Zhang et al., 2022)
QC	Procedure	2009	Qualitative and quantitative analysis in quality control of traditional Chinese medicines	(X.-m. Liang et al., 2009)
QC	Regulation	2010	Modern European Monographs for Quality Control of Chinese Herbs	(R. Bauer & Franz, 2010)
QC	Review	2022	Traditional uses, phytochemical, pharmacology, quality control and modern applications of two important Chinese medicines from Rosa laevigata Michx.	(Quan et al., 2022)
QC	Review	2013	Quality control of traditional Chinese Medicines: a review	(X. Y. Song, Li, Shi, Jin, & Chen, 2013)

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
QC	Strategy	2022	Key quality factors for Chinese herbal medicines entering the EU market	(M. Wang et al., 2022)
QC	Strategy	2021	How to identify Material basis-Quality markers more accurately in Chinese herbal medicines from modern chromatography-mass spectrometry data-sets: Opportunities and challenges of chemometric tools	(M. He & Zhou, 2021)
QC	Strategy	2018	Discovery of quality control markers from traditional Chinese medicines by fingerprint-efficacy modeling: Current status and future perspectives	(C. Zhang et al., 2018)
QC	Strategy	2018	Advanced strategies for quality control of Chinese medicines	(J. Zhao et al., 2018)
QC	Strategy	2017	Novel strategy for quality consistency evaluation of Chinese medicine YIQING tablet that combines the simultaneous quantification and screening of ten bioactive constituents	(Gong et al., 2017)
QC	Strategy	2017	A New Concept on Quality Marker for Quality Assessment and Process Control of Chinese Medicines	(C. X. Liu et al., 2017)

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
QC	Strategy	2017	Approaches to establish Q-markers for the quality standards of traditional Chinese medicines	(W. Z. Yang et al., 2017)
QC	Strategy	2017	Quantitative analysis of multi-components by single marker-a rational method for the internal quality of Chinese herbal medicine	(C. S. Zhu et al., 2017)
QC	Strategy	2013	Intestinal absorption and bioavailability of traditional Chinese medicines: a review of recent experimental progress and implication for quality control	(J. Y. Liu et al., 2013)
QC	Strategy	2011	The Quality Control and Pharmaceutical Analysis of Non-volatile and Volatile Bioactive Compounds in Chinese Herbal Medicine by HPLC and GC	(X. D. Yuan et al., 2011)
QC	Strategy	2010	Recent analytical approaches in quality control of traditional Chinese medicines-A review	(Y. Jiang, David, Tu, & Barbin, 2010)
QC	Strategy	2010	Chromatographic fingerprinting and related chemometric techniques for quality control of traditional Chinese medicines	(Y. Z. Liang et al., 2010)
QC	Strategy	2010	Application of Mid-Infrared Spectroscopy in the Quality Control of Traditional Chinese Medicines	(S. Q. Sun et al., 2010)

TABLE ALR 3 FIRST PHASE GENERAL LITERATURE REVIEW: 37 REVIEW ARTICLES INCLUDED				
Primary Quality concern **QC = Quality Control** **QA = Quality Assurance** **QAS – Quality Assurance**	**Secondary Quality concern**	**Publication Year**	**Article Title**	**Citation**
QC	Strategy	2009	Quality and safety of Chinese herbal medicines guided by a systems biology perspective	(J. S. Wang et al., 2009)
QC	Strategy	2009	Understanding the traditional aspect of Chinese medicine in order to achieve meaningful quality control of Chinese Materia Medica	(P. S. Xie & Leung, 2009)
QC	Strategy	2009	Identification and Quality Control of Chinese Medicine Based on the Fingerprint Techniques	(X. K. Zhong, Li, & Jiang, 2009)
Standards	Clinical practice	2020	Quality and Specific Concerns of Clinical Guidelines for Integrated Chinese and Western Medicine: A Critical Appraisal	(Xu Zhou, Xu, Ren, & Chen, 2020)

Appendix to the literature review 4: 122 journal articles included in the first phase general literature review

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
Characterisation	Strategy	2011	Top-geoherbs of traditional Chinese medicine: common traits, quality characteristics and formation	(L. Huang, Guo, Ma, Gao, & Yuan, 2011)
Classification	Pharmaceutical quality	2013	Establishing the Pharmaceutical Quality of Chinese Herbal Medicine: A Provisional BCS Classification	(S. Y. K. Fong et al., 2013)
Classification	Pharmaceutical quality	2012	Mining the Associations between Pharmic Quality and Ingredients of Traditional Chinese Medicines	(X. Wu, Wang, Chen, Zhu, & Long, 2012)
Clinical practice	Data	2018	Using the RIGHT statement to evaluate the reporting quality of clinical practice guidelines in traditional Chinese medicine	(Y. Xia et al., 2018)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
Clinical trial	Quality of life	2013	Chinese medicine improves postoperative quality of life in endometriosis patients: A randomized controlled trial	(Liao, Wu, Yu, & Zhang, 2017)
Education	Study challenges	2009	Meeting the Challenges of Studying Chinese Medicine: Quality, Pharmacology, and Clinical Issues	(Che, 2009)
QA	Strategy	2016	LC-MS-Based Quality Assessment of a Traditional Chinese Medicine YANG XIN Formulation	(Almalki et al., 2016)
QA	Strategy	2009	Improved quality assessment of proprietary Chinese medicines based on multi-chemical class fingerprinting	(D. Chen et al., 2009)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QA	Analytical methods	2016	Quality assessment of traditional Chinese medicine herb couple by high-performance liquid chromatography and mass spectrometry combined with chemometrics	(T. F. Cheng et al., 2016)
QA	Strategy	2019	Quality evaluation based on color grading: quality discrimination of the Chinese medicine Corni Fructus by an E-eye	(Y. X. Cui et al., 2019)
QA	Strategy	2018	Discovery and identification of quality markers of Chinese medicine based on pharmacokinetic analysis	(Jun He, Feng, Wang, Liu, & Qiu, 2018)
QA	Procedure	2013	Quality Assurance of Chinese Herbal Medicines: Procedure for Single-Herb Extraction	(Y. T. Lau et al., 2013)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QA	Strategy	2014	Quality Assurance of Chinese Herbal Medicines: Procedure for Multiple-Herb Extraction	(Y. T. Lau et al., 2014)
QA	Strategy	2022	An Exploratory Study on the Design and Management Model of Traditional Chinese Medicine Quality Safety Traceability System Based on Blockchain Technology	(D. Li, Gong, Zhang, & Huang, 2022)
QA	Data	2021	Evaluation of quality of pharmacoeconomic studies involved in traditional Chinese medicine in China	(Si et al., 2021)
QA	Post-Harvest Supply	2019	Postharvest storage quality of citrus fruit treated with a liquid ferment of Chinese herbs and probiotics	(L. Wang, Ning, & Chen, 2019)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QA	Strategy	2006	Chromatographic fingerprint analysis - a rational approach for quality assessment of traditional Chinese herbal medicine	(P. S. Xie et al., 2006)
QA	Data	2019	Quality assessment of clinical trial registration with traditional Chinese medicine in WHO registries	(X. Zhang, R. Tian, et al., 2019)
QA	Data	2018	SYSTEMATIC ANALYSIS AND QUALITY EVALUATION OF PHARMACOECONOMICS RESEARCHES ON TRADITIONAL CHINESE MEDICINES	(N. Yang, Liu, Bao, Zhou, & Hu, 2018)
QA	Data	2015	Traditional Chinese Medicine Instruments for Quality of Life: a systematic review of psychometric evidence	(C. H. Yu, Sun, He, Liu, & Bai, 2015)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QA	Standards	2015	What traditional chinese medicine told modern medicine about health status and quality of life: content analysis of traditional Chinese medicine instruments for quality of life comparing with the WHOQOL and SF-36	(C. H. Yu, Sun, He, Bai, & Liu, 2015)
QA	Data	2020	Data Granularity Gradable Quality Traceability Modeling Method of Traditional Chinese Medicine	(L. Yu et al., 2020)
QA	Data	2008	Data quality in traditional Chinese medicine	(Feng et al., 2008)
QAS	Strategy	2018	From quality markers to data mining and intelligence assessment: A smart quality-evaluation strategy for traditional Chinese medicine based on quality markers	(G. Bai et al., 2018)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2022	A new method for studying the mechanism of Feature Identification based quality assessment of Traditional Chinese Medicine, taking Gastrodiae Rhizoma as an example	(Bing, Yan-Tao, Wen-Han, Hui, & Ting-Guo, 2022)
QAS	Analytical methods	2020	Development of a comprehensive method combining UHPLC-CAD fingerprint, multi-components quantitative analysis for quality evaluation of Zishen Yutai Pills: A step towards quality control of Chinese patent medicine	(J. L. Cao et al., 2020)
QAS	Consultation	2022	Quality Evaluation and Reporting Specification for Real-World Studies of Traditional Chinese Medicine	(Q. Y. Chai et al., 2022)
QAS	Strategy	2022	A general procedure for establishing composite quality evaluation indices based on key quality attributes of traditional Chinese medicine	(J. Chen et al., 2022)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2022	An integration strategy combined progressive multivariate statistics with anticoagulant activity evaluation for screening anticoagulant quality markers in Chinese patent medicine	(Du et al., 2022)
QAS	Strategy	2020	A novel strategy for screening bioavailable quality markers of traditional Chinese medicine by integrating intestinal absorption and network pharmacology: Application to Wu Ji Bai Feng Pill	(S. Duan et al., 2020)
QAS	Statistical	2018	A full solution for multi-component quantification-oriented quality assessment of herbal medicines, Chinese agarwood as a case	(Huo et al., 2018)
QAS	Strategy	2018	Discrimination and identification of Q-markers based on 'Spider-web' mode for quality control of traditional Chinese medicine	(Z. Z. Jiang, Yang, & Wang, 2018)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2013	Application of a Rapid and Efficient Quantitative Analysis Method for Traditional Chinese Medicines: The Case Study of Quality Assessment of Salvia miltiorrhiza Bunge	(W. G. Jing et al., 2013)
QAS	Analytical methods	2017	Simultaneous Determination of 5 Flavonoids and 7 Saponins for Quality Control of Traditional Chinese Medicine Preparation Xinnaoshutong Capsule Using HPLC-VWD-ELSD	(J. Li et al., 2017)
QAS	Strategy	2019	A strategy for the discovery and validation of toxicity quality marker of Chinese medicine based on network toxicology	(Y. Li et al., 2019)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2020	Application of pseudotargeted method combined with multivariate statistical analysis for the quality assessment of traditional Chinese medicine preparation, Sanhuang Tablet as a case	(L. L. Li, Wang, & Liu, 2020)
QAS	Analytical methods	2021	An ultra-robust fingerprinting method for quality assessment of traditional Chinese medicine using multiple reaction monitoring mass spectrometry	(Z. Li, Zhang, Liao, Fan, & Cheng, 2021)
QAS	Strategy	2022	Development of a comprehensive method based on quantitative (1) H NMR for quality evaluation of Traditional Chinese Medicine injection: a case study of Danshen Injection	(W. Z. Li, F. Zhao, J. Y. Yang, J. Y. Pan, & H. B. Qu, 2022)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2022	Quality Status Analysis and Intrinsic Connection Research of Growing place, Morphological Characteristics, and Quality of Chinese Medicine: Cyperi Rhizoma (Xiangfu) as a Case Study	(J. Lu et al., 2022)
QAS	Strategy	2022	Multimodal integrated strategy for the discovery and identification of quality markers in traditional Chinese medicine	(X. Lu, Jin, Wang, Chen, & Fan, 2022)
QAS	Strategy	2021	Quality tracing evaluation strategies of compatible materials in Aconitum proprietary Chinese medicines	(Z. D. Qiu et al., 2021)
QAS	Strategy	2007	Development of an HPLC method for the quality evaluation of 'Ge-Gen-Qin-Lian' tablets derived from traditional Chinese medicine	(H. Qu, Ma, Yu, & Cheng, 2007)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2013	Qualitative analysis and quality control of Traditional Chinese Medicine preparation Tanreqing injection by LC-TOF/MS and HPLC-DAD-ELSD	(L. Sun et al., 2013)
QAS	Strategy	1992	Quality assessment of the traditional Chinese medicine gentian by chemical pattern recognition	(T. Wang, Luo, Wang, & He, 1992)
QAS	Strategy	2017	Quality assessment of Traditional Chinese Medicine using HPLC-PAD combined with Tchebichef image moments	(X. Wang, Li, Xu, Liu, & Zhai, 2017)
QAS	Holistic	2021	An integrated strategy for holistic quality identification of Chinese patent medicine: Liuwei Dihuang Pillsas a case study	(X. Wang, W. Y. Wu, et al., 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2022	Reliability evaluation of traditional Chinese medicine fingerprints combined with qualitative and quantitative analysis and antioxidant activity to comprehensively evaluate the quality of Citri Reticulatae Pericarpium	(X. Wang et al., 2022)
QAS	Strategy	1991	Study of chemical pattern recognition as applied to quality assessment of the traditional Chinese medicine "wei ling xian"	(M. Wei, Luo, Wang, & Zhu, 1991)
QAS	Strategy	2021	Comparative study and quality evaluation regarding morphology characters, volatile constituents, and triglycerides in seeds of five species used in traditional Chinese medicine	(N. Wei et al., 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Reporting quality	2013	The Reporting Quality Assessment of Complex Interventions' Articles in Traditional Chinese Medicine	(M. Wu, Hu, & Liu, 2013)
QAS	Characterisation	2022	Phytochemistry, Pharmacology and Quality Control of Xiasangju: A Traditional Chinese Medicine Formula	(S. Wu et al., 2022)
QAS	Strategy	2022	Quality Evaluation of Traditional Chinese Medicine Prescription in Naolingsu Capsule Based on Combinative Method of Fingerprint, Quantitative Determination, and Chemometrics	(L. Xu et al., 2022)
QAS	Strategy	2021	Discovery of minor quality evaluation marker compounds for Chinese patent medicine products using a two-leveled metabolomics strategy	(Z. Z. Xue et al., 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Strategy	2016	Quality Evaluation of Traditional Chinese Medicine Compounds in Xiaoyan Lidan Tablets: Fingerprint and Quantitative Analysis Using UPLC-MS	(N. Yang, Xiong, Wang, Yang, & Wang, 2016)
QAS	Strategy	2017	A Novel and Practical Chromatographic Fingerprint-ROC-SVM Strategy Applied to Quality Analysis of Traditional Chinese Medicine Injections: Using KuDieZi Injection as a Case Study	(B. Yang et al., 2017)
QAS	Strategy	2015	Simultaneous quantitation of five Panax notoginseng saponins by multi heart-cutting two-dimensional liquid chromatography: Method development and application to the quality control of eight Notoginseng containing Chinese patent medicines	(C. L. Yao et al., 2015)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Data	2011	Assessing the Quality of the First Batch of Evidence-Based Clinical Practice Guidelines in Traditional Chinese Medicine	(W. Y. Yu et al., 2011)
QAS	Data	2014	Quality assessment of clinical research on liver cancer treated by intra-arterial infusion of Chinese medicine	(Zhai, Qiao, Liu, Chen, & Ling, 2014)
QAS	Data	2020	Quality assessment of clinical practice guidelines of Chinese and western medicine for acute bronchitis	(F. Zhang & Liu, 2020)
QAS	Strategy	2003	Quality evaluation of volatile oils of traditional Chinese medicines by using comprehensive two-dimensional gas chromatography (GC x GC)	(Ruan et al., 2003)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QAS	Review	2001	On the quality assessment of Chinese patent medicine	(P. S. Xie & Yan, 2001)
QC	Strategy	2011	Validation of a high performance liquid chromatography (HPLC) method for the quality control of the Traditional Chinese Medicine (TCM) formulation, Traditional Chinese formula Huanglianjiedutang (HLJDT)	(B. L. Bian, Lower-Nedza, Song, Wang, & Brantner, 2011)
QC	Strategy	2015	Traceability and Quality Control in Traditional Chinese Medicine: From Chemical Fingerprint to Two-Dimensional Barcode	(Y. Cai et al., 2015)
QC	Strategy	2016	Quality Traceability System of Traditional Chinese Medicine Based on Two-Dimensional Barcode Using Mobile Intelligent Technology	(Y. Cai et al., 2016)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2014	Quality Control of Danggui Buxue Tang, a Traditional Chinese Medicine Decoction, by H-1-NMR Metabolic Profiling	(P. H. Chan, Zhang, Cheung, Tsim, & Lam, 2014)
QC	Strategy	2007	Clematis huchouensis TAMURA: A traditional Chinese herbal medicine and its quality control using a high performance liquid chromatography technique	(Chaudhary, Qing, Xiao, & Cheng, 2007)
QC	Mechanism	2011	Biological effects-based quality control of a traditional Chinese medicine	(J. X. Chen et al., 2011)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Holistic	2017	A holistic strategy for quality and safety control of traditional Chinese medicines by the iVarious standard system	(A. Chen et al., 2017)
QC	Analytical methods	2017	Raman spectroscopy in quality control of Chinese herbal medicine	(D. D. Chen, Xie, Ao, Liu, & Peng, 2017)
QC	Strategy	2018	The Scientific Basis and Advantage of Human Experiential Assessment in the quality control of Chinese Herbal Medicines exampling as Schisandrae Chinensis Fructus	(Y. F. Chen, R. Y. Yu, et al., 2019b)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2019	A Comprehensive and Rapid Quality Evaluation Method of Traditional Chinese Medicine Decoction by Integrating UPLC-QTOF-MS and UFLC-QQQ-MS and Its Application	(Y. F. Chen, R. Y. Yu, et al., 2019a)
QC	Strategy	2022	Development of a novel unified quality control strategy for proprietary Chinese medicines	(Z. Y. Chen et al., 2022)
QC	Strategy	2020	Use of a tolerance interval approach as a statistical quality control tool for traditional Chinese medicine	(Chiang et al., 2020)
QC	Strategy	2022	Study on Chinese patent medicine based on major component analysis and quality control evaluation: A case study of Jizhi Syrup	(H. Ding, Liu, Wang, Dong, & Li, 2022)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2021	A new strategy for quality evaluation and control of Chinese patent medicine based on chiral isomer ratio analysis: With Yuanhuzhitong tablet as an example	(Gou et al., 2021)
QC	Review	2019	Advances in Processing and Quality Control of Traditional Chinese Medicine Coptidis rhizoma (Huanglian): A Review	(L. Han et al., 2019)
QC	Analytical methods	2022	Advanced applications of mass spectrometry imaging technology in quality control and safety assessments of traditional Chinese medicines	(H. Y. Jiang et al., 2022)
QC	Strategy	2022	Application of near infrared spectroscopy and real time release testing combined with statistical process control charts for on-line quality control of industrial concentrating process of traditional Chinese medicine Jinyinhua	(Y. Jin, W. J. Du, X. S. Liu, & Y. J. Wu, 2022)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2019	Establishment of a quality marker (Q-marker) system for Chinese herbal medicines using burdock as an example	(T. G. Kang, Dou, & Xu, 2019)
QC	Analytical methods	2016	Analytical Method Validation and Quality Control of a Seven-Herb Chinese Medicine Formulation Used for the Treatment of Irritable Bowel Syndrome with Constipation	(S. Lee, Khoo, Pearson, Bourchier, & Bensoussan, 2016)
QC	Strategy	2010	Tradition- and Science-Based Quality Control of Chinese Medicines-Introducing the Phyto-True (TM) System	(A. Y. Leung, 2010)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2006	A rapid and simple determination of protoberberine alkaloids in cortex phellodendri by H-1 NMR and its application for quality control of commercial traditional Chinese medicine prescriptions	(C.-Y. Li, Lu, Lin, & Wu, 2006)
QC	Strategy	2011	Strategies for quality control of Chinese medicines	(S. P. Li, Zhao, & Yang, 2011)
QC	Strategy	2013	A Metabolomics-Based Strategy for the Quality Control of Traditional Chinese Medicine: Shengmai Injection as a Case Study	(X. D. Li, Chen, Jia, & Xie, 2013)
QC	Strategy	2016	A Green Antioxidant Activity-Integrated Dual-Standard Method for Rapid Evaluation of the Quality of Traditional Chinese Medicine Xuebijing Injection by On-Line DPPH-CE-DAD	(J. Li et al., 2016)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2018	Quality control of the traditional Chinese medicine Ruyi jinhuang powder based on high-throughput sequencing and real-time PCR	(Q. Li et al., 2018)
QC	Strategy	2018	Nuciferine and paeoniflorin can be quality markers of Tangzhiqing tablet, a Chinese traditional patent medicine, based on the qualitative, quantitative and dose-exposure-response analysis	(Z. Q. Li et al., 2018)
QC	Analytical methods	2022	A pseudotargeted method based on sequential window acquisition of all theoretical spectra mass spectrometry acquisition and its application in quality assessment of traditional Chinese medicine preparation-Yuanhu Zhitong tablet	(L. L. Li, Wang, Li, Zhu, & Feng, 2022)
QC	Fingerprinting	2011	Chromatographic Fingerprinting Coupled with Chemometrics for Quality Control of Traditional Chinese Medicines	(Y. Z. Liang & Wang, 2011)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Procedure	2017	Improving the quality of Sichuan pickle by adding a traditional Chinese medicinal herb Lycium barbarum in its fermentation	(Liao et al., 2017)
QC	Strategy	2010	Recent Advances in Quality Control of Traditional Chinese Medicines	(E. H. Liu, Qi, Li, Chu, & Li, 2010)
QC	Strategy	2015	Application of Fourier Transform Infrared Spectra (FTIR) Fingerprint in the Quality Control of Mineral Chinese Medicine Limonitum	(S. J. Liu et al., 2015)
QC	Metabolomics / Chemometrics	2016	Chemometrics applied to quality control and metabolomics for traditional Chinese medicines	(S. Liu, Liang, & Liu, 2016)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2020	Comprehensive quality evaluation strategy based on non-targeted, targeted and bioactive analyses for traditional Chinese medicine: Tianmeng oral liquid as a case study	(X. Y. Liu, H. Zhang, et al., 2020)
QC	Strategy	2022	Rapid Determination in the Quality Control of Chinese Patent Medicine	(S. H. Lu et al., 2022)
QC	Strategy	2022	The Application of UHPLC-HRMS for Quality Control of Traditional Chinese Medicine	(J. Ma et al., 2022)
QC	Strategy	2022	Quality Grade Evaluation of Niuhuang Qingwei Pills Based on UPLC a Components in Ready-Made Chinese Herbal Medicine	(L. X. Nie et al., 2022)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Review	2019	Considerations for the Quality Control of Newly Registered Traditional Chinese Medicine in China: A Review	(J. B. Qu, Zhang, Liu, Su, & Wang, 2019)
QC	Strategy	2011	Quality control of traditional chinese medicine by monoclonal antibody method	(M. Y. Shang et al., 2011)
QC	Strategy	2021	Development of chromatographic technologies for the quality control of Traditional Chinese Medicine in the Chinese Pharmacopoeia	(M.-R. Shen et al., 2021)
QC	Strategy	2016	Statistical modeling methods to analyze the impacts of multiunit process variability on critical quality attributes of Chinese herbal medicine tablets	(F. Sun et al., 2016)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2022	From metabolomic analysis to quality assessment and biosynthetic insight in traditional Chinese medicine: Mulberry tree as a case study	(M. Y. Tian et al., 2022)
QC	Strategy	2006	Statistical quality control process for traditional Chinese medicine	(Tse et al., 2006)
QC	Strategy	2011	A bio-activity guided in vitro pharmacokinetic method to improve the quality control of Chinese medicines, application to Si Wu Tang	(L. Wang et al., 2011)
QC	Strategy	2012	Colorimetric Grading Scale Can Promote the Standardization of Experiential and Sensory Evaluation in Quality Control of Traditional Chinese Medicines	(J. B. Wang et al., 2012)
QC	Strategy	2013	A novel strategy to evaluate the quality of traditional Chinese medicine based on the correlation analysis of chemical fingerprint and biological effect	(J. Wang et al., 2013)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2015	A Useful Strategy to Evaluate the Quality Consistency of Traditional Chinese Medicines Based on Liquid Chromatography and Chemometrics	(P. Wang, Nie, & Zang, 2015)
QC	Strategy	2017	Discovery of discriminatory quality control markers for Chinese herbal medicines and related processed products by combination of chromatographic analysis and chemometrics methods: Radix Scutellariae as a case study	(F. Wang et al., 2017)
QC	Strategy	2018	Quality Assessment of Kumu Injection, a Traditional Chinese Medicine Preparation, Using HPLC Combined with Chemometric Methods and Qualitative and Quantitative Analysis of Multiple Alkaloids by Single Marker	(N. Wang et al., 2018)
QC	Analytical methods	2021	A novel and comprehensive strategy for quality control in complex Chinese medicine formula using UHPLC-Q-Orbitrap HRMS and UHPLC-MS/MS	(X. Wang, W. Zhou, et al., 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
			combined with network pharmacology analysis: Take Tangshen formula as an example	
QC	Strategy	2008	Fourier transform mid-infrared (MIR) and near-infrared (NIR) spectroscopy for rapid quality assessment of Chinese medicine preparation Honghua Oil	(Y. W. Wu, Sun, Zhou, & Leung, 2008)
QC	Strategy	2018	Quality markers based on biological activity: A new strategy for the quality control of traditional Chinese medicine	(X. Wu et al., 2018)
QC	Strategy	2013	Nucleosides, a valuable chemical marker for quality control in traditional Chinese medicine Cordyceps	(J. H. Xiao, Qi, & Xiong, 2013)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2013	Utilization of Gene Expression Signature for Quality Control of Traditional Chinese Medicine Formula Si-Wu-Tang	(C. Xie et al., 2013)
QC	Strategy	2018	Promotion of quality standard of Chinese herbal medicine by the integrated and efficacy-oriented quality marker of Effect-constituent Index	(Y. Xiong et al., 2018)
QC	Characterisation	2013	Chemistry, bioactivity and quality control of Dendrobium, a commonly used tonic herb in traditional Chinese medicine	(J. Xu et al., 2013)
QC	Strategy	2011	Development of a novel method combining HPLC fingerprint and multi-ingredients quantitative analysis for quality evaluation of traditional chinese medicine preparation	(D.-Z. Yang et al., 2011)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Standards	2016	Development of a new certified reference material of high-purity chrysin for the quality control of traditional Chinese medicine	(S. Y. Yang et al., 2016)
QC	Strategy	2011	HPLC Fingerprint with Multi-components Analysis for Quality Consistency Evaluation of Traditional Chinese Medicine Si-Mo-Tang Oral Liquid Preparation	(Y. N. Yi et al., 2011)
QC	Strategy	2009	Simultaneous determination of 11 active components in two well-known traditional Chinese medicines by HPLC coupled with diode array detection for quality control	(L. H. Yin et al., 2009)
QC	Strategy	2015	Developing an activity and absorption-based quality control platform for Chinese traditional medicine: Application to Zeng-Sheng-Ping (Antitumor B)	(T. J. Yin et al., 2015)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2012	Direct analysis in real time mass spectrometry and multivariate data analysis: A novel approach to rapid identification of analytical markers for quality control of traditional Chinese medicine preparation	(S. Zeng et al., 2012)
QC	Strategy	2018	The method of quality marker research and quality evaluation of traditional Chinese medicine based on drug properties and effect characteristics	(T. Zhang et al., 2018)
QC	Strategy	2019	Establishing the chromatographic fingerprint of traditional Chinese medicine standard decoction based on quality by design approach: A case study of Licorice	(H. Zhang et al., 2019)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2019	Assessment of quality consistency in traditional Chinese medicine using multi-wavelength fusion profiling by integrated quantitative fingerprint method: Niuhuang Jiedu pill as an example	(J. Zhang & Sun, 2019)
QC	Strategy	2020	An integrated approach to uncover quality markers of Traditional Chinese medicine underlying chemical profiling, network target selection and metabolomics approach: Guan-Xin-Jing capsule as a model	(G. H. Zhang et al., 2020)
QC	Analytical methods	2021	An integrated approach to discriminate the quality markers of Traditional Chinese medicine preparation based on multi-dimensional characteristic network: Shenqi Jiangtang Granule as a case	(H. Zhang et al., 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2019	An Approach to Rapid Determination of Tween-80 for the Quality Control of Traditional Chinese Medicine Injection by Partial Least Squares Regression in Near-Infrared Spectral Modelling	(Y. F. Zhou et al., 2018)
QC	Strategy	2014	Fingerprint-efficacy study of Radix Aconiti Lateralis Preparata (Fuzi) in quality control of Chinese herbal medicine	(Y. Zhu et al., 2014)
QC	Mechanism	2017	Mechanism based quality control (MBQC) for the four-herb Chinese medicine formulation, PHY906(YIV-906) and other herbal products	(Lam et al., 2017)
QC	Strategy	2011	Application of near-infrared spectroscopy (NIRS) as a tool for quality control in Traditional Chinese Medicine (TCM)	(Huck et al., 2011)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2011	Fishing and Knockout (FAK) Strategy for Quality Control of Traditional Chinese Medicines (TCMs)	(P. Li, Qi, & Xin, 2011)
QC	Analytical methods	2009	HPTLC for Quality Control of Traditional Chinese Medicines: Identification and Detection of Adulteration	(Z. Li & Reich, 2009)
QC		2009	Quality Evaluation and Quality Control of Botanicals and Traditional Chinese Medicine	(G. Luo, Liang, Yang, & Wang, 2009)
QC	Strategy	2006	Systems biology: Scientific evidence and a novel quality control for Traditional Chinese Medicine (TCM)	(M Wang & van der Greef, 2006)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Strategy	2019	Research on the Evaluation of Chinese Herbal Medicine Quality and Safety Credit Index Based on TOPSIS	(Z. K. Wang & Guan, 2019)
QC	Quality management	2015	On the Quality Management of Traditional Chinese Medicine	(Mark, 2015)
QC	Analytical methods	2008	Design of an FT-NIR spectrometer for online quality analysis of traditional Chinese medicine manufacturing process - art. no. 68343B	(R. Zhu, Wu, Wang, Ye, & Ding, 2008)
QC	Strategy	2021	Comprehensive Analysis and Elaboration of Quality Standard for Traditional Chinese Medicines	(D. A. Guo, Wu, Yao, & Da, 2021)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
QC	Marker	2017	Determination of Quality Markers is Basis for Establishing Quality Standard and Control of Chinese Herbal Medicines	(C. X. Liu, 2017)
Quality	Analytical methods	2013	Advances in analytical technologies to evaluate the quality of traditional Chinese medicines	(Jing, Ren, Chen, Wei, & Parekh, 2013)
Quality	Improvement	2011	Polyphenol Quality and Energy Saving Property of Instantaneous Ultrasonic Extraction and Reverse Osmosis Concentration in the Process of Chinese Herbs	(Y. Ye, Luo, & Wang, 2012)
Survey	Regulation	2005	Are national quality standards for traditional Chinese herbal medicine sufficient? - Current governmental regulations for traditional Chinese herbal medicine in certain Western countries and China as the Eastern origin country	(Dobos et al., 2005)

TABLE ALR 4 FIRST PHASE GENERAL LITERATURE REVIEW: 122 JOURNAL ARTICLES INCLUDED

Primary Quality concern QC = Quality Control QA = Quality Assurance QAS – Quality Assurance	Secondary Quality concern	Publication Year	Article Title	Citation
Survey	Clinical effects	1997	Treating chronically ill patients with traditional Chinese Medicine - Its effects on their quality of life	(Weidenhammer, Melchart, & Hager, 1997)

Second phase specific literature review: 213 articles in total included, 40 review articles and 173 journal articles

Second phase specific literature review: 40 review articles included

Second phase specific literature review: 173 journal articles included

Appendix to the literature review 5: 40 review articles included in the second phase specific literature review

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Multiple types)	Multiple CMP	Review of DNA analytical techniques for detecting adulteration in Botanical drugs	Not detected due to misidentification of closely related species	Analytical development (Mutli-hyphenated - DNA Chromatographic fingerprinting with chemometrics)	2017	Review: DNA Barcoding and Chromatography Fingerprints for the Authentication of Botanicals in Herbal Medicinal Products	(Abubakar, Salleh, Omar, & Wagiran, 2017)
Adulteration (Multiple types)	Multiple CMP	Review of multiple adverse events	Not detected / Not known	Pharmacovigilance and education	2003	Herbal remedies and clinical biochemistry	(C. M. Corns, 2003)
Adulteration (Multiple types)	Multiple CMP	Review of misidentification and adulteration	Standardization and legislation insufficient	Standardization and stricter legislation	2011	Toxicities by Herbal Medicines with Emphasis to Traditional Chinese Medicine	(Efferth & Kaina, 2011)
Adulteration (Multiple types)	Multiple CMP	Review of NMR profiling plant metabolites	Not detected	Integration with NMR with omics	2006	The assessment of plant metabolite profiles by NMR-based methodologies	(Holmes, Tang, Wang, & Seger, 2006)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Multiple types)	Multiple CMP	High adulteration rates with CMP	Not detected / Difficult to detect	Legislation: More stringent quality control and enforcement	2013	Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews	(Posadzki, Watson and Ernst, 2013)
Adulteration (Substitution)	Rhodiola sachalinensis Boriss.	Review of Substitution (scarcity)	Value / Profit motivation	Further study	2021	Reviewing Threats to Wild Rhodiola sachalinensis, A Medicinally Valuable yet Vulnerable Species	(Brinckmann, Cunningham, & Harter, 2021)
Adulteration (Substitution)	Multiple CMP	Review of DNA analysis for detecting adulteration	Not Detected	Analytical development (DNA)	2018	Benefits and Limitations of DNA Barcoding and Metabarcoding in Herbal Product Authentication	(Raclariu, Heinrich, et al., 2018)
Adulteration (Substitution)	Multiple CMP	Molecular authentication as a tool for detecting adulteration (Substitution)	Not Detected	Analytical development (DNA)	2007	Molecular authentication of Chinese herbal materials	(Y. B. Zhang, Shaw, Sze, Wang, & Tong, 2007)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Substitution)	Multiple CMP	Commonly substituted species	Not detected	Standardise nomenclature, Education and Regulation	2006	A systematic study on confused species of Chinese Materia medica in the Hong Kong market	(Z. Z. Zhao, J. P. S. Yuen, J. L. Wu, T. Yu, & W. H. Huang, 2006)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) sexual enhancement, slimming, inflammatory disease - review	Perception of "natural herbs are safe"	Raise awareness	2019	Common risks of adulterated and mislabelled herbal preparations	(Ekar & Kreft, 2019)
Adulteration (Synthetic drugs)	Multiple CMP	Review CMP adulteration with synthetic drugs	Inadequate legislation	More relevant legislated	2002	Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review	(Ernst, 2002a)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) multiple	Not detected / Not known	Analytical development (CE)	2014	Capillary electrophoretic methods for the screening and determination of pharmacologic adulterants in herbal-based pharmaceutical formulations	(Moreira, Martini, & de Carvalho, 2014)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Synthetic drugs)	Multiple CMP	Review of toxic aspects of CMP including adulteration with steroids	Unknown / undetected toxicity	Deeper understanding through research	2003	Side-effects of complementary and alternative medicine	(Niggemann & Gruber, 2003)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) Sildenafil,Tadalafil, Vardenafil	Detection strategy insufficient	Better detection using MS	2009	Strategies for characterizing sildenafil, vardenafil, tadalafil and their analogues in herbal dietary supplements, and detecting counterfeit products containing these drugs	(S. Singh et al., 2009)
Adulteration (Synthetic drugs)	Multiple CMP	Review of Adulteration with synthetic drugs	Not Detected	Analytical development (GC-MS)	2014	Mass spectrometric analysis of pharmaceutical adulterants in products labelled as botanical dietary supplements or herbal remedies: a review	(Vaclavik, Krynitsky, & Rader, 2014a)
Adulteration and contamination	Multiple CMP	Review of Adulteration and Contamination in plant cosmetic products	Not detected / Difficult to detect	More pragmatic and conservative approaches to quality and safety standards	2011	Safety of botanical ingredients in personal care products/cosmetics	(Antignac, Nohynek, Re, Clouzeau, & Toutain, 2011)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration and risk of incorrect prescriptions	Multiple CMP	Integration with Western herbalism emerging issues	Misunderstanding of Chinese herbalism	Education	2001	Should we be concerned about herbal remedies	(Elvin-Lewis, 2001)
Adverse effects (CNS)	Panax ginseng	Toxicity (Multiple) sleep disturbance, bleeding, behavioural changes	Adulteration (undeclared pharmaceutical drugs)	Not specified	2003	Serious Psychiatric and Neurological Adverse Effects of Herbal Medicines - a Systematic Review. *Acta Psychiatrica Scandinavica* 108, no. 2 (Aug 2003): 83-91. https://doi.org/10.1034/j.1600-0447.2003.00158.x. <Go to ISI>://WOS:000183594800002.	(Ernst, 2003)
Adverse events (Cardiac and CNS)	Tussilago farfara	pyrrolizidine alkaloids	Unknown toxicity	Legislation (restricted use) recommended	2013	Evidence-based toxicity evaluation and scheduling of Chinese herbal medicines. J. Ethnopharmacol. 146, 40–61. doi: 10.1016/j.jep.2012.12.027 in Ekor, 2014	(E. J. Kim et al., 2013)
Adverse events (Cardiac)	Aconitum Species	aconitine, mesaconitine, hypaconitine, and other Aconitum alkaloids	Unverified, suspected drug interaction, assumption of being "safe"	Standardise processing, regulation, communication between health practitioners	2018	Bradycardia and hypotension from improper use of aconite root: a case report and brief review. *Complementary medicine research*, *25*(5), 338-343.	(Chou et al., 2018)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adverse events (Digestive)	Bo He	Mild digestive upset in a mixture with other herbs	Drug trial for patent product	Use of standardised patent product Lomatol® drops	1998	Harmless Herbs? A Review of the Recent Literature." [In English]. Review. *American Journal of Medicine* 104, no. 2 (Feb 1998): 170-78. https://doi.org/10.1016/s0002-9343(97)00397-5. <Go to ISI>://WOS:000072337700011.	(E. Ernst, 1998)
Adverse events (General)	Multiple CMP	Adverse events (General)	Not detected / Not known	Pharmacovigilance	2014	Quality and Safety of Chinese Medicine Drugs in Germany - an Update	(Hempen & Huber, 2014)
Adverse events (Organ Failure)	Xiong huang (Arsenic sulphide)	Incorrect usage - high potency Arsenic poisoning	High potency usage	Risk analysis, authentication and quality control measures	1995	Attitudes and Approaches of Traditional Chinese Medicine to Herbal Toxicity." *Journal of Natural Toxins* 4, no. 2 (Sep 1995): 207-17. <Go to ISI>://WOS:A1995RY24200014.	(But, 1995)
Adverse events (Pain and CNS)	Ginkgo biloba	Ginkgolides inhibiting platelet-activating factor	High potency usage	None recommended	2000	Safety issues with herbal medicine. Pharmacotherapy 20, 257–269. doi: 10.1592/phco.20.4.257.34886 in Ekor, 2014	(Boullata & Nace, 2000)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adverse events (Systematic review)	Multiple CMP	multiple	none specified (review)	Further clinic trials and reviews recommended	2020	The Safety of Chinese Herbal Medicine: A Systematic Review of Adverse Events in Randomized Controlled Trials." *Longhua Chinese Medicine* 3 (2020). https://lcm.amegroups.com/article/view/6489.	(Jing Hu et al., 2020)
Adverse events (Toxicity)	Multiple CMP	Review of multiple adverse events including adulteration and a case report	Not Detected	Education	2018	Nephrotoxicity and Chinese Herbal Medicine	(B. Yang et al., 2018)
Historical review	Multiple CMP	Review of multiple quality issues and legislation	Multiple reasons including cultural perception differences	Multiple including legislation	2016	Herbal medicines: challenges in the modern world. Part 2. European Union and Russia	(Sammons et al., 2016)
Review of detection methods for Ginsengs	*Panax ginseng* C.A. Meyer	Panax ginseng C.A. Meyer substitution	Not detected due to visual obscuration by different formulations	Analytical development (Fibre optic biosensors)	2005	Overview on the analytical tools for quality control of natural product-based supplements: A case study of ginseng	(K. Y. Yap, Chan, Weng Chan, & Sing Lim, 2005)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Review of quality issues in healthcare	Multiple CMP	Review of multiple quality issues	Perception of "natural herbs are safe"	Not proposed	2012	Herbal Medicine in Healthcare-An Overview	(Mosihuzzaman , 2012)
Review of quality issues with CMP in Cancer treatment	Multiple CMP	Review of multiple quality issues	Not detected	Not proposed	2009	Complications of traditional Chinese/herbal medicines (TCM)-a guide for perplexed oncologists and other cancer caregivers	(J. Chiu et al., 2009)
Review of safety assessment of botanicals in food supplements in EU	Multiple CMP	Safety of botanicals cannot be assumed based on traditional use	Not detected due to misidentification and poor characterisation	Multi-tiered strategy	2010	Safety assessment of botanicals and botanical preparations used as ingredients in food supplements: Testing an European Food Safety Authority-tiered approach	(Speijers et al., 2010)
Toxic (heavy metals) and undeclared drugs	Multiple CMP	Multiple CMP contaminated with heavy metals and undeclared drugs	Not known / detected	More comparable data	2002	Toxic heavy metals and undeclared drugs in Asian herbal medicines	(Ernst, 2002b)
Toxicity (Hepatoxicity)	Multiple CMP	Review of adverse events with hepatoxic herbs	Not Detected (not recorded)	More research and education	2003	Systematic review: hepatotoxic events associated with herbal medicinal products	(Pittler & Ernst, 2003)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Toxicity (Hepatoxicity)	Multiple CMP	Review of adverse events with hepatoxic herbs	Not Detected (not recorded)	Pharmacovigilance	2015	Hepatotoxicity of herbal and dietary supplements: an update	(Stickel & Shouval, 2015)
Toxicity (Hepatoxicity)	Multiple CMP	Review of injury from Chines herbal medicine including An Shu Ling, Bai Fang, Bai Xian Pi	Unknown / undetected toxicity	Reconsideration of TCM usage based on Risk / Benefit Analysis	2014	Traditional Chinese Medicine Induced Liver Injury	(Teschke, 2014)
Toxicity (intrinsic)	Multiple CMP	Toxicity (intrinsic CNS and others)	Not detected / Difficult to detect	Regulation and monitoring	2019	Metals and metalloids in traditional medicines (Ayurvedic medicines, nutraceuticals and traditional Chinese medicines)	(Gyamfi, 2019)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED

CMP Quality issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Toxicity (intrinsic)	Aconite spp., Aristolochia spp., Polygonum multiflorum, Realgar, and Tripterygium wilfordii spp.	Toxicity (intrinsic CNS and others)	Toxicity (Intrinsic)	Predictive toxicology and omics	2021	The toxicity and safety of Chinese medicine from the bench to the bedside	(H. Y. Zhu et al., 2021)
Toxicity (Renal carcinogenic)	*Aristolochia genus*	Review of toxic effects of aristolochic acids		Legislation (restricted use)	2021	Herbal products containing aristolochic acids: A call to revisit the context of safety	(Ang et al., 2021)
Toxicity (Renal carcinogenic)	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	aristolochic acids nephrotoxic and carcinogenic	Not specified	Legislation (restricted use)	2008	Aristolochic acid nephropathy: A worldwide problem	(Debelle et al., 2008)

TABLE ALR 5 SECOND PHASE SPECIFIC LITERATURE REVIEW: 40 REVIEW ARTICLES INCLUDED							
CMP Quality issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Toxicity (Renal carcinogenic)	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	aristolochic acids nephrotoxic and carcinogenic	Not specified	Education and regulation	2010	Herbal medicines and chronic kidney disease	(Jha, 2010)

Appendix to the literature review 6: 173 journal articles included in the second phase specific literature review

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulterants (multiple)	Multiple CMP	Adulteration (Multiple)	Multiple reasons - complex	Analytical development (mobile screening and databases)	2016	Chemical Adulterants in Herbal Medicinal Products: A Review	(Calahan et al., 2016)
Adulteration (Bulking with dextrin)	Salvia miltiorrhiza	Adding excipients to danshen Danshen (Salvia miltiorrhiza)	Not detected / Difficult to detect	Not proposed	2016	Fourier transform mid-infrared spectroscopy (FT-MIR) combined with chemometrics for quantitative analysis of dextrin in Danshen (Salvia miltiorrhiza) granule	(T. Guo et al., 2016)
Adulteration (Dyes)	Ganoderma lucidum	Adulteration of Ganoderma lucidum by Starch dyes	Value motivation / not known	Analytical development (NIR)	2022	Rapid detection of Ganoderma lucidum spore powder adulterated with dyed starch by NIR spectroscopy and chemometrics	(X. Shi et al., 2022)
Adulteration (Dyes)	Multiple CMP	Development of a methods for Adulteration of Multiple CMP with Sudan Red Dyes	Value motivation and difficult to detect	Analytical development (Raman scattering SERS)	2021	Defective cuprous oxide as a selective surface-enhanced Raman scattering sensor of dye adulteration in Chinese herbal medicines	(Y. Jiang et al., 2021)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (misidentification)	Fritillaria species (Liliaceae)	Confusion of Bulbus Fritillariae species	Not Detected	Analytical development (HPLC-MS)	2009	Characterizing distribution of steroidal alkaloids in Fritillaria spp. and related compound formulas by liquid chromatography-mass spectrometry combined with hierarchical cluster analysis	(H. J. Li, Jiang, & Li, 2009)
Adulteration (misidentification)	Pueraria montana var. lobata (gegen)	Adulteration of Pueraria montana var. lobata (gegen) with Pueraria montana var. thomsonii, Pueraria wallichii, and Pueraria peduncularis	Difficult to detect / unknown	Analytical development FTIR-LC)	2022	Detection of Gegen Adulteration Using Multiple Fingerprints Coupled With Chemometric Strategy	(X.-J. Huang et al., 2022)
Adulteration (Multiple types)	Multiple CMP	166 adulterants found using 184 standard testing methods in years 2003 to 2017	Difficult to detect	GMP and regulation of cultivation	2019	Assessment of Adulterated Traditional Chinese Medicines in China: 2003-2017	(M. Z. Xu et al., 2019)
Adulteration (Multiple types)	Multiple CMP	Development of muli-method approach to improving pharmacovigilance	Not detected / Difficult to detect	Muti-method detection	2015	Combined DNA, toxicological and heavy metal analyses provides an auditing toolkit to improve pharmacovigilance of traditional Chinese medicine (TCM)	(Coghlan et al., 2015b)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Multiple types)	Multiple CMP	Intrinsic contamination and external, adulteration and misidentification	Phytochemical complexity - variable CMP	Legislation (GxP) and analytical testing	2012	Quality of herbal medicines: Challenges and solutions	(J. Zhang et al., 2012)
Adulteration (Multiple types)	Multiple CMP	Review of Adulteration and use of UHPLC-MS	Not Detected	Analytical development (HPLC-MS)	2014	Targeted analysis of multiple pharmaceuticals, plant toxins and other secondary metabolites in herbal dietary supplements by ultra-high performance liquid chromatography quadrupole-orbital ion trap mass spectrometry	(Vaclavik, Krynitsky, & Rader, 2014b)
Adulteration (Multiple types)	Chinese proprietary medicines in Singapore	Review of the effect of regulation on adulteration	Unlicenced herbs not tested	Licencing	2005	Regulatory control of Chinese proprietary medicines in Singapore	(Yee et al., 2005)
Adulteration (Multiple types)	Multiple CMP	Review of contamination, misidentification, interactions with other herbs and drugs	CMP not perceived as low risk	Predictive toxicology and omics	2010	Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment	(Jordan et al., 2010)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Multiple types)	Multiple CMP	Review of adverse events	Not investigated sufficiently	Pharmacovigilance	2012	Adverse events associated with the use of complementary medicine and health supplements: An analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009	(Patel et al., 2012)
Adulteration (Multiple types)	Hypericum perforatum L. and other psycotrophics	Adulteration (Multiple types)	Not detected / not known	Pharmacovigilance / risk-based testing and	2018	Adulterants and Contaminants in Psychotropic Herbal Medicines Detected with Mass Spectrometry and Next-Generation DNA Sequencing	(Hoban et al., 2018)
Adulteration (Multiple types)	Multiple CMP	Adulteration (Value)	Value / Profit motivation	Supply chain study and pharmacovigilance	2019	Linking resource supplies and price drivers: Lessons from Traditional Chinese Medicine (TCM) price volatility and change, 2002-2017	(A. B. Cunningham & X. C. Long, 2019)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Adulteration (Multiple types)	Multiple CMP	Review of adulteration	Perception of "natural herbs are safe"	Not proposed	2007	Complexities of the herbal nomenclature system in traditional Chinese medicine (TCM): Lessons learned from the misuse of Aristolochia-related species and the importance of the pharmaceutical name during botanical drug product development	(K. M. Wu, Farrelly, Upton, & Chen, 2007)
Adulteration (Multiple types)	Notopterygium incisum Ting ex H.T.Chang	Adulteration (Multiple types) of Notopterygium incisum Ting ex H.T.Chang	Not detected / Difficult to detect	Analytical development (UHPLC-QTOF-MS/MS)	2020	Rapid discrimination of Notopterygium incisum and Notopterygium franchetii based on characteristic compound profiles detected by UHPLC-QTOF-MS/MS coupled with multivariate analysis	(X. Ma et al., 2020)
Adulteration (Multiple types)	Astragalus membranaceus	Common multiple adulterants of Astragalus membranaceus	Difficult to detect / unknown	Analytical development(NIR)	2022	Adulteration identification of Astragalus polysaccharides by NIR spectroscopy combined with SIMCA AND PLS-DA	(F. Zhao et al., 2022)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Pesticides)	Panax ginseng C.A. Meyer and Panax quinquefolius L.	High pesticide residues of pentachloronitrobenzene (PCNB), hexachlorocyclohexane (HCH), aldrin, and dichlorodiphenyltrichloroethane (DDT)	Difficult to detect / unknown	Analytical development(Colourimetric-pH)	2022	Detection of Adulteration and Pesticide Residues in Chinese Patent Medicine Qipi Pill Using KASP Technology and GC-MS/MS	(G. Wang et al., 2022)
Adulteration (Pesticides)	Multiple CMP	Over-fumigation of ginsengs, Salvia miltiorrhiza, and bitter almonds	Value motivation and difficult to detect	Analytical development (Raman-SERS)	2022	Si@Ag@PEI substrate-based SERS sensor for rapid detection of illegally adulterated sulfur dioxide in traditional Chinese medicine	(B. Fan et al., 2022)
Adulteration (Substitution)	Panax notoginseng	Adulteration of ginsengs with sawadust and Platycodon grandiflorum	Value motiviation and not detected	Analytical development (IR-Multi sensor with chemometrics)	2020	Origin identification of Panax notoginseng by multi-sensor information fusion strategy of infrared spectra combined with random forest	(Y. H. Zhou et al., 2020)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Substitution)	Panax notoginseng (Burkill) F.H.Chen ex C.Y.Wu & K.M.Feng	Authenticity of Ginsengs by using NIR to determine geographic variation	Value motiviation and not detected	Analytical development (NIR-Chemometrics)	2018	Fast discrimination of the geographical origins of notoginseng by near-infrared spectroscopy and chemometrics	(H. Chen, Lin, & Tan, 2018)
Adulteration (Substitution)	Crocus sativus	Substitution of C. sativa with C. tinctorius, H. fulva and H. citrina	Not detected due to similar appearace	Analytical development (DNA)	2001	Authentic identification of stigma croci (Stigma of Crocus sativus) from its adulterants by molecular genetic analysis	(X. Q. Ma, Zhu, Li, Dong, & Tsim, 2001)
Adulteration (Substitution)	Panax notoginseng	Adulteration of ginsengs with other materals	Value motiviation and not detected	Analytical development (NIR with chemometrics)	2020	Untargeted identification of adulterated Sanqi powder by near-infrared spectroscopy and one-class model	(H. Chen et al., 2020)
Adulteration (Substitution)	Bupleurum chinense Franch.	Adulteration (Toxic substitute) Aristolochia manshuriensis	Not detected / Difficult to detect	Quality control measures	2020	Discovery of GABA(A) Receptor Modulator Aristolactone in a Commercial Sample of the Chinese Herbal Drug Chaihu (Bupleurum chinense Roots) Unravels Adulteration by Nephrotoxic Aristolochia manshuriensis Roots	(H. Chen et al., 2020)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Adulteration (Substitution)	Crocus sativus	Substitution of C. sativa with Carthamus tinctorius petals (safflower), Curcuma longa powdered rhizomes (turmeric), Calendula officinalis, Daucus carota, Zea mays and Nelumbo nucifera	Not detected due to similar appearace	Analytical development (DNA)	2016	Rapid authentication of the precious herb saffron by loop-mediated isothermal amplification (LAMP) based on internal transcribed spacer 2 (ITS2) sequence	(M. M. Zhao et al., 2016)
Adulteration (Substitution)	Cynanchum stauntonii (Decne.) Schltr. ex H.Lév.	Adulteration (Value) of Cynanchum stauntonii (Decne.) Schltr. ex H.Lév. With cheaper materials	Value motiviation and not detected	Analytical development (NIR with chemometrics)	2012	Quantitative analysis of two adulterants in Cynanchum stauntonii by near-infrared spectroscopy combined with multi-variate calibrations	(W. J. Dong, Ni, & Kokot, 2012)
Adulteration (Substitution)	Crocus sativus	Substitution of C. sativa with Bezoar	Difficult to detect similar appearance	Analytical development (Tetrahertz spectroscopy)	2019	Identification of Two Types of Safflower and Bezoar by Terahertz Spectroscopy	(Y. P. Yang, Zhang, Liu, & Zhang, 2019)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Substitution)	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	Subtitution of non-toxic Stephania tetrandra (Fangji) substituted by Aristolochia fangchi (Guang fangji)	Not Detected	Analytical development (HPLC-MS)	2006	Detection of aristolochic acid I, tetrandrine and fangchinoline in medicinal plants by high performance liquid chromatography and liquid chromatography/mass spectrometry	(Koh, Wang, Zhou, Chan, & Woo, 2006)
Adulteration (Substitution)	Multiple CMP	Adulteration of multiple Panax species	Not Detected	Analytical development (DNA)	2015	The complete chloroplast genome provides insight into the evolution and polymorphism of Panax ginseng	(Y. B. Zhao et al., 2015)
Adulteration (Substitution)	Panax notoginseng	Substitution of Notoginseng Sophora flavescens powder, corn flour and other low grade adulterants	Value motiviation and Not detected due to similar appearace	Analytical development (Visible and NIR-Multi sensor with chemometrics)	2013	Potential of Visible and Near Infrared Spectroscopy and Pattern Recognition for Rapid Quantification of Notoginseng Powder with Adulterants	(P. C. Nie et al., 2013)
Adulteration (Substitution)	Cistanches Herba	Adulteration (Value)	Value motiviation and not detected	Analytical development (DNA)	2018	Detection of Cistanches Herba (Rou Cong Rong) Medicinal Products Using Species-Specific Nucleotide Signatures	(X. Y. Wang et al., 2018)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Substitution)	Honghua Oil	Substiution of Hong hua with mutiple compounds incluing synthetic substances	Not Detected	Analytical development (IR)	2008	Fourier transform mid-infrared (MIR) and near-infrared (NIR) spectroscopy for rapid quality assessment of Chinese medicine preparation Honghua Oil	(Y. W. Wu et al., 2008)
Adulteration (Substitution)	Pleurothallis aspergillum Luer & Hirtz	Substitution (Misidentification) of Pleurothallis aspergillum Luer & Hirtz	Not detected / Not known	Analytical development (DNA-HPLC)	2020	Combination of c oxidase subunit I based deoxyribonucleic acid barcoding and HPLC techniques for the identification and quality evaluation of Pheretima aspergillum	(X. Liu et al., 2020)
Adulteration (Substitution)	Herba Dendrobii (Shihu) i	Substitutionof Herba Dendrobii (Shihu) with other non-orchids and Pholidota	Not Detected (not possible)	Analytical developemtn (DNA)	2001	Authentication of medicinal Dendrobium species by the internal transcribed spacer of ribosomal DNA	(D. T. W. Lau, Shaw, Wang, & But, 2001)
Adulteration (Substitution)	Illicium verum (Chinese star anise)	Substitution of I. verum with toxic Illicium anisatum (Japanese star anise)	Not Detected	Analytical development (combined LC-MS and imaging)	2013	Hyperspectral imaging in the quality control of herbal medicines - The case of neurotoxic Japanese star anise	(Vermaak, Viljoen, & Lindstrom, 2013)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Substitution)	Panax ginseng C.A. Meyer and Panax quinquefolius L.	Adulteration of ginsengs with sawadust and Platycodon grandiflorum	Value motiviation and not detected	Analytical development (IR-Chemometrics)	2010	A rapid and reliable UPLC-MS/MS method for the identification and quantification of fourteen synthetic anti-diabetic drugs in adulterated Chinese proprietary medicines and dietary supplements	(N. Li et al., 2010)
Adulteration (Substitution)	Panax notoginseng (Burkill) F.H.Chen ex C.Y.Wu & K.M.Feng	Substitution of Notoginseng Sophora flavescens powder, corn flour and other low grade adulterants	Not detected	Analytical development (NIR-Chemometrics)	2019	Quantifying several adulterants of notoginseng powder by near-infrared spectroscopy and multivariate calibration	(H. Chen, Tan, Lin, & Li, 2019)
Adulteration (Substitution)	Rhodiola rosea L. and Rhodiola crenulata (Hook. f. & Thomson) H. Ohba	Adulteration of Rhodiola species	Value motiviation and not detected	Study quality issues in context of whole supply chain (value chain)	2016	From Traditional Resource to Global Commodities: - A Comparison of Rhodiola Species Using NMR Spectroscopy - Metabolomics and HPTLC	(Booker, Zhai, et al., 2016)
Adulteration (Substitution)	Rhodiola rosea L. Crassulaceae	Substiution of Rhodiola rosea L. Crassulaceae with Rhodiola crenulata (Hook. f. & Thomoson)	Value motivation and not detected	Good quality systems and manufacturing practice improvemnents	2016	The authenticity and quality of Rhodiola rosea products	(Booker, Jalil, et al., 2016)

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Adulteration (Substitution)	Panax ginseng C.A. Meyer	Panax ginseng C.A. Meyer substitution	Not detected due to similar appearace	Analytical development (Mutli-hyphenated - UHPLC-TOF/MS coupled with Chemometrics)	2017	A new approach for authentication of four ginseng herbs and their related products based on the simultaneous quantification of 19 ginseng saponins by UHPLC-TOF/MS coupled with OPLS-DA	(B. M. Huang et al., 2017)
Adulteration (Substitution)	Pulsatilla chinensis (Bge.) Regel	93% of 30 samples surveyed were Substituted	Not Detected	Analytical development (DNA)	2017	Rapidly discriminate commercial medicinal Pulsatilla chinensis (Bge.) Regel from its adulterants using ITS2 barcoding and specific PCR-RFLP assay	(Y. H. Shi et al., 2017)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Adulteration (Substitution)	Pinelliae Rhizoma (Banxia)	Pinelliae Rhizoma (Banxia) adulterated with Pinelliapedatisecta (found in 57% of the assayed products), Arisaemaerubescens (9%), Typhoniumgiganteum (2%) and Typhoniumflagelliforme (2%)	Difficult to detect	Analytical development(DNA)	2022	A nucleotide signature for the identification of Pinelliae Rhizoma (Banxia) and its products	(T. Zhang et al., 2022)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) five nonsteroidal anti-inflammatory drugs (NSAIDs) and two glucocorticoids	Not detected / Not known	Analytical development (LC-MS)	2011	SIMULTANEOUS DETERMINATION OF FIVE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND TWO GLUCOCORTICOIDS IN ADULTERATED TRADITIONAL HERBAL MEDICINES FOR THE TREATMENT OF RHEUMATISM	(C. Y. Zhang, Chang, & Chen, 2011)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) acetaminophen, piroxicam, hydrochlorothiazide	Not detected / Not known	Analytical development (TLC)	1996	Quantitative analysis of acetaminophen, ethoxybenzamide, piroxicam, hydrochlorothiazide, caffeine, chlorzoxazone and nicotinamide illegally adulterated in Chinese medicinal pills	(Tseng, Tsai, & Wen, 1996)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) steroids	Difficult to detect	Pharmacovigilance	2017	Steroids in traditional Chinese medicine: what is the evidence?	(F. Y. Fung & Linn, 2017)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration with 18 synthetic drugs	Difficult to detect	Analytical development (LC-MS)	2010	Detection of adulteration of anti-hypertension dietary supplements and traditional Chinese medicines with synthetic drugs using LC/MS	(Y. L. Lu et al., 2010)
Adulteration (Synthetic drugs)	Multiple CMP	Review of adulteration (Synthetic antidiabetic drugs) in TCM formuala from years 2005 to 2010	Not detected	Education and regulation	2012	Adulteration of herbal antidiabetic products with undeclared pharmaceuticals: a case series in Hong Kong	(Ching, Lam, Chan, & Mak, 2012)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (Synthetic drugs)	"Gold Nine capsules"	Analysis of Anti-hypertensive drugs: amlodipine, indapamide and valsartan	Not Detected (not recorded)	Analytical development (HPLC-MS-NMR)	2010	Identification of adulterants in a Chinese herbal medicine by LC-HRMS and LC-MS-SPE/NMR and comparative in vivo study with standards in a hypertensive rat model	(Kesting, Huang, & Sorensen, 2010)
Adulteration (Synthetic drugs)	Multiple CMP	Review of Chinese herbal slimming capsule adverse event adulterated with synthetic drug substances atomoxetine and methylphenidate and with citalopram, olanzapine, and chlorprothixene	Not detected / Difficult to detect	Legislation for labelling	2009	Chinese Slimming Capsules Containing Sibutramine Sold Over the Internet A Case Series	(Muller, Weinmann, & Hermanns-Clausen, 2009)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) multiple	Not detected / Not known	Analytical development (FTIR-Chemometrics)	2007	Discrimination of adulterated traditional chinese medicines by infrared Spectroscopy-Two dimensional correlation analysis	(S. Li, Le, Chen, Chai, & Lu, 2007)

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Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) antihypertensive	Not detected / Not known	Analytical development (MS - Compound Database)	2020	Targeted and nontargeted screening and identification of 50 antihypertensive adulterants in dietary supplements and herbal medicines using quadrupole-orbitrap high resolution mass spectrometry with compound database	(C. Guo et al., 2020)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (undeclared pharmaceutical drugs) Sibutramine and others	Difficult to detect	Public education and effective regulatory measures	2018	Adulteration of proprietary Chinese medicines and health products with undeclared drugs: experience of a tertiary toxicology laboratory in Hong Kong	(C. K. Ching et al., 2018)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs)	Not detected / Difficult to detect	Analytical development (UHPLC-MS)	2018	Simultaneous analysis of 23 illegal adulterated aphrodisiac chemical ingredients in health foods and Chinese traditional patent medicines by ultrahigh performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry	(X. B. Wang et al., 2018)

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Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) nicardipine hydrochloride, doxazosin mesylate	Not detected / Not known	Analytical development (TLC-SERS)	2014	Rapid Detection of Four Antipertensive Chemicals Adulterated in Traditional Chinese Medicine for Hypertension Using TLC-SERS	(Q. X. Zhu, Cao, Cao, & Lu, 2014)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) non-steroidal and anti-inflammatory	Value motiviation and not detected	Pharmacovigilance and education	2018	Re: Adulteration of Proprietary Chinese Medicines and Health Products with Undeclared Drugs: Experience of a Tertiary Toxicology Laboratory in Hong Kong	(Seftel, 2018)
Adulteration (Synthetic drugs)	Formulas Zhong Gan Ling and Formula Suxiao Gan Mao Pian (Yulin)	Adulteration (undeclared pharmaceutical drugs) sildenafil	Not Detected	Analytical development (LC-MS)	2006	Application of LC-ESI-MS-MS for detection of synthetic adulterants in herbal remedies	(Bogusz et al., 2006)
Adulteration (Synthetic drugs)	Multiple CMP	Review of Adulteration with syntetic drugs	Not Detected	Analytical developemtn (HPLC-MS)	2009	Determination of synthetic drugs used to adulterate botanical dietary supplements using QTRAP LC-MS/MS	(Y. Chen et al., 2009)

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Adulteration (Synthetic drugs)	Multiple CMP	Review of adulteration (Synthetic drugs) in Asian herbal medicines including chinese slimming aids containing N-nitrose-fenfluramine.	Low public awareness of risks	Education and improved licensing of practitioners	2002	Risks associated with herbal slimming remedies	(C. Corns & Metcalfe, 2002)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) steroids	Not detected / Not known	Clinical surveillance	2015	Corticosteroid adulteration in proprietary Chinese medicines: a recurring problem	(Chong, Ching, Ng, & Mak, 2015)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) antipyretic-analgesic	Not detected / Not known	Analytical development (Raman-SERS)	2014	Aminopyrine Raman spectral features characterised by experimental and theoretical methods: toward rapid SERS detection of synthetic antipyretic-analgesic drug in traditional Chinese medicine	(L. Zheng et al., 2014)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) for Thyroid	Difficult to detect	Correct labelling and Pharmacovigilance	2013	Adulteration of products sold as Chinese Herbal medicines for weight loss with thyroid hormones and PCP	(Khazan, Hedayati, Askari, & Azizi, 2013)

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Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) sleep drugs	Not detected / Not known	Analytical development (TLC-SERS onsite)	2018	Rapid on-site TLC-SERS Detection of Four Sleep Problems Drugs Used as Adulterants in Health-Care Food	(J. H. Li, Cheng, Liu, Li, & Jia, 2018)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration (Synthetic drugs) triazolam, estazolam, clonazepam and oxazepam	Not detected / Not known	Analytical development (2D-TLC)	1997	Quantitative analysis of caffeine, ethoxybenzamide, chlorzoxazone, diazepam and indomethacine illegally adulterated in Chinese medical pills	(Tsene, Tsai, & Wen, 1997)
Adulteration (Synthetic drugs)	Zhen Qi formula conttaining ginseng, pearl, ram's horn, bark, frog extract	Cognative distubance, chest pain, hypoglycemia from Glibenclamide contained in ormuala	increase efficacy	Not specified	2001	Contaminated medication precipitating hypoglycaemia. MJA 2001; 175: 257. in Ernst, 2002a	(Goudie & Kaye, 2001)
Adulteration (Synthetic drugs)	Jiangtangning capsules	Jiangtangning capsules adulterated with metformin hydrochloride	Difficult to detect / unknown	Analytical development(Machine Learning)	2022	Detection of adulterants in medicinal products by infrared spectroscopy and ensemble of window extreme learning machine	(Hui Chen, Huang, Lin, & Tan, 2022)

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Adulteration (Synthetic drugs)	Multiple CMP	Patent CMP adulteratioed with 28 types of corticosteroids	Value motivation and difficult to detect	Analytical development(LC-MS)	2021	Detection of 28 Corticosteroids in Pharmaceutical and Proprietary Chinese Medicinal Products Using Liquid Chromatography-Tandem Mass Spectrometry	(C. Y. Chan, Ng, Ching, & Mak, 2021)
Adulteration (Synthetic drugs)	Multiple CMP	Adulteration of Patent Herbal Medicine with glibenclamid	Difficult to detect	Analytical development(ATR-MIR)	2021	Detection of glibenclamide adulterated in antidiabetic Chinese patent medicine by attenuated total reflectance -infrared spectroscopy and chemometrics	(C. Tan, Chen, & Lin, 2021)
Adulteration (Toxic heavy metals and synthetic drugs)	Formula Yan Sheng Hu Bao Jiao Nang (Shen Yang Tonic Fei Longa)	Adulteration of herbs with Berberine	Not Detected	Clinical surveillance	2000	Chinese proprietary medicine in Singapore - Regulatory control of toxic heavy metals and undeclared drugs	(Koh & Woo, 2000)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adulteration (undeclared pharmaceutical drugs, including anti-inflammatories, steroids, and analgesics)	Multiple CMP	Pharmaceutical drugs	Not Detected	Better Pharmacovigilance and product labelling	1997	Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan	(W. F. Huang, K. C. Wen, & M. L. Hsiao, 1997)
Adulteration and contamination	Astragalus membranaceus var. mongholicus (Bunge) P.K. Hsiao	Adulteration of Astragalus membranaceus var. mongholicus (Bunge) P.K. Hsiao	Value motivation and not detected	Supply chain study and pharmacovigilance	2020	Quality Control of Radix Astragali (The Root of Astragalus membranaceus var. mongholicus) Along Its Value Chains	(Y. Q. Bi et al., 2020)
Adulteration and risk of incorrect prescriptions	Multiple CMP	Review of safety issues with herbal medicine	Not proposed	Reporting and recording of quality and safty issues improved	1997	Safety issues in herbal medicine: Implications for the health professions	(Drew &Myers, 1997)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Adverse events (Cardiac, CNS and Hepatoxicity)	Ephedra sinica	alkaloids ephedrine and pseudoephedrine	High potency in dietary supplements	Legislation (restricted use)	2010	Acute effects of *Ephedra* on autonomic nervous modulation in healthy young adults. *Clin. Pharmacol. Ther.* 88, 39–44. doi: 10.1038/clpt.2010.66, Hackman, R. M., Havel, P. J., Schwartz, H. J., Rutledge, J. C., Watnik, M. R., Noceti, E. M., et al. (2006). Multinutrient supplement containing Ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial. Int. J. Obes. 30, 1545–1556. doi: 10.1038/sj.ijo.0803283, Hallas, J., Bjerrum, L., Stovring, H., and Andersen, M. (2008). Use of a prescribed ephedrine/caffeine combination and the risk of serious cardiovascular events: a registry-based case-crossover study. Am. J. Epidemiol. 168, 966–973. doi: 10.1093/aje/kwn191 in Ekor, 2014	(W. L. Chen et al., 2010)
Adverse events (Cardiac)	Gan Cao (Liquorice root)	hypertesion, arrhythmia in drug trial	Drug interaction with prednisolone	Not specified	1995	Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. J Pharm Pharmacol. 1995;47: 687–692. in Ernst, 1998	(Homma et al., 1995)

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Adverse events (Cushing's syndrome)	Formual Chuei-Fong - Tou-Geu-Wan	Cushing's syndrome reported from Dexamethasone, indomethacin added to formula	Value motivation and difficult to detect	Pubic warnings	2002	Chuei-Fong-Tou-Geu-Wan in rheumatoid arthritis. BMJ 1979; ii: 308 and Offerhaus L, Dukes MNG. 'Herbal' medicines and rheumatoid arthritis. BMJ 1979; ii: 668, in Ernst 2002a	(Forster, Calverley, Hubball, & McConkey, 1979)
Adverse events (General)	Multiple CMP	Adverse events (General)	Not detected / Not known	Regulation and Education	2013	Acute adverse events from over-the-counter Chinese herbal medicines: a population-based survey of Hong Kong Chinese	(J. H. Kim et al., 2013)
Adverse events (General)	Multiple CMP	Adverse events (General)	Not detected / Not known	Pharmacovigilance	2018	Retrospective Study of Reported Adverse Events Due to Complementary Health Products in Singapore From 2010 to 2016	(Y. M. Xu et al., 2018)
Adverse events (General)	Multiple CMP	Toxicity (adulteration)	Not detected / not known	Pharmacovigilance	2018	Potential forensic issues in overseas travellers exposed to local herbal products	(Farrington, Musgrave, Nash, & Byard, 2018)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED							
CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Adverse events (Hepatoxicity)	She xiang (Moschus, secretio)	Hepatoxicity CYP450 modification	Drug interaction (liver clearance reduced)	Restricted usage	2000	Risks Associated with the Practice of Traditional Chinese Medicine - an Australian Study." *Archives of Family Medicine* 9, no. 10 (Nov-Dec 2000): 1071-78. https://doi.org/10.1001/archfami.9.10.1071. <Go to ISI>://WOS:000165934400020.	(Bensoussan et al., 2000)
Adverse events (Nephrotoxic)	Tung Shueh herbal pills	Adulteration (Synthetic drugs)	Difficult to detect	Pharmacovigilance	2000	Clinical and Laboratory Investigations in Herbal Poisonings	(Bensoussan et al., 2000)
Adverse events (pain, CNS, vascular and haematological)	Ginseng (Panax quinquefolius, Panax Ginseng, and Panax pseudoginseng)	Not specified	High potency usage	Increased pharmacovigalence and training	2013	What pharmacists should know about Ginseng. Pharm. J. 237, 583–586 and Dunnick, J. K., and Nyska, A. (2013). The toxicity and pathology of selected dietary herbal medicines. Toxicol. Pathol. 41, 374–386. doi: 10.1177/0192623312466451 in Ekor, 2014	(Baldwin, Anderson, & Phillipson, 1986)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Adverse events (Renal toxicity)	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	aristolochic acids nephrotoxic and carcinogenic	Misidentification (similar name)	Legislation (restricted use)	2020	A Fatal Case of Aconite Poisoning: Accidental Intake of a Monkshood Extract." *Forensic Toxicology* 38, no. 2 (2020/07/01 2020): 511-16. https://doi.org/10.1007/s11419-020-00526-x. https://doi.org/10.1007/s11419-020-00526-x.	(Hofmann et al., 2020a)
Adverse events (Toxicity)	Datura/Brugmansia poisoning	Poisoning from 203 cases involving 114 Datura exposures and 89 Brugmansia suaveolens	Unknown / undetected toxicity	Supervised prescription by TCM Practitioner	2019	Datura and Brugmansia plants related antimuscarinic toxicity: an analysis of poisoning cases reported to the Taiwan poison control center	(Doan et al., 2019)
Case study	Bajiaolian rhizome Dysosma pleianthum	Adverse CNS and multi-symptom effects	Intrinsic toxicity	Analytical testing and herbal screening	1992	Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. In Deng, 2002 Human & experimental toxicology, 11(6), 480-487.	(Kao, Hung, Tsai, Lin, & Deng, 1992)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Clinical blood test	Formual Chuifong Toukuwan	Agranulocytosis reported from Phenylbutazone, phenacetin, aminopyrine added to formuala	Value motivation and difficult to detect	Not specified	2002	Chinese herbal arthritis cure and agranulocytosis. Med J Aust 1977; 2: 860–1. in Ernst, 2002a	(Brooks & Lowenthal, 1977)
Contamination (Viral)	Paris yunnanensis	Viral contamination (diseased) Paris yunnanensis	Unknown / undetected	Analytical development(DNA)	2022	High-throughput sequencing reveals the presence of novel and known viruses in diseased Paris yunnanensis	(Lan et al., 2022)
Misidentification	Lonicerae Japonicae	Poor quality characterisation and non-detection	Not Detected	Analytical development (New HPLC-MS method)	2013	Diagnostic fragment-ion-based and extension strategy coupled to DFIs intensity analysis for identification of chlorogenic acids isomers in Flos Lonicerae Japonicae by HPLC-ESI-MSn	(J. Y. Zhang et al., 2013)
Misidentification	Uncaria (Rubiaceae)	Species Substitutionof Uncaria (Rubiaceae)	Not detected / Difficult to detect	Analytical development (DNA)	2018	Phylogenetic analysis of Uncaria species based on internal transcribed spacer (ITS) region and ITS2 secondary structure	(S. Zhu et al., 2018)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Misidentification	G. dahurica, G. siphonantha and G. officinalis	Development of a DNA methods to aid identificaiotn	Not Detected (not possible)	Analytical development (DNA)	2018	Comparative Chloroplast Genome Analyses of Species in Gentiana section Cruciata (Gentianaceae) and the Development of Authentication Markers	(T. Zhou et al., 2018)
Misidentification	Celosia argentea	Celosia argentea commonly misidentifed with Celosia cristata seed (CCS), Amaranthus tricolor seed (ATS), Amaranthus retroflexus seed (ARS), Amaranthus cruentus seed (ACS), and Amaranthus spinosus seed (ASS).	Difficult to detect similar looking species	Analytical developemtn (HPLC-QTOF-MS/MS)	2022	Precise identification of Celosia argentea seed and its five adulterants by multiple morphological and chemical means	(J. X. Sun et al., 2022)
Misidentification	Fritillaria spp. Chuanbeimu, Hubeibeimu, Pingbeimu, Yibeimu, Zhebeimu	Misidentification of Regional Fritillaria spp. Chuanbeimu, Hubeibeimu, Pingbeimu, Yibeimu, Zhebeimu	Difficult to detect similar looking species	Analytical development(Colourimetric-pH)	2021	Rapid Discrimination of Fritillary Herbs by A Photochemical Colorimetric Sensor Array	(M.-Y. Jia, Yang, Peng, Mei, & Feng, 2021)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Misidentification	Conioselinum vaginatum, Ligusticum sinense, and Ligusticum jeholense	Developemnt of methods for differentiating misidentified Conioselinum vaginatum, Ligusticum sinense, and Ligusticum jeholense	Difficult to detect similar appearance	Analytical development(DNA)	2022	Molecular Structure and Phylogenetic Analyses of the Complete Chloroplast Genomes of Three Medicinal Plants Conioselinum vaginatum, Ligusticum sinense, and Ligusticum jeholense	(X. P. Wei et al., 2022)
Misidentification	Euphorbia Spp.	Developemnt of a methods to differentiate Euphorbia fischeriana and Euphorbia ebracteolata commonly misidentifed	Difficult to detect similar looking and named species	Analytical development(DNA)	2022	Comparative Transcriptomics and Metabolites Analysis of Two Closely Related Euphorbia Species Reveal Environmental Adaptation Mechanism and Active Ingredients Difference	(H. Zheng et al., 2022)
Misidentification (toxic species)	Caulis clematidis armandii), named "Chuan-Mu-Tong"	Clemetis spp. misidentifed as Guan-Mutong (Aristolochia manshuriensis),	Difficult to detect similar looking and named species	Analytical developmentFTIR)	2021	Comparison of FTIR spectrum with chemometric and machine learning classifying analysis for differentiating guan-mutong a nephrotoxic and carcinogenic traditional chinese medicine with chuan-mutong	(C. S. Tan et al., 2021)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substituion	Psammosilene tunicoides W.C.Wu & C.Y.Wu	Species Substitution Psammosilene tunicoides W.C.Wu & C.Y.Wu with Silene viscidula Kom.	Not detected / Difficult to detect	Analytical development (DNA)	2016	Application of barcode high-resolution melting for rapid authentication of the medicinal plant Psammosilene tunicoides	(J. J. Li, Song, Xiong, Zhao, & Sun, 2016)
Species Substituion	Hyoscyamus niger L.	Species Substitution Hyoscyamus niger L.	Not detected / Difficult to detect	Analytical development (DNA - Melting point)	2016	ITS2 barcoding DNA region combined with high resolution melting (HRM) analysis of Hyoscyami Semen, the mature seed of Hyoscyamus niger	(C. Xiong et al., 2016)
Species Substituion	Glycyrrhiza species	Species Substitution Glycyrrhiza species	Not detected / Difficult to detect	Analytical development (DNA - Melting point)	2018	Using SSR-HRM to Identify Closely Related Species in Herbal Medicine Products: A Case Study on Licorice	(J. J. Li et al., 2018)
Species Substituion	Illicium verum Hook.f.	Species Substitutionof Illicium verum Hook with Illicium religiosum	Not detected / Difficult to detect	Not proposed	2011	Apparent life-threatening event in infants: Think about star anise intoxication!	(Perret, Tabin, Marcoz, Llor, & Cheseaux, 2011)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substituion	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	Species Substitution(misidentification) Stephania tetrandra ("hang fang ji") and Aristolochia fangchi ("guang fang ji")	Not detected due to misidentifictio n of closely related species	Analytical development (Hyperspectra imaging)	2016	Differentiation between two fang ji herbal medicines, Stephania tetrandra and the nephrotoxic Aristolochia fangchi, using hyperspectral imaging	(S. Tankeu, I. Vermaak, W. Chen, M. Sandasi, & A. Viljoen, 2016)
Species Substituion	Curcuma longa L.	Species Substitution Curcuma longa L.	Not detected / Difficult to detect	Analytical development (DNA)	2016	Development of intron length polymorphism markers in genes encoding diketide-CoA synthase and curcumin synthase for discriminating Curcuma species	(Kita et al., 2016)
Species Substituion	Schisandrae Chinensis Fructus	Species Substitution Schisandrae Chinensis Fructus with Schisandrae Sphenantherae Fructus	Not detected / Difficult to detect	Analytical development (DNA)	2019	Detecting Schisandrae Chinensis Fructus and Its Chinese Patent Medicines with a Nucleotide Signature	(W. J. Jiang et al., 2019)
Species Substituion	Schisandra chinensis (Turcz.) Baill.	Substiution of Schisandra chinensis (Turcz.) Baill. with Schisandra sphenanthera Rehder & E.H.Wilson	Difficult to detect similar looking and named species	Analytical development (HPLC-DAD-MS)	2016	Authentication of Schisandra chinensis and Schisandra sphenanthera in Chinese patent medicines	(P. Jiang, Y. Lu, & D. Chen, 2016)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substituion	Herba Dendrobii	Species Substitution Herba Dendrobii with P. articulata and F. comate	Not detected / Difficult to detect	Analytical development (DNA)	2012	Internal Transcribed Spacer Sequence Based Identification and Phylogenic Relationship of Herba Dendrobii	(C. T. Wu et al., 2012)
Species Substituion	Panax ginseng C.A. Meyer	Species Substitution Panax ginseng C.A. Meyer	Not detected / Difficult to detect	Analytical development (FTIR-Chemometrics)	2008	The reliability of traditional authentication - A case of ginseng misfit	(K. Y. L. Yap et al., 2008)
Species Substituion	Lycium chinense Mill.	Substiution of Lycium chinense Mill.with Lycium barbarum Mill.	Not detected - similar appearance	Analytical development (DNA)	2018	Goji Who? Morphological and DNA Based Authentication of a Superfood	(Wetters, Horn, & Nick, 2018)
Species Substituion	Lycium chinense Mill.	Adulteration of Lycium chinense Mill. With multiple adulterants	Not detected - similar appearance	Analytical development (UHPLC-Q-TOF-MS)	2020	Discovery and validation of biomarkers for Zhongning goji berries using liquid chromatography mass spectrometry	(W. Lv et al., 2020)
Species Substitution(Misidentification)	Panax ginseng C.A. Meyer	Species Substitution Ginsengs	Value motivation and not detected	Analytical development (IR)	2007	Authentication of traditional Chinese medicine using infrared spectroscopy: distinguishing between ginseng and its morphological fakes	(K. Y. L. Yap et al., 2007)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substitution(Misidentification)	Bupleurum kaoi Liu, C.Y.Chao & Chuang	Substitution of B. kaoi Liu, C.Y.Chao & Chuang with B. falcatum L. and B. chinense DC.	Profit motivation and difficult to detect	Analytical development (DNA)	2008	Rapid authentication of Blupleurum species using an array of immobilized sequence-specific oligonucleotide probes	(W. Y. Lin, Chen, & Lin, 2008)
Species Substitution(Misidentification)	Adenophora stricta Miq.	Substitution (Misidentification) of Adenophora stricta Miq.	Not deteected / Not known	Analytical development (DNA)	2017	Differentiating Authentic Adenophorae Radix from Its Adulterants in Commercially-Processed Samples Using Multiplexed ITS Sequence-Based SCAR Markers	(Moon et al., 2017)
Species Substitution(misidentification)	Fritillariae Cirrhosae Bulbus	Substitution of Fritillariae Cirrhosae Bulbus with other material	Difficult to detect similar looking and named species	Analytical development (UPLC-ELSD)	2018	Rapid identification of Fritillariae Cirrhosae Bulbus and its adulterants by UPLC-ELSD fingerprint combined with chemometrics methods	(D. D. Luo et al., 2018)
Species Substitution(misidentification)	Illicium verum Hook.f.	Species Substitution of Chinese Star anise with Japanese equivalent	Accepted substitution (pharmacopeia)	Not proposed	2003	Star anise poisoning in infants	(Minodier et al., 2003)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substitution(misidentification)	Lonicerae Japonicae Flos	Substitution of Lonicerae Japonicae Flos with other Lonicera species	Difficult to detect similar looking species	Analytical development (FTIR hand held)	2017	Rapid and automatic chemical identification of the medicinal flower buds of Lonicera plants by the benchtop and hand-held Fourier transform infrared spectroscopy	(J. Chen, Guo, Yan, Sun, & Zhou, 2017)
Species Substitution(misidentification)	Astragalus membranaceus var. mongholicus	Species Substitution(misidentification) of Astragalus membranaceus var. mongholicus seeds with other close species	Difficult to detect similar looking species	Analytical development(hyperspectral imaging (HSI)	2022	Hyperspectral imaging with machine learning for non-destructive classification of Astragalus membranaceus var. mongholicus, Astragalus membranaceus, and similar seeds	(Y. Xu et al., 2022)
Species Substitution(misidentification)	Fritillariae cirrhosae bulbus	laser-induced breakdown spectroscopy (LIBS); learning vector quantization; chemometric models; robustness of model	Difficult to detect similar looking species	Analytical development (LIBS-LVQ)	2021	Distinguish Fritillaria cirrhosa and non-Fritillaria cirrhosa using laser-induced breakdown spectroscopy	(Kai et al., 2021)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substitution(misidentification)	Fritillariae cirrhosae bulbus	Fritillariae cirrhosae bulbus; MLPA-HRM; Simultaneous identification method; Traditional Chinese medicine	Difficult to detect similar looking species	Analytical development(MLPA-HRM)	2021	Simultaneous identification of Fritillariae cirrhosae bulbus and its common adulterants in one reaction by multiplex ligation-dependent probe amplification and high-resolution melting curve assay	(H. Zhu, Wang, Zhou, Wang, & Nie, 2021)
Species Substitution(Value)	Zanthoxylum schinifolium f. microphyllum (Nakai ex T.Mori) W.Lee	Adulteration of Zanthoxyli Pericarpium with cheaper materail	Difficult to detect	Analytical development (Imaging)	2020	Identification of different species of Zanthoxyli Pericarpium based on convolution neural network	(C. Q. Tan et al., 2020)
Species Substitution(Value)	Ophiocordyceps sinensis syn. Miscanthus sinensis var. sinensis Andersson	Substitution of Ophiocordyceps sinensis with similar looking material	Profit motivation and difficult to detect	Analytical development (DNA)	2017	Detection of Ophiocordyceps sinensis and Its Common Adulterates Using Species-Specific Primers	(Y. Liu, Wang, Gao, Han, & Xiang, 2017)
Species Substitution(Value)	Rhizoma Paridis syn. Macromitrium paridis Besch.	Rhizoma Paridis (Chonglou) with seven simialr looking species and herbal material	Not detected - similar appearance	Analytical development (DNA Barcoding and Melting point analysis)	2018	Authenticity analyses of Rhizoma Paridis using barcoding coupled with high resolution melting (Bar-HRM) analysis to control its quality for medicinal plant product	(B. Z. Duan et al., 2018)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Species Substitution(Value)	Chaenomelis Fructus	Subsitution of Chaenomelis Fructus with its Common Adulterant, Guangpi Mugua	Value motivation and difficult to detect	Analytical development(TLC-HPLC)	2021	Differentiation Between Chaenomelis Fructus and its Common Adulterant, Guangpi Mugua	(Lyu et al., 2021)
Species Substitutionof Ginsengs	Panax ginseng C.A. Meyer	Panax ginseng C.A. Meyer substitution with Panax quinquefolius L.	Not detected - similar appearance	Analytical development (NMR with Chemometrics)	2015	Metabolomic quality control of commercial Asian ginseng, and cultivated and wild American ginseng using H-1 NMR and multi-step PCA	(H. Y. Zhao, Xu, Ghebrezadik, & Hylands, 2015)
Species substitution	Ziziphi Spinosae Semen	Adulteration (Substitution) of Ziziphi Spinosae Semen	Not detected / Difficult to detect	Analytical development (UPLC-MSS)	2016	Rapid characterization of Ziziphi Spinosae Semen by UPLC/Qtof MS with novel informatics platform and its application in evaluation of two seeds from Ziziphus species	(F. X. Zhang et al., 2016)
Species substitution (error)	Schisandra chinensis (Turcz.) Baill.	Substitution of Schisandra chinensis (Turcz.) Baill. with similar looking species	Not detected due to misidentification of closely related species	Analytical development (DNA)	2015	Evaluation of Four Commonly Used DNA Barcoding Loci for Chinese Medicinal Plants of the Family Schisandraceae	(J. Zhang et al., 2015)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution (Scarcity)	Swertia cordata Wall.	Substitution of S. cordata Wall. with S. paniculata	Value motivation and not detected	Analytical development (Microscopic - Hyphenated with Analytical instruments)	2019	Microscopic and phytochemical techniques as a tool for authentication of herbal drug chiraita: Swertia cordata (G. Don) CB Clarke	(Rashid et al., 2019)
Substitution (Value)	Dimocarpus longan Lour.	Substitution of Dimocarpus longan Lour. with cheaper material	Difficult to detect similar appearance	Analytical development (DNA)	2020	Accurate and Rapid Identification of Longan Arillus and Litchi Semen by a Multiplex PCR Assay	(W. J. Kim et al., 2020)
Substitution (Value)	hyriopsis cumingii	Substitution(Value) Pearl powder by shells	Not detected / Difficult to detect	Analytical development (IE and E-eye with chemometrics)	2018	Rapid identification of pearl powder from Hyriopsis cumingii by Tri-step infrared spectroscopy combined with computer vision technology	(S. Q. Liu et al., 2018)
Substitution (Value)	Dendrobium huoshanense	Substitution of Dendrobium huoshanense with cheaper Dendrobium henanese	Value motiviation and not detected	Analytical development(NIR)	2021	Rapid Detection of Adulteration in Dendrobium huoshanense Using NIR Spectroscopy Coupled with Chemometric Methods	(J. W. Hao et al., 2021)

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CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Substitution (Value)	Panax notoginseng	Substitution of Panax notoginseng with chaper species: rhizoma curcumae (RC), Curcuma longa (CL) and rhizoma alpiniae officinarum (RAO)	Value motiviation and not detected	Analytical development (UV-Vis) diffuse reflectance	2022	Rapid quantification of adulterated Panax notoginseng powder by ultraviolet-visible diffuse reflectance spectroscopy combined with chemometrics	(Xi-Hui et al., 2022)
Substitution (Value)	Paris yunnanensis	Substitution of different species of high value Scutellaria including tsinyunensis and Scutellaria tuberifera (Lamiaceae)	Value motiviation and not detected	Analytical development (DNA)	2021	Analysis of the complete chloroplast genomes of Scutellaria tsinyunensis and Scutellaria tuberifera (Lamiaceae)	(Y. Shan et al., 2021)
Substitution	Black cohosh (Actaea racemosa L.)	Other Actaea species substiuted for racemosa	Analytical fraud	Analytical testing (DNA)	2011	Phytochemical fingerprinting to thwart black cohosh adulteration: a 15 Actaea species analysis. Phytochem Anal 2011;22:339–51. in Mudge, 2016	(B. Jiang et al., 2011)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution (Misidentification)	Portulaca oleracea	Portulaca oleracea substituted with Bacopa monnieri (BM)	Difficult to detect similar looking species	Analytical development (DNA)	2022	Molecular authentication of the medicinal crop Portulaca oleracea and discrimination from its adulterants in herbal markets using PCR-restriction fragment length polymorphism (PCR-RFLP) analysis	(M.-R. Xu et al., 2022)
Substitution (Regional)	Gastrodia elata Blume	Substitution of with regional substututes for Gastrodia elata Blume	Difficult to detect similar looking species	Analytical development (NIR-Chemometrics)	2017	Fine classification and untargeted detection of multiple adulterants of Gastrodia elata Bl. (GE) by near-infrared spectroscopy coupled with chemometrics	(G. F. Li et al., 2017)
Substitution (Regional)	Angelica sinensis (Oliv.) Diels	Substitution (Regional) of Chinese with EU	Difficult to detect quality differences	Analytical development (NMR with fingerprinting)	2015	Comparative analysis of Danggui and European Danggui using nuclear magnetic resonance-based metabolic fingerprinting	(Z. Y. Li, Zhang, Du, & Qin, 2015)
Substitution (Regional)	Astragalus membranaceus Fisch. ex Bunge	Substitution (regional) Astragalus membranaceus Fisch. ex Bunge	Difficult to detect similar looking species	Analytical development (DNA)	2017	Nuclear magnetic resonance based metabolomic differentiation of different Astragali Radix	(A. P. Li, Li, Qu, Qin, & Du, 2017)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution (Regional)	Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. And Corydalis yanhusuo W. T. Wang	Substitution (regional) Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. And Corydalis yanhusuo W. T. Wang	Difficult to detect similar regional species	Analytical development (NIR-MIR)	2019	Rapid Recognition of Geoherbalism and Authenticity of a Chinese Herb by Data Fusion of Near-Infrared Spectroscopy (NIR) and Mid-Infrared (MIR) Spectroscopy Combined with Chemometrics	(Fu et al., 2019)
Substitution (Regional)	Ephedra sinica Stapf.	Substitution of Ephedra sinica Stapf with regional substitutes	Difficult to detect similar looking species	Analytical development (ICPMS-Fingerprinting)	2018	Discrimination of three Ephedra species and their geographical origins based on multi-element fingerprinting by inductively coupled plasma mass spectrometry	(X. F. Ma et al., 2018)
Substitution (Regional)	Dioscorea polystachya Turczaninow cv. Tiegun	Substitution of Dioscorea polystachya Turczaninow cv. Tiegun from regions	Difficult to detect similar regional species	Analytical development (NMR)	2021	H-1 NMR-based metabolic profiling approach to identify the geo-authentic Chinese yam (Dioscorea polystachya Turczaninow cv. Tiegun)	(Qiang Wang et al., 2021)

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Substitution (Regional)	Eucommia ulmoides	Eucommia ulmoides is substituted from other regions	Difficult to detect similar regional species	Analytical development (Emission fluorescence)	2022	Rapid identification of the geographical origin of Eucommia ulmoides by using excitation-emission matrix fluorescence combined with chemometric methods	(T. Liu et al., 2022)
Substitution (Regional)	Gastrodia elata spp.	Substitution of Gastrodia elata spp. with regional substitutes	Difficult to detect similar regional species	Analytical development (Fluorescence-LC)	2021	Fast identification of the geographical origin of Gastrodia elata using excitation-emission matrix fluorescence and chemometric methods	(Long et al., 2021)
Substitution (Regional)	Atractylodes macrocephala Koidz	Substitution of Atractylodes macrocephala Koidz from regions not specifed	Difficult to detect similar regional species	Analytical development (Florescence-Chemometrics)	2022	Geographical origin traceability of traditional Chinese medicine Atractylodes macrocephala Koidz. by using multi-way fluorescence fingerprint and chemometric methods	(Y.-Y. Chang et al., 2022)
Substitution (Regional)	Astragali Radix	Substitution of Astragali Radix with cultivated or other regional species	Difficult to detect similar regional species	Analytical development (UHPLC/Q-TOF-MS).	2022	Chemical comparison of Astragali Radix by UHPLC/Q-TOF-MS with different growing patterns	(L. Yang et al., 2022)

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CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution of species	Cynanchum wilfordii (Maxim.) Hemsl.	Species Substitution C. wilfordii with C. auriculatum	Not detected / Difficult to detect	Analytical development (DNA)	2018	Molecular Discrimination of Cynanchum wilfordii and Cynanchum auriculatum by InDel Markers of Chloroplast DNA	(Y. Kim et al., 2018)
Substitution of species	Brassica juncea (L.) Czern.	Substitution of species Brassica juncea (L.) Czern.	Difficult to detect similar appearance	Analytical development (DNA)	2018	Authentication of Brassicae Semen and Brassicae Campestris Semen by DNA Barcode Analysis	(Noh et al., 2018)
Substitution of species	Polygoni Multifiori Radix	Substitution of species Polygoni Multifiori Radix with Cynanchi Wilfordii Radix	Difficult to detect similar appearance	Analytical development (DNA-HPTLC)	2017	Survey on the Original Plant Species of Crude Drugs Distributed as Cynanchi Wilfordii Radix and Its Related Crude Drugs in the Korean and Chinese Markets	(Sato-Masumoto et al., 2017)
Substitution of species	Campsis grandiflora K.Schum.P	Substitution(Value) of Campsis grandiflora K.Schum. With toxic Flos Daturae Metelis	Error	Supply chain study, inspection and pharmacovigilance	2013	Chinese herbal medicine-induced anticholinergic poisoning in Hong Kong	(K. L. Cheng, Chan, Mak, Tse, & Lau, 2013)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution of species	Fritillariae Bulbus	Substitution of species Fritillariae Bulbus	Not detected / Difficult to detect	Analytical development (FT-NIR with chemometrics)	2018	Two-dimensional correlation spectroscopy reveals the underlying compositions for Fr-NIR identification of the medicinal bulbs of the genus Fritillaria	(J. B. Chen, Wang, Liu, Rong, & Wang, 2018)
Substitution of species	Hippophae rhamnoides L.	Substitution of species Hippophae rhamnoides L.	Not detected / Difficult to detect	Analytical development (FT-NIR with chemometrics)	2018	Rapid discrimination of sea buckthorn berries from different H. rhamnoides subspecies by multi-step IR spectroscopy coupled with multivariate data analysis	(Y. Liu et al., 2018)
Substitution of species	Amomum villosum Lour	Substitution of species Amomum villosum Lour	Difficult to detect similar appearance	Analytical development (DNA)	2009	Sequence Analysis Based on ITS1 Region of Nuclear Ribosomal DNA of Amomum villosum and Ten Species of Alpinia	(Qiao et al., 2009)
Substitution of species	Paris polyphylla Smith var. chinensis (Franck) Hara	Substitution of 8 Paris species	Difficult to detect similar appearance	Analytical development (DNA)	2019	From Electrophoresis Detection to Visual Judgment: New Application of SYBR Green I in the Authentication of the Traditional Medicine Rhizoma Paridis	(X. M. Yin et al., 2019)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution of species	Pinellia ternata (Thunb.) Makino	Substitution of species Pinellia ternata (Thunb.) Makino	Difficult to detect similar appearance	Analytical development (NIR-PCA-DA)	2020	Systematic vs. stepwise parameter optimization for discriminant model development: A case study of differentiatingPinellia ternatafromPinellia pedatisectawith near infrared spectroscopy	(F. Sun, Chen, Qiu, Wang, & Liang, 2020)
Substitution of species	Multiple CMP Flowers	Substitution (Misidentification) of Flower herbs	Difficult to detect similar appearance	Analytical development (DNA)	2019	Identification of flower herbs in Chinese pharmacopoeia based on DNA barcoding	(X. M. Wei et al., 2019)
Substitution of species	Ophiocordyceps sinensis	Substitution of Ophiocordyceps sinensis with cultured mycelia, and mimics	Value motiviation and Not detected due to similar appearace	Analytical development (combined LC-MS)	2015	A metabolomics approach for authentication of Ophiocordyceps sinensis by liquid chromatography coupled with quadrupole time-of-flight mass spectrometry	(J. K. Zhang et al., 2015)
Substitution of species	Rhodiola crenulata (Hook.f. & Thomson) H.Ohba	Substitution of species Rhodiola crenulata (Hook.f. & Thomson) H.Ohba with other Rhodiola species	Difficult to detect similar appearance	Analytical development (Multistep-IR)	2020	Rapid identification of three Rhodiola species by multi-step IR spectroscopy coupled with multivariate data analysis	(C. Tang et al., 2020)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Substitution of species	Isodon rubescens (Hemsley) H. Hara	Species Substitution of rubescens (Hemsley) H. Hara	Difficult to detect similar looking species	Analytical development(DNA)	2022	Comparative analysis of medicinal plant Isodon rubescens and its common adulterants based on chloroplast genome sequencing	(Z. Zhou et al., 2022)
Substitution (Plant parts)	Panax ginseng C.A. Meyer and Panax quinquefolius L.	Substitutionof Panax notoginseng aerial for root parts	Value motivation and difficult to detect	Analytical development(LC-MS)	2021	Ultra-high performance liquid chromatography/ion mobility time-of-flight mass spectrometry-based untargeted metabolomics combined with quantitative assay unveiled the metabolic difference among the root, leaf, and flower bud of Panax notoginseng	(W. Li et al., 2021)
Toxicity (Adulteration)	Multiple CMP	Review of multiple quality issues	Perception of "natural herbs are safe"	Not proposed	2012	Nephrotoxicity of Alternative Medicine Practice	(Luyckx, 2012)
Toxicity (Adulteration)	Multiple CMP	Review of role of forensic analysis in detecting toxic adulterants	Not investigated suffiently	Forensics improved	2010	A Review of the Potential Forensic Significance of Traditional Herbal Medicines	(Byard, 2010)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Toxicity (Adulteration)	Aconitum carmichaelii Debx.	Developemnt of method to detect Aconitum carmichaelii substitution	Difficult to detect similar looking and named species	Analytical development(UP LC-qToF-MS)	2021	Aconitum Diterpenoid Alkaloid Profiling to Distinguish between the Official Traditional Chinese Medicine (TCM) Fuzi and Adulterant Species Using LC-qToF-MS with Chemometrics	(Y. Shi et al., 2021)
Toxicity (adulteration)	LiDa Dai Dai Hua Jiao Nang Formula	Toxicity (adulteration)	Not detected / Not known	Pharmacovigilance	2009	Use of Chinese herbal medicine 'meizitanc' in pregnancy: Report of three cases	(Cayan, Dilek, Akbay, Gen, & Dilek, 2009)
Toxicity (Hepatoxicity)	Bupleuri radix and Scutellariae radix	Review (retrospective) liver injury from Chines herbal medicine	Perception of "natural herbs are safe"	Education	2009	Herbal Traditional Chinese Medicine and suspected liver injury: A prospective study	
Toxicity (Hepatoxicity)	Scutellaria lateriflora	Scutellaria lateriflora likely caused by germander substitution	Intrinsic toxicity	Not specified	2009	Comparison of the phenolic component profiles of skullcap (Scutellaria lateriflora) and germander (Teucrium canadense and T. chamaedrys), a potentially hepatotoxic adulterant. Phytochem Anal 2009;20:298–306. in Mudge, 2016	(L. Z. Lin et al., 2009)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Toxicity (intrinsic)	Aristolochia clematitis	Endemic (Balkan) nephropathy (EN) from bread ingestion	Toxicity of Aristolochia clematitis ingredients was unknown by bakers of bread	None suggested	2007	Aristolochic acid and the etiology of endemic (Balkan) nephropathy	(Grollman et al., 2007)
Toxicity (intrinsic)	Ginseng-Fuzi decoction	Variable toxicity of Fuzi with Ginseng and processing	Toxicity	Analytical development(MS)	2022	Discovery of the directionally detoxification effect and chemical mechanism of Ginseng-Fuzi co-decoction based on real-time online filtration electrospray ionization mass spectrometry	(Z. D. Qiu et al., 2022)
Toxicity (Multiple)	Multiple CMP	Review of Liver injury from CMP usage	Toxicity	Better detection and analysis. Mutiple recommendations	2018	Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury	(J. B. Wang et al., 2018)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Toxicity (pyrrolizidine alkaloid)	Gynura segetum	Hepatic toxicity from ingestion of PA containing Gynura segetum unintentionally in place of non-PA containing S. aizoon	Unknown / undetected substitution	Analytical development (New HPLC-MS method)	2011	Hepatic sinusoidal obstruction syndrome associated with consumption of Gynura segetum	(G. Lin et al., 2011)
Toxicity (Renal carcinogenic)	Stephania tetrandra S.Moore	Aristolochic acids nephrotoxic and carcinogenic	Not detected / not known	Analytical development (HPTLC)	2004	High performance thin-layer chromatographic analysis of aristolochic acids in Chinese drugs	(Blatter & Reich, 2004)
Toxicity (Renal carcinogenic)	Aristolochia fangchi Y.C.Wu ex L.D.Chow & S.M.Hwang	aristolochic acids nephrotoxic and carcinogenic	Misidentification (similar name)	Legislation (restricted use)	1993	RAPIDLY PROGRESSIVE INTERSTITIAL RENAL FIBROSIS IN YOUNG-WOMEN - ASSOCIATION WITH SLIMMING REGIMEN INCLUDING CHINESE HERBS	(J. L. Vanherweghem et al., 1993)
Toxicity (Neurotoxicity)	Aconitum carmichaeli Debx.	Toxicity (intrinisic CNS and others)	Unknown / undetected toxicity	Analytical development (Visible and NIR-Multi sensor with chemocmetrics)	2021	Quality tracing evaluation strategies of compatible materials in Aconitum proprietary Chinese medicines	(Z. D. Qiu et al., 2021)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED

CMP Quality Issue	CMP	Specifics of Issue	Why it Persisted	Solutions	Publication Year	Article Title	Citation
Traceability difficult	Multiple CMP	Development of a DNA methods to aid identification	Difficult to detect / unknown	Analytical development(DNA)	2022	Microbial spore genetic marker technology, a potential technology for traditional Chinese medicine traceability system	(D. Zhao, Tian, Cai, & He, 2022)
Value substitution	Lonicerae japonicae Flos	Survey of Lonicera japonica Flos, 67 samples, 17% of the extracts and 22% of the CPMs were authentic	Not detected	Analytical development (DNA)	2017	Derivative Technology of DNA Barcoding (Nucleotide Signature and SNP Double Peak Methods) Detects Adulterants and Substitution in Chinese Patent Medicines	(Z. T. Gao et al., 2017)
Value substitution	Anoectochilus roxburghii	Anoectochilus roxburghii substituted with cheaper Goodyera Schlechtendaliana and Ludisia discolor	Value motivation and difficult to detect	Analytical development(NIR)	2021	Improved 1D convolutional neural network adapted to near-infrared spectroscopy for rapid discrimination of Anoectochilus roxburghii and its counterfeits	(Q. Chai et al., 2021)
Variable quality	Astragalus membranaceus Fisch. ex Bunge	Quality variation of Astragalus membranaceus Fisch. ex Bunge	Difficult to detect	Analytical development (FTIR-Chemometrics)	2010	Discrimination of Geographical Origin and Adulteration of Radix Astragali using Fourier Transform Infrared Spectroscopy and Chemometric Methods	(L. Zhang & Nie, 2010)

TABLE ALR 6 SECOND PHASE SPECIFIC LITERATURE REVIEW: 173 JOURNAL ARTICLES INCLUDED							
CMP Quality Issue	**CMP**	**Specifics of Issue**	**Why it Persisted**	**Solutions**	**Publication Year**	**Article Title**	**Citation**
Variable quality	Hypericum perforatum L.	Quality variation of Hypericum perforatum L. from different origins	Regulation absent	Selective sourcing and regulation	2019	St. John's Wort (Hypericum perforatum) Products - How Variable Is the Primary Material?	(Scotti et al., 2019a)
Variable quality	Chrysanthemum spp.	Chrysanthemum flower; Quality assurance; Global market; Cadmium; Quality control; TCM	Difficult to detect / unknown	Legislation (better definition)	2022	Chrysanthemum species used as food and medicine: Understanding quality differences on the global market	(J. Gu et al., 2022)

Emergent quality issues in the supply of Chinese medicinal plants

中草藥供應中發生的品質問題

A mixed methods investigation
of their contemporary occurrence
and historical persistence

當代發生和歷史延續混合調查法

VOLUME III of III

A

Doctoral Thesis

By Martin Fitzgerald

李馬丁

School of Life Sciences

College of Liberal Arts and Sciences

University of Westminster

London

2023

Appendix to the KI study (AKI)

AKI 1 Ethics application

AKI 2 Questionnaire participant information sheet

AKI 3 Questionnaire consent form sample

AKI 4 Questionnaire tool

AKI 5 Questionnaire participant anonymised transcripts sample

AKI 6 Pre-interview pilot questionnaire and trial data analysis

AKI 7 Interview participant information sheet

AKI 8 Interview consent form

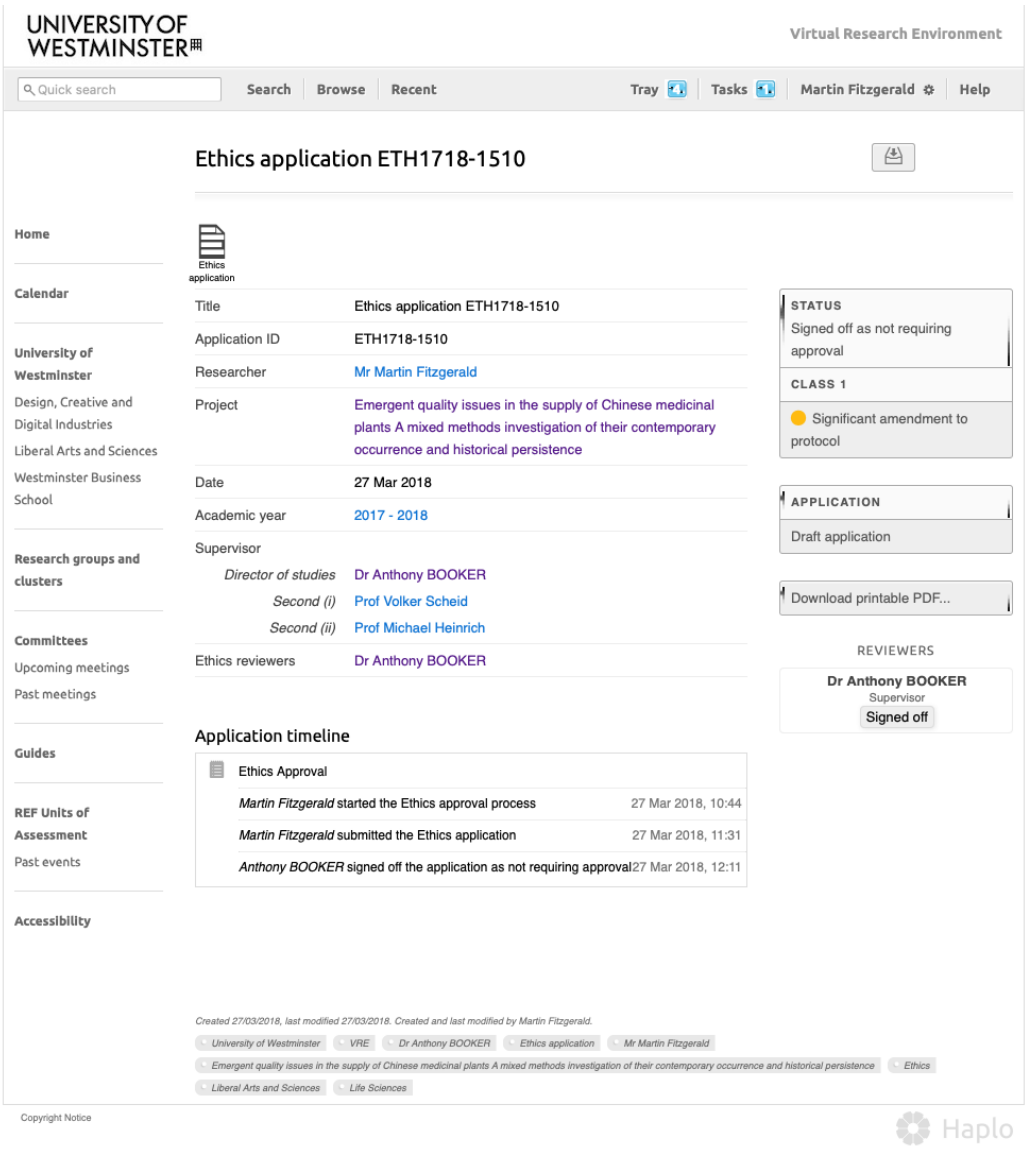
AKI 9 Interview tool

AKI 10 Interview participant anonymised transcripts sample

AKI 11 Summary of key contributions from interview participant responses

AKI 12 KI Master Table, analysis of specific examples by key informants

AKI 1 Ethics application



AKI 2 Questionnaire participant information sheet

Participant information sheets

PARTICIPATION INFORMATION SHEET 参与信息表

AN INVESTIGATION OF QUALITY IN CHINESE HERBAL MEDICINE SUPPLY: The problems that exist and why they persist?

中草药供应质量量调查:存在的问题及其存在的原因?

Researcher(s): 研究员:主管 Martin Fitzgerald. **Supervisor:** Dr. Anthony Booker.博士士.

You are being invited to take part in a research study questionnaire on the quality of Chinese herbal medicine. It involves identifying the quality problems with Chinese herbal medicines supplied mainly, but not exclusively to the UK. Many efforts have been made to control the quality of herbal medicine but problems still occur. This research focuses on why the quality problem exist and why they recur after measures have been introduced.

您被邀请参加一份关于中草药质量的调查问卷。 它涉及识别主要供应但不限于英国的中草药的质量问题。 为控制草药的质量做出了许多努力，但问题仍然存在。 本研究的重点是为什么质量问题会存在，以及为什么在采取措施后它们会再次出现。

This research is being undertaken as part of the researcher's studies for a PhD in Ethnopharmacology (Chinese Medicine) programme at the University of Westminster. The study will involve:

该研究正在作为威斯敏敏斯特大大学民民族药理理学(中医)博士士研究员研究的一一部分进行行行。 该研究将涉及到您:

A questionnaire asking opinions on a number of topics around the quality of Chinese herbal medicines is attached. I would be grateful if you would consider completing this and returning to the email to which it is attached. M.fitzgerald@my.westminater.ac.uk.

附上一份关于中草药质量问题的问卷调查。 如果您考虑完成此并返回到它所附的电子邮件，我将不胜感激。M.fitzgerald@my.westminer.ac.uk。

Please note: • 请注意:

• Your participation in this research is entirely voluntary. •您参与本研究完全是自自愿的。

- You have the right to withdraw at any time without giving a reason.
- 您有权在不不给出理理由的情况下随时退出。
- Withdrawal from the research is without prejudice.
- 退出研究是不不偏不不倚的。
- You have the right to ask for your data to be withdrawn as long as this is practical, and for personal information to be destroyed.
- 只要可行行行，您有权要求撤销您的数据，并且有权销毁您的个人人信息。
- You do not have to answer particular questions if you

  do not wish to do so.

- 如果您不不想这样做，您无无需在问卷调查或面面谈中回答特定问题。
- Your responses will normally be made anonymous, unless indicated above to the contrary, and will be kept confidential unless you provide explicit consent to do otherwise.
- 您的回复通常会以匿匿名方方式提出，除非非上文文另有说明，除非非您明确表示同意，否则将予以保密。
- No individuals will be identifiable from any collated data, written report of the research, or any

  publications arising from it.

- 任何整理理的数据，研究的书面面报告或由此产生生的任何出版物都不不会识别任何个人人。
- All computer data files will be encrypted and password protected. The researcher will keep files in a secure place and will comply with the requirements of the Data Protection Act including GDPR 2016/ 679 which addresses your personal data and its confidentiality.
- 所有计算机数据文文件都将加密并受密码保护。 研究人人员将文文件保存在安全的地方方，并符合数据保 护法的要求，包括 GDPR 2016/679，其中涉及您的个人人数据及其机密性。
- All hard copy documents, e.g. consent forms, completed questionnaires, etc. will be kept securely and in a locked cupboard, wherever possible on University premises. Documents may

be scanned and stored electronically. This may be done to enable secure transmission of data to the university's secure computer systems.

• 所有硬拷贝贝文文件，例例如 同意书，填妥的问卷等将尽可能安全地存放在一一个带锁的橱柜中，尽可能 放在大大学校舍内。 可以电子子方方式扫描和存储文文档。 可以这样做以便便能够将数据安全地传输到大大学 的安全计算机系统。

• Please notify the researcher immediately if you feel psychologically or physically uncomfortable during or after the research. 如果您在研究期间或之后感到心心理理或身体不不适，请立立即通知研究人人员。

- If you wish you, can receive information on the results of the research. Please indicate on the consent form if you would like to receive this information.如果您愿意，可以获得有关研究结果的 信息。 如果您希望收到此信息，请在同意书上注明。
- The researcher can be contacted during and after participation by email (m.fitzgerald@my.westminster.ac.uk).
- 可以通过电子子邮件(m.fitzgerald@my.westminster.ac.uk)在参与期间和之后联系研究人人员。

  • If you have a complaint about this research project you can contact the project supervisor, Dr. Anthony Booker by e-mail (A.Booker@westminster.ac.uk).

  • 如果您对此研究项目目有任何投诉，您可以通过电子子邮件联系项目目主管 Anthony Booker 博士士 (A.Booker@westminster.ac.uk)。

AKI 3 Questionnaire consent form

CONSENT FORM 同意书

Title of Study: **AN INVESTIGATION OF QUALITY IN CHINESE HERBAL MEDICINE SUPPLY:** *The problems that exist and why they persist?* **研究题目目:中草药供应质量量调查:**存在的问题及其存在的原因?

Lead researcher:首首席研究员: Martin Fitzgerald
I have read the information in the Participation Information Sheet, and I am willing to act as a participant in the above research study.

我已阅读参与信息表中的信息，我愿意作为上述研究的参与者。

Name:名称: _____

Signature:签名: _____

Date: 日日期:_____

This consent form will be stored separately from any data you provide so that your responses remain anonymous.

此同意书将与您提供的任何数据分开存储
你的回答是匿匿名的。

I have provided an appropriate explanation of the study to the participant

我已向参与者提供了了对研究的适当解释

Researcher Signature 研究员签名:

_____ Martin Fitzgerald

AKI 4 Questionnaire tool

Questionnaire of key informants

Thank you for responding to the request for participation in this research.

It is a pilot exploratory questionnaire relating to attitudes and opinions.

Please be aware that you can change you mind at any time and not complete or return this questionnaire without any consequence or prejudice.

Your response is voluntarily and confidential.

All correspondence and data linking back to your email and the response will be deleted within 3 months of your reply.

Introduction

This questionnaire is designed to explore expert opinion on the supply of Chinese herbal medicines to the UK. Particularly (but not exclusively) around quality related problems.

There is room for any further comments and thoughts that come to mind during your response. This it is very valuable.

As this is a pilot exploratory questionnaire, any additional inputs you may wish to include are very useful in forming a final questionnaire design.

The first part, preliminary questions will determine how your responses are included in the research.

(All responses will be included even if your expertise is not directly related to Chinese herbal medicine).

The second part asks you opinion and comments on a quality theme.

Part 1 of 2 – Preliminary Questions

You have been identified as an expert in your field.

Please indicate which field(s) you feel most closely represents in your area(s) of expertise

(You May select more than 1)

Research and Development	Education	Regulation	Legislation	Herbal Supply	Other

Have you been working or studying in your own speciality field for more than 10 years?

Yes	No

Have you been involved in any capacity through work or study with Chinese herbal medicine?
(For example, this could include policy, legislation, supply, teaching, research and so on)

Yes	No

What percentage of your career would you approximate has been spent involved or any way related to Chinese herbal medicine?

(For example; 0%, 1%, 12%, 50%, 64%, 100%. You can enter any percentage)

%

End of Part 1 of 2 – Preliminary Questions

Part 2 of 2

Main Questions

Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?

Yes	No

If No, please go to question 14.

If yes, what are the main issues?

On what scale would you say a quality problem exist?

Small	Medium	Large

Could you give examples of issues you have had to deal with personally?

Part 2 of 2 continues next page.

What is the origin of the problems?

Are we effective at detecting these problems?

What circumstances or factors have allowed these problems to occur?

Are there specific Chinese herbs that present higher risk?

Do you think there are higher risks at specific stages of the herbal supply from Asia or the UK?

Do you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?

What main problems would you say unlicensed Chinese herbal medicines present?

On what scale would you say unlicensed Chinese herbs exist?

Small	Medium	Large

How effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?

Are there non-quality related problems with Chinese herbal medicine?

Please give your thoughts on these including a sense of their scale.

Thank you for completing, this is the END OF THE QUESTIONNAIRE

Please review your answers, amend, edit or append as desired.
Please save and forward this file back to the email address from which it was sent.

Your expertise and time is greatly appreciated.

AKI 5 Questionnaire participant anonymised transcripts sample

Sample of questionnaire respondent data, three examples (cases 1 to 3, of total 5).

Case 1 Questionnaire participant response data

1.1 Please indicate which field(s) you feel most closely represents in your area(s) of expertise

Research and development

1.2 Have you been working or studying in your own speciality field for more than 10 years?

Yes

1.3 Have you been involved in any capacity through work or study with Chinese herbal medicine?

Yes

1.4 What percentage of your career would you approximate has been spent involved or any way related to Chinese herbal medicine?

100%

2.1 Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?

Yes

2.2 If yes, what are the main issues?

Quality control issues, including principal components analysis, active components analysis and evidence-based medicine of TCM

2.3 On what scale would you say a quality problem exist?

Medium

2.4 Could you give examples of issues you have had to deal with personally?

Same products from different company will display this issue.
Most of customers will choose the products based on the price.

2.5 What is the origin of the problems?

Customers choose the products based on the price

2.6 Are we effective at detecting these problems?

Yes

2.7 What circumstances or factors have allowed these problems to occur?

Customers choose the products based on the price

2.8 Are there specific Chinese herbs that you feel present higher risk?

All TCM herbs

2.9 Do you think there are higher risks at specific stages of the herbal supply from Asia to the UK?

Yes

2.10 Do you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?

Both unlicensed herbs and licensed herbs

2.11 What main problems would you say unlicensed Chinese herbal medicines present?

Price of unlicensed Chinese herbal medicines is cheaper

2.12 On what scale would you say unlicensed Chinese herbs exist?

Medium

2.13 How effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?

Much effective

2.14 Are there non-quality related problems with Chinese herbal medicine?

No

2.15 Please give your thoughts on these including a sense of their scale.

N/A

2.16 Do people cause quality problems for Chinese herbal medicine?

Yes

2.17 If so, please give your thoughts including how big are these problems?.

Because most herbs are cultivated today, the problem will become more seriously.

Case 2 Questionnaire participant response data

1.1 Please indicate which field(s) you feel most closely represents in your area(s) of expertise

Education

1.2 Have you been working or studying in your own speciality field for more than 10 years?

Yes

1.3 Have you been involved in any capacity through work or study with Chinese herbal medicine?

1.4 What percentage of your career would you approximate has been spent involved or any way related to Chinese herbal medicine?

0%

2.1 Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?

2.2 If yes, what are the main issues?

There is a quality problem with all herbal medicine in the UK – 30-40% of OTC and practitioner medicines do not contain the correct herb or part of the herb. I would say that adulteration and substitution are the most likely issues with CHM products in the UK

2.3 On what scale would you say a quality problem exist?

Large

2.4 Could you give examples of issues you have had to deal with personally?

None with CHM supplies, as I am a WHM practitioner.

2.5 What is the origin of the problems?

Genuine errors, misidentification of similar species, together with purposeful adulteration with similar species, cheaper synthetic phytomarkers (in some Ginkgo products), fillers (glass and fuller's earth I have seen in some WHM supplies) and dyes (in St John's wort) etc.

2.6 Are we effective at detecting these problems?

It really depends on the practitioner supplier. Some are very good whereas others do not have the infrastructure or finances to carry out sufficient testing.

2.7 What circumstances or factors have allowed these problems to occur?

Misidentification, poor GACP compliance and financial gain from selling adulterated products. Lack of routine testing by some suppliers means that some farmers etc. in the supply chain think they can get away with adulteration.

2.8 Are there specific Chinese herbs that you feel present higher risk?

The more expensive ones, I should imagine, e.g. those that are endangered or difficult to grow.

2.9 Do you think there are higher risks at specific stages of the herbal supply from Asia to the UK?

It depends on the supplier and how much they comply to GACP.

2.10 Do you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?

By licensed herbs I assume you mean THRs? There are not many THRs for CHM products, but (so far) all the THRs meet the quality criteria required for their registration. I would therefore think that the issue mainly affects unlicensed herbs.

2.11 What main problems would you say unlicensed Chinese herbal medicines present?

Contamination, substitution and adulteration.

2.12 On what scale would you say unlicensed Chinese herbs exist?
Large

2.13 How effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?

What legislation? I wish we had legally binding registration. Seriously though, any herbal practitioner supplier who meets GACP and GMP standards is far more likely to have dependable products compared to one that does not.

2.14 Are there non-quality related problems with Chinese herbal medicine?

Some poor and misguided media coverage has damaged the sector to some degree (but more with medical practitioners rather than the public, it would seem. Other than that, not that I can think of personally.

2.15 Please give your thoughts on these including a sense of their scale.

N/A

2.16 Do people cause quality problems for Chinese herbal medicine?

Yes.

2.17 If so, please give your thoughts including how big are these problems?.

It depends. You could argue that the people who cause/allow the adulteration, substitution and contamination issues due to ignorance or financial greed are a big problem. There are a number of CHM practitioners who do not belong to a PA, and who are not practicing safely or within the UK law – some of these people undoubtedly damage the reputation of CHM in the UK. Some of the CHM PAs do not have as high a standard as others (no names mentioned!).

Case 3 Questionnaire participant response data

Please indicate which field(s) you feel most closely represents in your area(s) of expertise

Herbal supply

Have you been working or studying in your own speciality field for more than 10 years?

Yes

Have you been involved in any capacity through work or study with Chinese herbal medicine?

Yes

What percentage of your career would you approximate has been spent involved or any way related to Chinese herbal medicine?

80%

Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?

Yes

If yes, what are the main issues?

Examples of problems arising from problems in quality control:

1. Toxic, so2, pesticide, aflatoxin

2. Misleading labelling and false advertising (see attached reference as example) -Incorrect ingredients

-Cheaper substitutions

-Lack of key effective ingredients

3. False test reports

Together, these issues not only reduce the effectiveness of treatment but could also lead to more serious health damage to patients. There is also an issue with non-qualified entities claiming to offer herbalist certifications. The quality and integrity of these courses, which are often very short and lack qualified instructors, is questionable and propagates the environment of poor quality.

Addressing these issues will require introduction of stricter regulation coupled with more stringent due diligence. The current regulatory bodies are limited in what they can do to address the problems above as the current strategy relies only on paperwork supplied to the authorities. Within the industry, there are several known instances of certain entities taking fraudulent actions taken to circumvent these checks in order to become an approved supplier. For example, misleading Information provided by the wholesaler *Figure, AKI 5.1* and false claim of MHRA & CE certification on wholesaler's website, *Figure, AKI 5.2.*

FIGURE AKI 5.1 VISUAL ILLUSTRATION OF MISLEADING LABEL INFORMATION PROVIDED BY HERBAL WHOLESALER

No ingredients list provided in the label

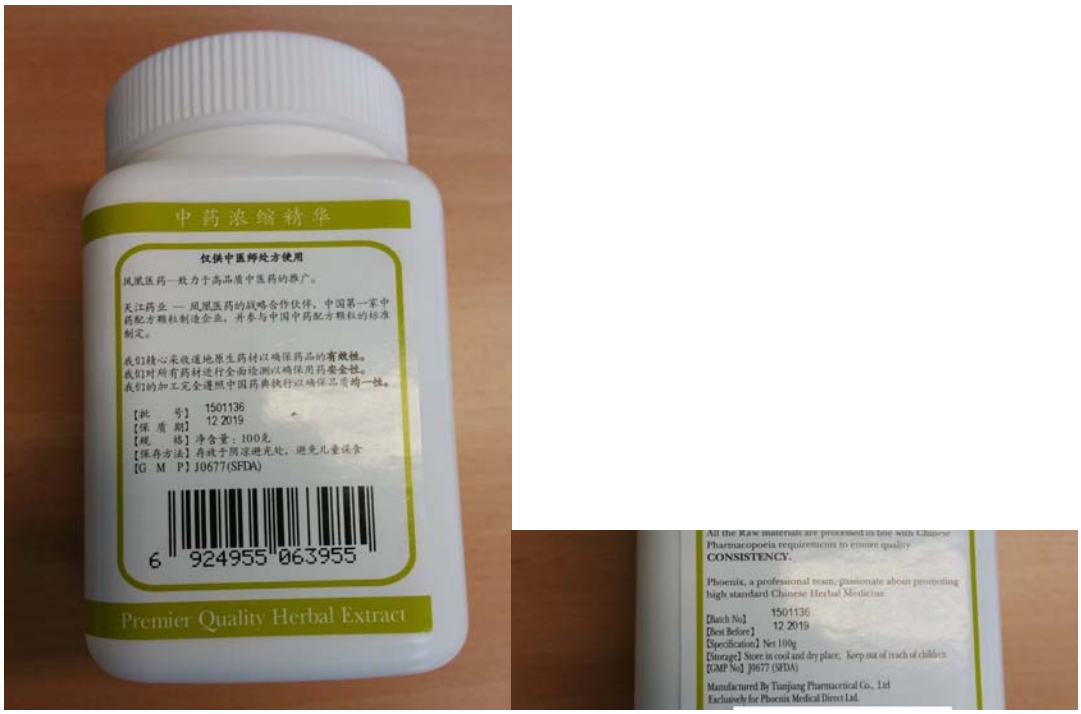
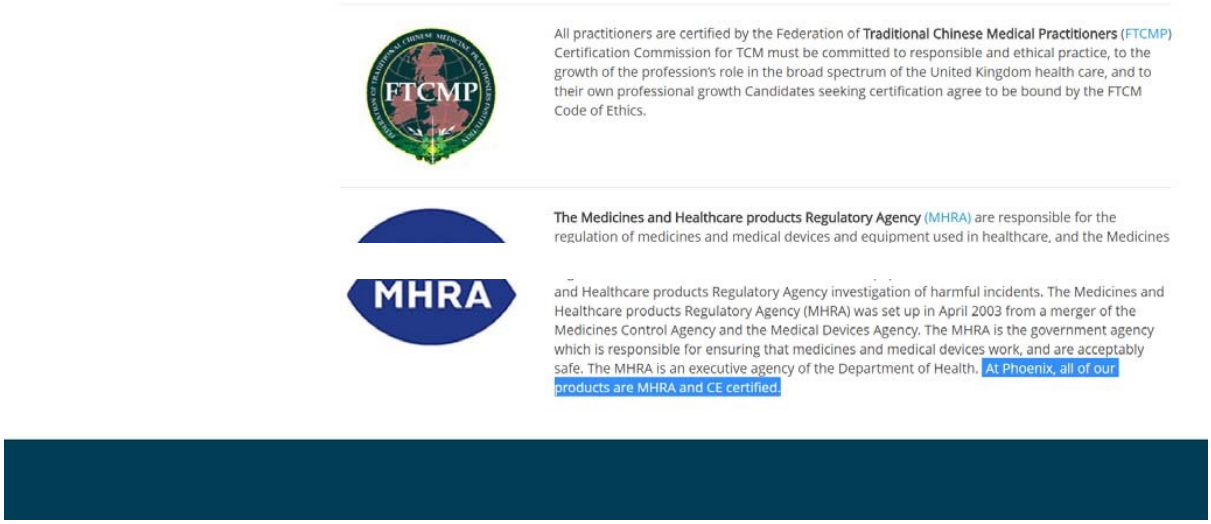


FIGURE AKI 5.2 FALSE CLAIMS OF MHRA & CE CERTIFICATION ON WHOLESALER'S WEBSITE



On what scale would you say a quality problem exist?

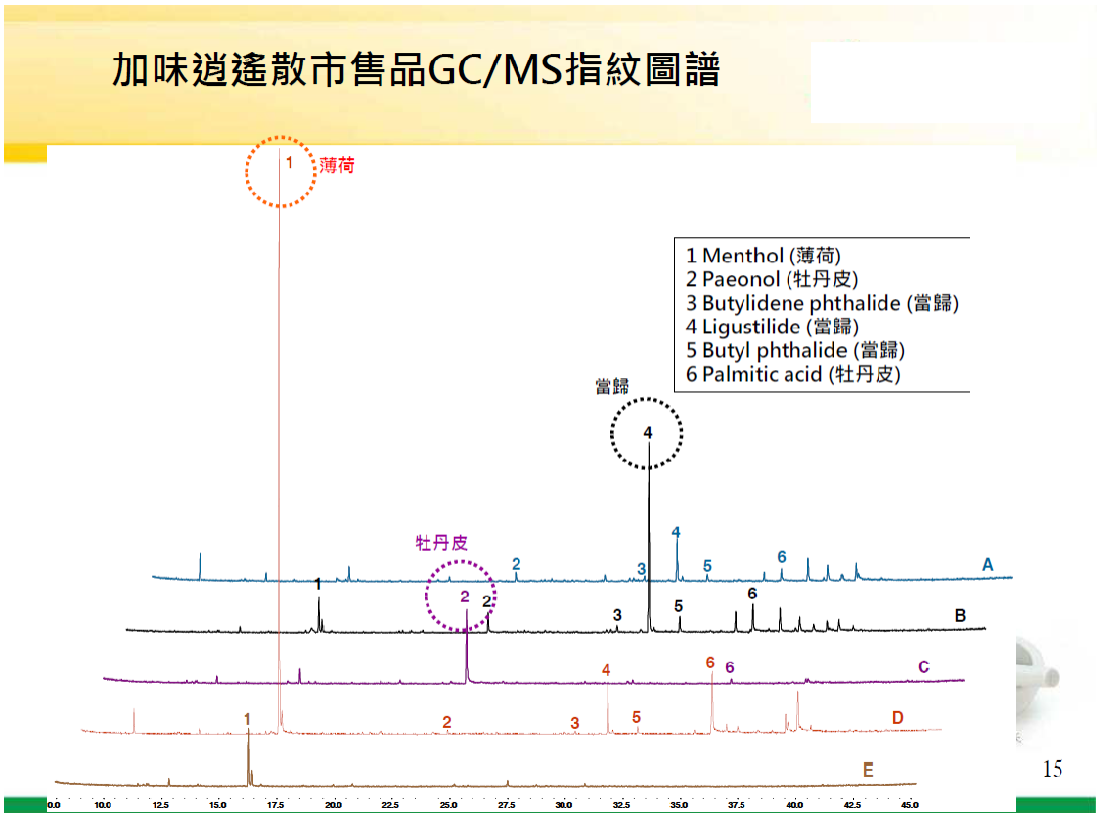
Large

Could you give examples of issues you have had to deal with personally

We have purchased raw herb and concentrate granules from both UK high street and wholesale suppliers that showed unacceptable levels of toxic substances in independent test reports (see attached) as well as lack of clear information on bottle. In one example, a product contained very high levels of sugar but did not indicate this, nor did it indicate that the product may be unsuitable for diabetes patients. Products often state they are 100% natural but actually contain up to 40% binder (e.g. lactose or an unidentifiable sugar). It is disturbing that these products are from well known suppliers in the UK. Furthermore, several of these wholesalers will re-package and re-brand their products, thus making it impossible to trace back to the actual pharmaceutical manufacturer. This presents issues with responsibility when problems arise as the manufacturers can deny involvement.

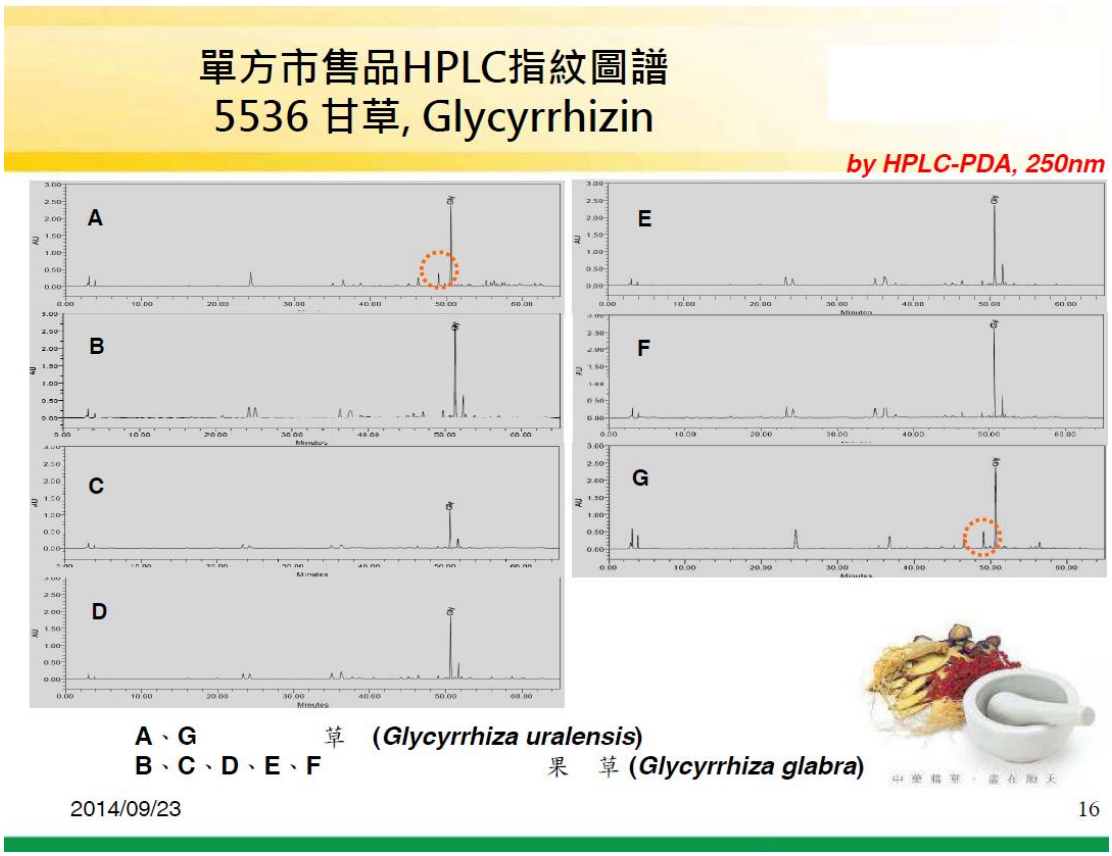
JIA WEI XIAO YAO SAN analysis, in order to make the formulae smell differently, some of the manufacturer intentionally put in the scent of certain herb in the formula, for example, B put extra DANG GUI scent into the formula to make JIA WEI XIAO YAO SAN to have a special DANG GUI smell, *Figure, AKI 5.3.*

FIGURE AKI 5.3 LABORATORY TEST REPORT SHOWING ADDITION OF SYNTHETIC AROMA TO CHINESE HERBAL FORMUAL JIA WEI XIAO YAO SAN TO ARTIFICALLY ENHANCE SENORY QUALITY



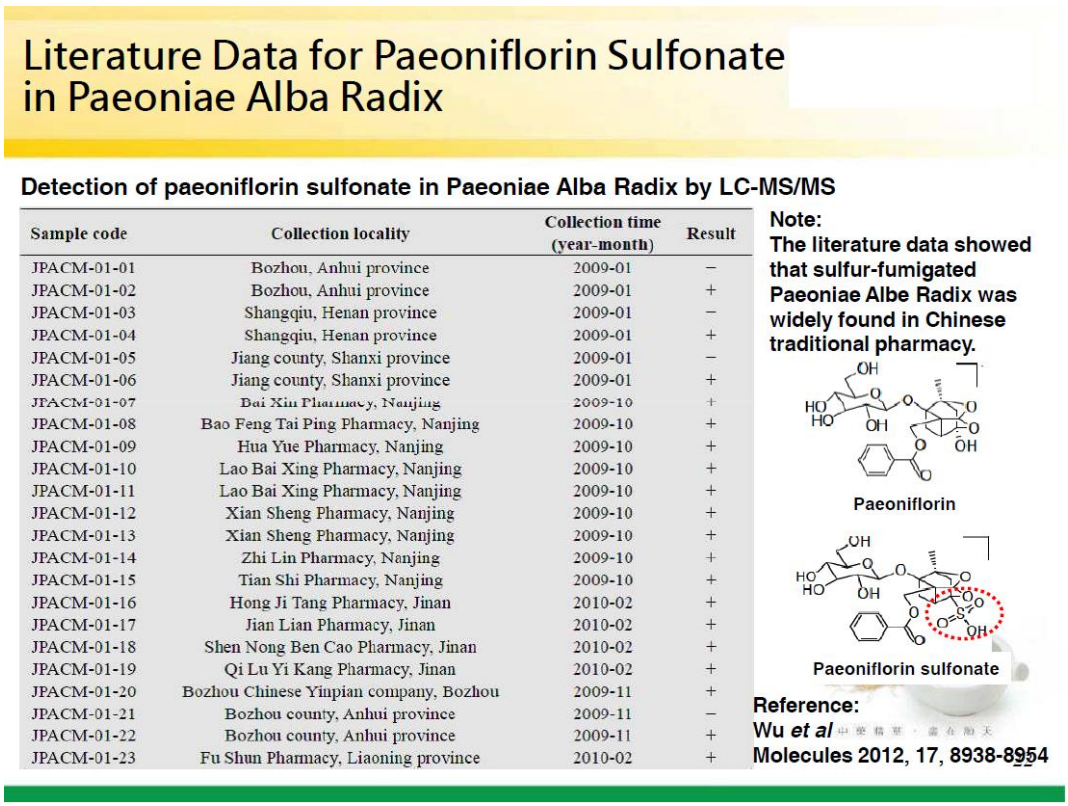
Each herb has its own active ingredient, or mark to show it is made from genuine raw material, this is to test GAN CAO concentrated granule, only A and G has the actual active ingredient shown in the chart, all the rest of the manufacturer's GAN CAO does not have such mark, *Figure, AKI 5.4.*

FIGURE AKI 5.4 LABORATORY TEST REPORT SHOWING GAN CAO HERBAL PRODUCT SOLD ON MARKET IS MISSING ACTIVE INGREDIENT



This is to show that report shows that over 70% of the raw materials collected in mainland China has been detected being sulphured, *Figure, AKI 5.5.*

FIGURE AKI 5.5 LARGE SCALE ANALYSIS REPROT OF HERBAL MATERIALS SHOWING 70% OF THE RAW MATERIALS COLLECTED IN MAINLAND CHINA WERE CONTAMINATED WITH SULPHUR



Literature Data for Paeoniflorin Sulfonate in Paeoniae Alba Radix

Detection of paeoniflorin sulfonate in Paeoniae Alba Radix by LC-MS/MS

Sample code	Collection locality	Collection time (year-month)	Result
JPACM-01-01	Bozhou, Anhui province	2009-01	−
JPACM-01-02	Bozhou, Anhui province	2009-01	+
JPACM-01-03	Shangqiu, Henan province	2009-01	−
JPACM-01-04	Shangqiu, Henan province	2009-01	+
JPACM-01-05	Jiang county, Shanxi province	2009-01	−
JPACM-01-06	Jiang county, Shanxi province	2009-01	+
JPACM-01-07	Bai Xin Pharmacy, Nanjing	2009-10	+
JPACM-01-08	Bao Feng Tai Ping Pharmacy, Nanjing	2009-10	+
JPACM-01-09	Hua Yue Pharmacy, Nanjing	2009-10	+
JPACM-01-10	Lao Bai Xing Pharmacy, Nanjing	2009-10	+
JPACM-01-11	Lao Bai Xing Pharmacy, Nanjing	2009-10	+
JPACM-01-12	Xian Sheng Pharmacy, Nanjing	2009-10	+
JPACM-01-13	Xian Sheng Pharmacy, Nanjing	2009-10	+
JPACM-01-14	Zhi Lin Pharmacy, Nanjing	2009-10	+
JPACM-01-15	Tian Shi Pharmacy, Nanjing	2009-10	+
JPACM-01-16	Hong Ji Tang Pharmacy, Jinan	2010-02	+
JPACM-01-17	Jian Lian Pharmacy, Jinan	2010-02	+
JPACM-01-18	Shen Nong Ben Cao Pharmacy, Jinan	2010-02	+
JPACM-01-19	Qi Lu Yi Kang Pharmacy, Jinan	2010-02	+
JPACM-01-20	Bozhou Chinese Yinpian company, Bozhou	2009-11	+
JPACM-01-21	Bozhou county, Anhui province	2009-11	−
JPACM-01-22	Bozhou county, Anhui province	2009-11	+
JPACM-01-23	Fu Shun Pharmacy, Liaoning province	2010-02	+

Note:
The literature data showed that sulfur-fumigated Paeoniae Albe Radix was widely found in Chinese traditional pharmacy.

Paeoniflorin

Paeoniflorin sulfonate

Reference:
Wu *et al*
Molecules 2012, 17, 8938-8954

This to show the aflatoxin toxic in BAI ZI REN concentrated granules, and it shows that D, E and C products have extreme high level of toxic, *Figure, AKI 5.6.*

FIGURE AKI 5.6 LABORATORY TEST REPORT OF HERB BAI ZI REN CONTAINING HIGH LEVELS OF AFLATOXINS

單方市售品黃麴毒素分析
5921 柏子仁

單方	黃麴毒素 (Aflatoxin)	成分量 (ppb), *by HPLC-Fluorescence*				
		A	B	C	D	E
柏子仁	B1	9.12	9.45	12.86	22.58	67.43
	B2	1.55	1.91	3.05	3.42	10.91
	G1	0.39	0.20	0.85	0.54	1.96
	G2	0.08	0.11	0.52	0.35	1.11
	Total	11.14	11.67	17.28	26.89	81.41

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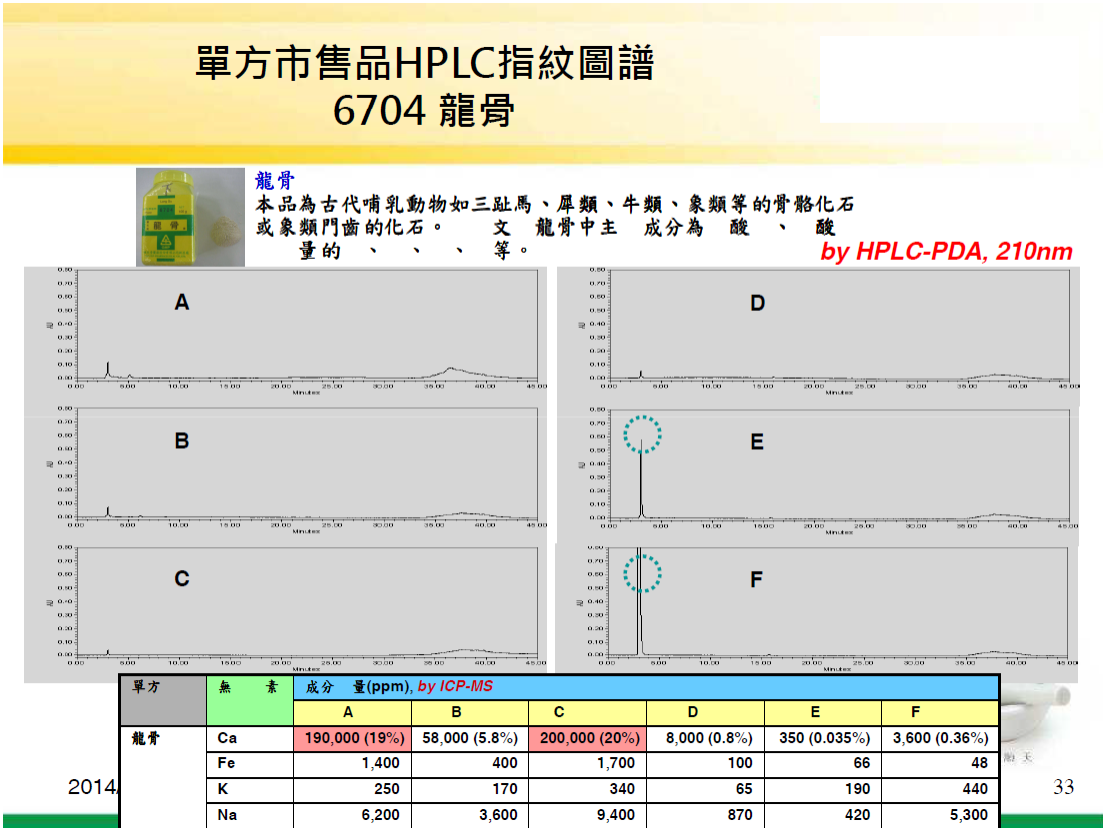
This is to show that LONG GU, as a mineral content product, should have main ingredient as Calcium, but B, E and F products have very low level of calcium in LONG GU, which means, it is not genuine LONG GU, *Figure,* AKI 5.7.

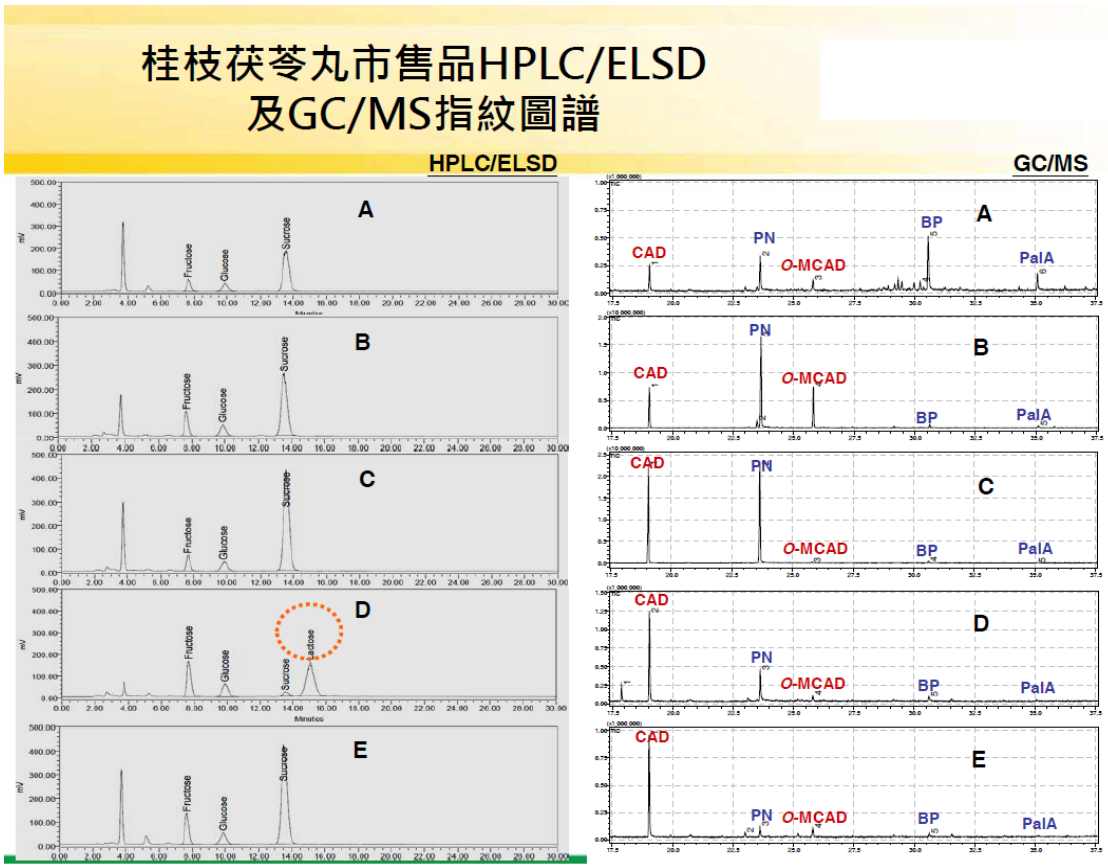
FIGURE AKI 5.7 LABORATORY TEST REPORT OF CHINESE MEDICINE SHOWING PRODUCT DOES NOT CONTAIN LONG GU AS STATED ON LABEL



單方	無 素	成分 量(ppm), *by ICP-MS*					
		A	B	C	D	E	F
龍骨	Ca	190,000 (19%)	58,000 (5.8%)	200,000 (20%)	8,000 (0.8%)	350 (0.035%)	3,600 (0.36%)
	Fe	1,400	400	1,700	100	66	48
	K	250	170	340	65	190	440
	Na	6,200	3,600	9,400	870	420	5,300

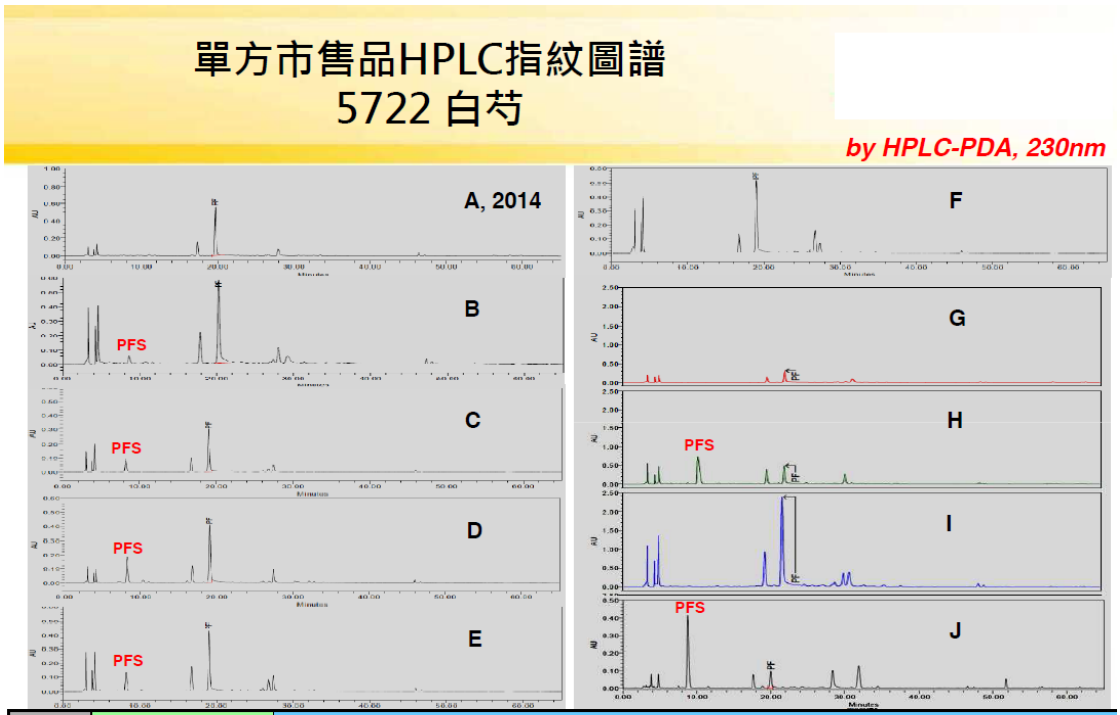
From the HPLC/ELSD test result, shows that D products do contain Lactose, all other four suppliers does not, *Figure,* AKI 5.8.

FIGURE AKI 5.8 LABORATORY TEST REPORT OF CHINESE MEDICINE SHOWING SOME WHOLESALER'S PRODUCTS CONTAIN LACTOSE



Through the HPLC-PDA analysis, most of the common manufacturer such as D, B, H the raw material used in concentrated BAI SHAO YAO contains trace of Paeoniflorin sulfonate, which means the raw material has been contaminated with sulphur, *Figure,* AKI 5.9.

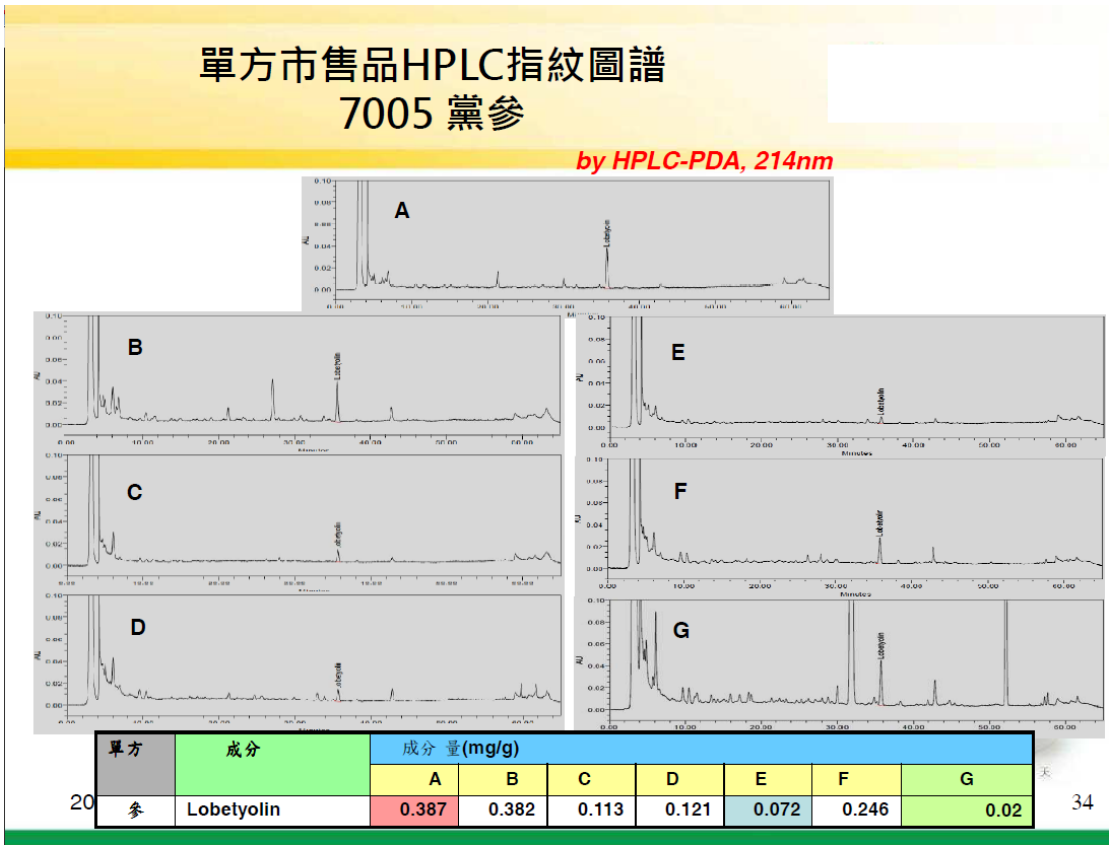
FIGURE AKI 5.9 LABORATORY TEST REPORT OF CHINESE MEDICINE BAI SHAO YAO SHOWING WHOLESALER'S PRODUCTS ARE CONTAMINATED WITH SUPHUR



單方	成分	成分 量(mg/g)									
		A	B	C	D	E	F	G	H	I	J
	Paeoniflorin	19.53	37.41	14.03	18.93	19.87	24.13	12.38	7.88	63.84	0.41

The active ingredient in DANG SHEN concentrated extract called Lobetyolin, and from the chart we could see that products such as D are only 1/3 of the amount to A, *Figure,* AKI 5.10.

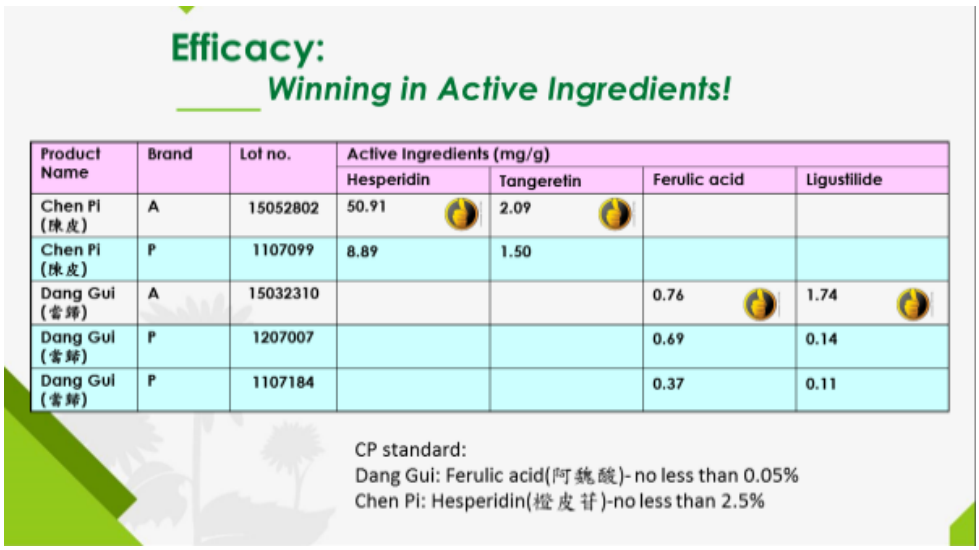
FIGURE AKI 5.10 LABORATORY TEST REPORT OF CHINESE MEDICINE DAN SHEN PRODUCTS SHOWING LOW LEVELS OF ACTIVE INGREDIENT LOBETYOLIN



單方	成分	成分 量(mg/g)						
		A	B	C	D	E	F	G
參	Lobetyolin	0.387	0.382	0.113	0.121	0.072	0.246	0.02

Lab test shows that the active ingredients are with significant different amongst TCM products on the market, e.g. CHEN PI, are with 6 times difference, *Figure,* AKI 5.11.

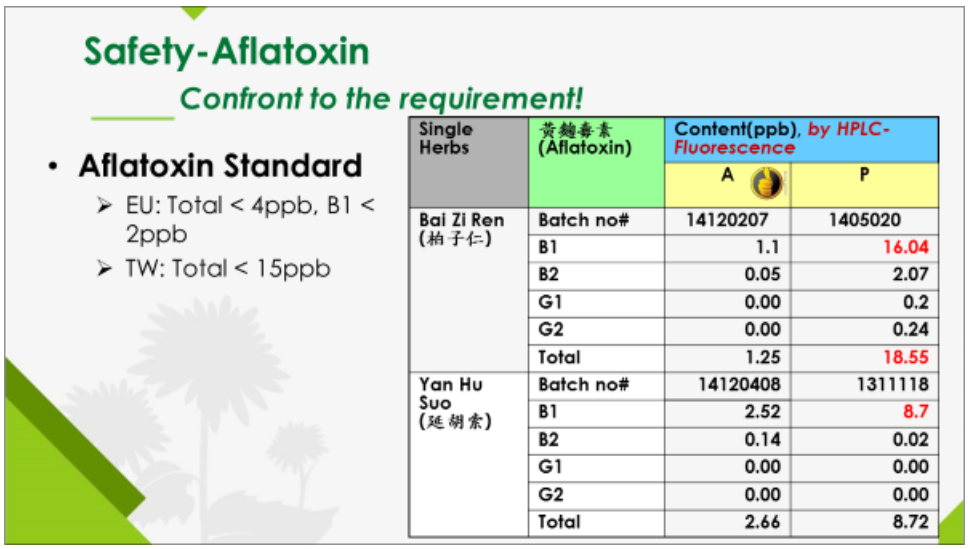
FIGURE AKI 5.11 LABORATORY TEST REPORT OF CHINESE MEDICINE CHEN PI PRODUCT ON THE MARKET SHOWING SIX-FOLD VARIATION IN CONTENT



Product Name	Brand	Lot no.	Active Ingredients (mg/g)			
			Hesperidin	Tangeretin	Ferulic acid	Ligustilide
Chen Pi (陳皮)	A	15052802	50.91	2.09		
Chen Pi (陳皮)	P	1107099	8.89	1.50		
Dang Gui (當歸)	A	15032310			0.76	1.74
Dang Gui (當歸)	P	1207007			0.69	0.14
Dang Gui (當歸)	P	1107184			0.37	0.11

Lab test shows the toxicity of herbs. Aflatoxin figures are much higher than EU standard, *Figure,* AKI 5.12.

FIGURE AKI 5.12 LABORATORY TEST REPORT OF CHINESE MEDICINE PRODUCTS BAI ZI REN AND YAN HU SUO CONTAINING OVER-LIMIT PERMITTED LEVELS OF TOXIN, AFLATOXINS



Single Herbs	黃麴毒素 (Aflatoxin)	Content(ppb), by HPLC-Fluorescence	
		A	P
Bai Zi Ren (柏子仁)	Batch no#	14120207	1405020
	B1	1.1	16.04
	B2	0.05	2.07
	G1	0.00	0.2
	G2	0.00	0.24
	Total	1.25	18.55
Yan Hu Suo (延胡索)	Batch no#	14120408	1311118
	B1	2.52	8.7
	B2	0.14	0.02
	G1	0.00	0.00
	G2	0.00	0.00
	Total	2.66	8.72

What is the origin of the problems?

Top-down: limitations in regulation and due diligence of testing & labelling

Bottom-up: both qualified and unqualified herbalists unable to perform due diligence (don't understand how to read CoAs or verify validity of CoAs) by themselves. Favouring of price of quality. A lack of prioritisation of quality with some wholesalers.

Are we effective at detecting these problems?

Evidently, no. Testing needs to extend to actual testing of products. It will no doubt be a challenge to balance comprehensiveness of testing without suffocating the industry with time and money constraints.

What circumstances or factors have allowed these problems to occur?

Good suppliers are not protected by regulation and bad suppliers can easily circumvent the current regulatory structure. The regulatory system needs to be reviewed (perhaps taking lessons from other countries like Australia, Switzerland, Taiwan, Japan). The shortfalls in regulation will ultimately end in the compromise of patient safety. Currently, a lot of the global supply of herbs which fail regulation in other countries are able to enter the UK.

Are there specific Chinese herbs that you feel present higher risk?

Do you think there are higher risks at specific stages of the herbal supply from Asia to the UK?

Both high and low standards in manufacturing can be found in Asia. However, the stringency of the import process in the UK fails to identify and filter out poor quality. Once these poor quality products enter into the UK, patients are put at risk by entities which do not understand/do not care/purposely mislead about the quality of their products.

Do you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?

Given the fundamental flaws in the current licensing system, the problems that exist are not specific to whether herbs are licensed or unlicensed. Currently, having a license in the UK does not ensure quality. Combined with a lack of attention to unlicensed herbs, entities are actually capable of operating without licenses at all.

What main problems would you say unlicensed Chinese herbal medicines present?

On what scale would you say unlicensed Chinese herbs exist?

Large

How effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?

Regulating Chinese herbal medicine without suffocating the industry is a challenge due to the difficult balance of stringency and flexibility given the nature of the treatment. Treatments may feature a diverse composition of several herbs selected from a repository of hundreds of different herbs. This makes it commercially unfeasible to enforce strict licenses on individual herbs. The current legislation needs to look towards other countries in which herbal medicine is part of the healthcare system like

Switzerland and Germany. Valuable lessons taken from these countries will be helpful in establishing a better regulatory environment in the UK.

Are there non-quality related problems with Chinese herbal medicine?

Poor quality of supply can only be propagated by entities which have an irresponsible disregard for patient welfare or are insufficiently educated.

One key issue mentioned previously is the poor quality of TCM/herbalist education which lead to questionable certification and ‘experts opinions’.

Another is a lack of regulation of online shops.

Please give your thoughts on these including a sense of their scale.

huge problem

Do people cause quality problems for Chinese herbal medicine?

Yes. The state of the current Chinese herbal medicine industry in the UK is a result of people not understanding or caring about quality and patient welfare. If things are to continue the same way, serious issues in patient welfare will inevitably arise, thus leading to condemnation of the practice. Chinese herbal medicine has great potential, as realised by countries such as Switzerland, Germany Australia, Taiwan, Japan, Hong Kong etc. This potential will not be realised under the status quo in the UK.

AKI 6 Pre-interview pilot questionnaire and trial data analysis

AKI 6.1 Questionnaire findings

AKI 6.1.1 Questionnaire invitee profile

The expertise profile of the 15 invited key informants spanned the fields of manufacture (one), education (four), herbal supply (three), regulation (four), herbal clinical practice (one) and research (two), The five respondents who participated were in the fields of manufacture (one), education (one), herbal supply (two) and regulation (one), those invited from the fields of clinical practice and research did not participate in the questionnaire, *Table AKI 6.1.*

TABLE AKI 6.1 EXPERTISE PROFILE OF QUESTIONNAIRE INVITEES AND PARTICIPANTS

EXPERTISE FIELD	NUMBER OF INVITED KEY INFORMANTS (N=15)	NUMBER OF PARTICIPANTS RESPONDED (N=5)
Manufacture	*1*	1
Education	*4*	1
Supply	*3*	2
Regulation	*4*	1
Practitioner	*1*	0
Research	*2*	0

AKI 6.1.2 Questionnaire respondents profile

The participants possessed secondary expertise in areas of research, regulation, company management, herbal clinical practice, supply consultancy, herbal sourcing, and sales. The five questionnaire participants responses are referred to further as cases numbers one to five, abbreviated to C1 to C5, inclusive, *Table AKI 6.2.*

TABLE AKI 6.2 OVERVIEW OF PROFILE QUESTIONNAIRE PARTICIPANTS

CASE NUMBER	PRIMARY EXPERTISE	SECONDARY EXPERTISE	ETHNICITY	RESIDENCY
C1	*Manufacturing*	*Research*	*China*	*China*
C2	*Education*	*Regulation*	*British*	*UK*
C3	*Supply*	*Company Management*	*China*	*UK*
C4	*Regulation*	*Practitioner*	*British*	*UK*
C5	*Supply*	*Sales*	*China*	*China*

Three of the five participant were of Chinese ethnicity, native mandarin Chinese and fluent English speakers. Two were of British ethnicity and native English speakers. Four were long-term residents in the UK, and one (Chinese ethnicity) is a full-time resident in Taiwan. Residents in the Republic of China (ROC) and Taiwan, People's Republic of China (PRC) and are for the purposes of brevity, noted as China resident throughout. All questionnaire responses were completed in the English language.

AKI 6.1.3 Participant contributions to the questionnaire

The contributions of the participants to the questionnaire varied with their expertise, ethnicity and residency profile.

Consultation with the participants using the questionnaire with seventeen questions generated a total of 27 unique codes formed from narrative elements, that were relevant to answering the three research questions. These in summary described; areas relating to the influence of human actions on herbal quality, the controls on quality including legislation, issues affecting integrity of CMP, and opinions on how to improve current quality issues, among others.

Table AKI 6.3 shows the coding distribution for questionnaire questions in a combined numeric and heat-map format. The numbers indicate the number of codes formed from participants responses to each of the seventeen questions. The scale of colours from red to green represent relative proportion of the number questionnaire codes formed. Those coloured red are in the highest 10% fraction of the total number of codes formed from all questionnaire codes, and green for the lowest 10% proportion, respectively.

TABLE AKI 6.3 OVERVIEW OF CODING FOR RESPONESES TO THE 17 QUESTIONNAIRE QUESTIONS FROM FIVE PARTICIPANTS

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the total number of codes formed. 9 codes the highest, 0 the low

Questionnaire Codes	Q2.1 Opinions on Quality	Q2.10 Licencing status	Q2.11 Unlicenced herb problems	Q2.12 Scale of unlicenced herbs	Q2.13 Effectiveness of legislation	Q2.14 Non-quality related issues	Q2.15 Scale of Non-quality issues	Q2.16 Human influence on quality	Q2.17 Human degree of influence	Q2.2 Main quality issues	Q2.3 Scale of quality problems	Q2.4 Personal experience with quality issues	Q2.5 Origin of quality issues	Q2.6 Effectiveness at detecting problems	Q2.7 Circumstances for problems to occur	Q2.8 Higher risk herbs	Q2.9 Risk stages of supply chain
Ability	0	1	0	0	0	3	2	0	0	0	0	0	0	1	0	0	0
Adulteration	0	0	1	0	0	0	0	0	1	2	0	0	2	0	1	1	0
Analysis	0	0	0	0	0	0	0	0	0	3	0	0	2	2	1	0	1
Authenticity	0	0	0	0	0	0	0	0	0	2	0	0	0	0	1	1	0
Contamination	0	0	1	0	0	0	0	0	0	5	0	1	1	0	0	0	0
Controls	0	2	0	0	0	1	1	0	3	2	0	0	2	2	4	0	2
Cost	0	0	1	0	0	0	0	1	1	1	0	1	0	0	2	0	0
Dishonesty	0	0	0	0	0	2	0	1	2	0	0	0	3	0	2	1	0
Education	0	0	0	0	0	9	0	2	7	0	0	0	3	0	1	0	0
False Advertising	0	0	0	0	0	3	1	1	2	1	0	1	0	0	0	0	0
False Certification	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	1
Financial motivation	0	0	1	0	0	0	0	1	2	0	0	0	5	0	1	0	0
Honesty	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	1
Improvements	0	0	0	0	1	1	1	0	0	0	0	0	0	2	2	0	0
Incentive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	1
Labelling	0	0	0	0	0	0	0	1	0	4	0	2	1	0	0	0	0
Legislation	0	0	0	0	3	1	0	0	1	0	0	0	0	0	0	0	0
Licencing	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Misidentification	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0
Mistakes	0	0	0	0	0	2	0	0	0	0	0	0	3	0	0	0	0
Online sales	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Potency	0	0	0	0	0	0	0	0	0	1	0	3	0	0	0	0	0
Professional associations	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
Quality control	0	0	1	0	0	0	0	0	0	2	0	7	2	1	1	0	0
Regulation	0	0	0	0	3	1	1	0	0	3	0	0	2	0	5	0	0
Substitution	0	0	1	0	0	0	0	0	1	2	0	1	0	0	0	1	0
Toxicity	0	0	0	0	0	0	0	0	0	3	0	3	0	0	0	1	0
Sum of number of codes	0	11	6	0	7	25	8	8	23	33	0	19	26	11	28	5	6

These unique codes were coded 179 times to question responses from which they originated, and cross-coded a further 37 times to relevant topics, comprising a total of 216 coding incidences. For example, descriptions of herbal contamination in response to question 4, personal experience of quality issues were further coded to question 5 intended to identify the origin of quality issues, *Table AKI 6.3.*

The majority of the coding (175 codes), were attributed to questions 1, 2, 5 and 7 that related to general opinions on Chinese herbal quality (88 codes from Q2.1 to 2.17 inclusive), identifying the main CMP quality issues (33 codes from Q2.2), origin of these issues (26 codes from Q2.5) opinions on the circumstances in which quality issues emerged (28 codes), respectively. Followed by question 4, personal experiences of herbal quality issues (19 codes), question 6, how effectively problematic quality issues are detected, (11 codes), question 9, identifying higher risk stages of supply chains (6 codes) and question 8, seeking to identifying the more problematic herbs (5 codes), *Table AKI 6.3.*

The greatest general contribution to the codes overall was made by those in the field of supply (83 codes) and education (36 codes). The least from those in regulation (42 codes) and manufacturing (18 codes), *Table AKI 6.4.*

TABLE AKI 6.4 OVERVIEW OF CODING FOR ALL QUESTIONNAIRE RESPONESES FOR EACH QUESTION BY OCUPATION, EHTNICITY AND RESIDENCY

Numbers indicate the number of individual codes formed, heat map colours indicate a lower or higher proportion of the sum total number of codes formed. 143 codes the highest, 0 the lowest. n = number of participants

Questionnaire Questions	Occupation = Education (n=1)	Occupation = Supply (n=2)	Occupation = Regulation (n=1)	Occupation = Manufacturing (n=1)	Ethnicity = Chinese (n=4)	Ethnicity = British (n=1)	Residency = China (n=2)	Residency = UK (n=3)
	OCCUPATION				ETHNICITY		RESIDENCY	
Q2.1 Opinions on Quality	1	2	1	1	4	1	2	3
Q2.10 Licencing status	2	3	2	1	6	2	2	6
Q2.11 Unlicenced herb problems	3	1	0	1	2	3	2	3
Q2.12 Scale of unlicenced herbs	1	2	0	1	3	1	2	2
Q2.13 Effectiveness of legislation	2	4	3	1	8	2	2	8
Q2.14 Non-quality related issues	1	8	2	1	11	1	5	7
Q2.15 Scale of Non-quality issues	0	1	3	0	4	0	0	4
Q2.16 Human influence on quality	2	4	2	1	7	2	2	7
Q2.17 Human degree of influence	4	11	0	1	12	4	11	5
Q2.2 Main quality issues	2	20	11	2	33	2	9	26
Q2.3 Scale of quality problems	1	1	1	1	3	1	2	2
Q2.4 Personal experience with quality issues	1	4	2	2	8	1	5	4
Q2.5 Origin of quality issues	4	7	7	1	15	4	3	16
Q2.6 Effectiveness at detecting problems	2	4	3	1	8	2	2	8
Q2.7 Circumstances for problems to occur	6	7	2	1	10	6	2	14
Q2.8 Higher risk herbs	3	0	2	1	3	3	1	5
Q2.9 Risk stages of supply chain	1	4	1	1	6	1	4	3
Sum of number of codes	36	83	42	18	143	36	56	123

Ethnic Chinese were the main contributors to coding in 143 instances, followed by ethnic British responses who were coded 36 times. United Kingdom resident participants constituted the most coding (123 codes), and Chinese resident least (56 codes), *Table AKI 6.4.*

AKI 6.1.4 Contributions to the questionnaire by expertise

The expertise of the participants in the supply network appear to influenced their observation of herbal quality issues when asked question 2.4 relating to personal experience with quality issues. Those in regulation and herbal practice knew of, but did not directly witness quality problems in the recent past, whereas those in herbal manufacture and suppliers had personally experienced such issues, *Table AKI 6.4.*

Experts in the supply field contributed most to opinions that both identified quality issues, the human influences on herbal quality, and their origins. Whereas those in manufacturing and education remarked most on codes that referred to the circumstances and origin of herbal quality issues, in addition to their human influences, *Table AKI 6.4.* The one expert in regulation similarly so, while also contributing to effectiveness in detecting and legislating for quality issues, however notably not to herbal licencing, or human influences on quality issues, as described further throughout the questionnaire responses in *section AKI 6.1.6.,* case 4.

AKI 6.1.5 Contributions to the questionnaire by ethnicity and residency

Respondents of Chinese ethnicity were the most verbose contributors to the questionnaires, both in general and on average per participant when their four-fifth majority was taken into account. However, this verbosity is only evident for those resident in the UK. The least contribution to coded responses was from an ethnic Chinese key informant expert in the area of manufacturing and resident in

China, *Table AKI 6.4* and described further throughout the questionnaire responses in *section AKI 6.1.6.,* case 1.

Chinese contributed most to opinions on the identifying the main quality issues, their origin and qualifying whether they believed they were from human and non-quality related influences, in addition views on the circumstances in which they occur, *Table AKI 6.4.*

AKI 6.1.6 Questionnaire participant responses

AKI 6.1.6.1 Opinions on quality

Posed as questions:

“Do you think there is a problem with the quality of Chinese herbal medicines supplied to the UK?” with tick box options “Yes” and “No”.

“if yes, what are the main issues?” and,

“On what scale would you say a quality problem exists?”, with tick box options “small”, “medium” and “large”

Quotations from participants are indicated by both quotations marks and are italicised.

All of the five questionnaire participants, cases one to five inclusive, (C1 to 5), when asked; “do you think there is a problem with the quality of Chinese herbal

medicines supplied to the UK?", felt that there was a problem with quality. C1, on a medium scale, while the others expressed that this was on a large scale.

Responses to the substantive question 2, C1, C4 and C3 thought that herbal quality problems relate to a lack of quality control, arising from a mixture of inadequacies in analysis and regulatory controls. C1 stating that the main chemical ingredients, in herbs, "*principal components*" were not analysed. C5 due to inadequate regulation allowing, "*misleading*" practices such as "*dishonest product labels*...[and.."...*certificates*..[and]..*quality reports*", leading to "*herb misuse*" and toxicity in herbs, including aflatoxins.

C2 agreed with C3 on the matter of incorrect herb misuse, saying that they believed as much as "*30-40% of OTC and practitioner medicines do not contain the correct herb*" and that in general, "*adulteration and substitution are the most likely issues with CHM products*", however they did not supply further information to verify this opinion.

C3 felt that dishonesty extended further, into "*non-qualified entities claiming to offer herbalist certifications*", reducing the quality of herbal medicine therapeutic practice, and through documentation to authorities including, "*fraudulent actions taken to circumvent these checks in order to become an approved supplier*", by suppliers in the UK. Although the last claim was not substantiated by the participant, the others were with commercial laboratory test reports they provided in their capacity as a herbal supplier, this is detailed further in the next section AKI 6.1.6.2, asking about personal experience with quality issues.

All agreed with C3 upon these points, C4 described more specific types of adulteration, including usage of sulphur dioxide and pesticides, C4 offered "*pharmaceutical ingredients*" and "*heavy metals*" as examples of a problematic contamination issues. C2 further adding they believed undeclared "*cheaper synthetic phytomarkers*" were being added to herbs to appear more potent in analyses.

Participant opinions offered in response to this question of what were the main quality issues expanded and detailed in their responses in subsequent questions.

The quotations selected were from the question 2 paragraph, of the participant transcripts.

Codes formed from the selected and quoted participant responses to question 2 were; adulteration, analysis, authenticity, contamination, controls, cost, false advertising, false certification, labelling, misidentification, potency, quality control, regulation, substitution, and toxicity.

AKI 6.1.6.2 Personal experience with quality issues

Posed as question 4, “could you give examples of issues you have had to deal with personally?”.

Though all participants agreed that there were significant quality problems with CHM, there was clear divergence in the observations of those with expertise in clinical practice and others. C4 and C2 in addition to their primary roles as a regulator and an educator respectively, were practicing herbalists who did not have any recent personal experience of quality problems.

C4 believed that things are continually improving with the introduction of approved suppliers in the UK, “*15 years ago though, I noticed that the stock was very poor – no smell to the herbs, dusty, badly packaged and sometimes the incorrect species. I switched to a better supplier and the problems resolved*”. C2, had not seen any quality problem in their herbal practice.

C1, who was primarily involved in manufacturing and also conducts research for a herbal company had seen problems with one herb throughout the whole supplier market, with “[the]..*same products from different company will display*..[the same]..*issue*”, though they did not specify which herb(s). Supplier C5, had previously conducted a survey of UK high street outlets, claiming to find some herbs tested had as much as twenty times the EU allowed levels of aflatoxin, and also they had seen products with low levels of herbal content. Although this publication as verified by the researcher, it is not referenced here to maintain the participant’s anonymity. C3, also a supplier, included a detailed list of quality

problems and laboratory test reports confirming C3's experience attached in the thesis appendix, *section AKI 5* questionnaire participant anonymised transcript sample, case 3.

In summary, C3 substantiated the following points:

Labelling

- Picture of herbal product with no ingredients listed on a bottle label.

False certification claims

- Copy of online approved supplier webpage supplier with unsubstantiated certification claim relating to MHRA (supplier name redacted by researcher).

Variability in quality

Laboratory test reports provided for:

- Variable active ingredient content of Gan cao, glycyrrhizin.
- Chen pi content 6 times lower than detected in others.
- Dang Shen concentrate, less than 33% content.

Additions to herbs

Laboratory test reports provided for:

- Preservative (sulphur): More than 70% of surveyed herbal material sulphated.
- Paeoniflorin sulfonate detected in Bai Shao Yao.
- Unusually high levels of binder / filler, lactose detected.

Non-authentic herbs

Laboratory test reports provided for:

- Long gu with low calcium content.

Toxicity

Laboratory test reports provided for:

- Aflatoxin detected in Bai Zi Ren with aflatoxin levels high.
- Aflatoxin detected in Yan Hu Suo and Bai Zi Ren.

The quotations selected were from the question 4 paragraph of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the selected participant responses for question 4 were; contamination, cost, false advertising, labelling, potency, quality control, substitution and toxicity.

AKI 6.1.6.3 Opinions on the origin of quality issues

Posed as question 5, “what is the origin of the problems?”.

When asked what was the origin of these herbal quality problems, opinions diverged into two areas. First, those around mistaken and wilful adulteration without detection and secondly, the pursuit of profit. Though the participant opinion was divergent, the nature of these is not necessarily so, as the motivation for profit many incite such intentional nefarious practices, as recorded throughout the commercial herbal industry (Galvin-King, 2020).

C2 thought that a there was a mixture of inadvertent and purposeful action, "*genuine errors, misidentification of similar species, together with purposeful adulteration with similar species*". Adding that they were aware of intentional Ginkgo product adulteration with synthetic chemicals to pass quality tests. Such practices were previously reported, where the presence of a 5-hydroxytryptophan derivative. The non-natural constituent of *Ginkgo biloba* L. was detected in a central London survey of thirty-five herb samples using a combination of HPTLC and NMR with principle component analysis (Booker, Frommenwiler, et al., 2016). Further revealing unusual concentrations of rutin, a relatively cheap extract from buckwheat possibly added to enhance the levels of low quality which would not pass the *G. biloba* minimum 24% flavonol glycoside content standard (Harnly, Luthria, & Chen, 2012). Further, studies contained dyes and flavonoid adulterants not allowed in United States Pharmacopeia specifications (Frommenwiler et al., 2016).

Both C5 and C3, supported this view, C5 saying that current regulation and testing are not sufficient "*the quality*..[and]..*authenticity of the herbal products* [have]..*no way to be regulated and ensured*", and asserted by C3, due to the "*limitations in regulation and due diligence*".

The other participants C1, C3, and C4, however held a different general view from C2 and C5, believing that the origin of herbal quality problems stemmed from the issue of financial motivation. C1 stated that "*customers choose the products based on the price*", interpreted in context here as, if the product quality costs a lot then it may not be competitive in the market and cheaper (possibly lesser quality herbs) will predominate. This may be due in-part perhaps to

prescribing herbalist's lack of knowledge about how to discern better from lesser quality herbs, for example, due complicated terminology used for current certificates of analysis (CoA) leaving herbalists, "*unable to perform due diligence*..[as they]..*don't understand how to read CoAs or verify validity of CoAs*.", suggested by C3.

Participant C4 held a view in common with aspects of that held by C1, C3, C5. C4 who expressed that where business is concerned, profit is the priority, as "*herbal suppliers often simply want to make the most money that they can at any human price..",* and believed fundamentally that "*the consumer wants quality products which are cheap and those two desires are incompatible*".

The quotations selected were from the question 5 paragraph of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 5 were; adulteration, analysis, contamination, controls, dishonestly, education, financial motivation, labelling, mistakes, quality control and regulation.

AKI 6.1.6.4 Opinions on effective detection of quality problems

Posed as question 6, "are we effective at detecting these problems?".

Overall, there was a prevailing opinion apparent around an inadequacy to detect problems with herbal quality with one exception, However, these expressions of effectiveness in detecting issues were on a spectrum ranging from direct "*no*" in

the case of C3, to occasionally, as expressed by C2 that "*It really depends*" on whether those involved have the infrastructure and finances to conduct testing.

C4 qualified C2's opinion somewhat, "..[the]..*knowledge and capability is there to grow herbs sustainably, with a fair rate of pay to growers, with good QA in place and to pass this down from 'field to patient' but I think that a small sector of the market wants to engage with it*", feeling that "*there is a need for practitioner, patient and public education*" to motivate further engagement. C3's felt quality problems were not being detected because, "..[it is]..*a challenge to balance comprehensiveness of testing without suffocating the industry with time and money constraints.*" C5 thought that there was "*far from enough*" detection of quality issues because of reliance on laboratory-based testing, also expressed by Chinese medicine cultivators who have stated "*as a small grower, I cannot afford to do lab testing of the herbs I grow as it is very expensive.*" (Schafer, 2011, p. 12), generally only available at scale to larger commercial interests and academic institutions.

The quotations selected were from the question 6 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the selected participant responses to question 6 were; ability, analysis, controls, honesty, potential improvements and quality control.

AKI 6.1.6.5 Opinions on circumstances allowing quality problems to occur

Posed as question 7, "what circumstances or factors have allowed these problems to occur?

When asked what circumstances or factors have allowed quality problems to occur, there was a central belief apparent in the participants' responses not only around financial gain as mentioned in responses to earlier questions, but more specifically in relation to the idea of incentive. Lack of incentives to be compliant, and in some cases disincentivising attention from authorities and cost burden, while those who chose non-compliant, who did not seem to suffer such disadvantages.

C1 and C4 clearly reaffirmed the above-mentioned cost factor influencing poor herbal quality, with C1 repeating that "*customers choose the products based on the price*" and C4 with "*money largely*", and that their exists "*a general global market which is built on securing the lowest price for goods rather than paying for quality*", leaving little financial incentive for higher quality products. This is echoed by authors who described the incentives for non-compliance and the consequences of profit-priority behaviour, which appears almost necessary for some businesses to survive in the sometimes highly price volatile global Chinese herbal market (A. B. Cunningham & X. C. Long, 2019).

C2 believes it's not so complicated and it is simply a matter that, "[those]..*in the supply chain think they can get away with adulteration*" and C3 going further to say that "*good suppliers are not protected by regulation and bad suppliers can easily circumvent the current regulatory structure*", leaving little incentive to adhere to costly and time consuming regulation. C5 took a broad view on the circumstances in which quality issues have emerged, that it is "*self-regulated by self-organised bodies*", with little external oversight.

The quotations selected were from the question 7 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 7 included; ability, adulteration, analysis, authenticity, controls, cost, dishonestly, education, financial motivation, honesty, improvements, incentives, misidentification, quality control and regulation.

AKI 6.1.6.6 Opinions on specific herbs at higher risk

Posed as question 8, “are there specific Chinese herbs that you feel present higher risk?”.

When participants considered which herbs presented a relatively higher risk of quality issues than others, a harmonised opinion surfaced around herbs of high value. Value of expense, and plants’ rarity. They specified different types of quality issues for different types of herbs, authenticity for expensive ones, and toxicity for seeds.

Most, C2, C4 and C5, directly referred to more expensive herbs. With C4 herbs stating ““*herbs*”..*which are expensive to grow will be at risk of forgery or substitution specifically diving herbs*” and C5 further specifying that for “*authenticity problems, mainly for the expensive and rare herbs*” and “*toxicity issues, mainly in herbs with used part as seeds*”. C4 also added specifically “*those containing pyrrolizidine alkaloids*”.

More expensive herbs are targeted for adulteration (Perkin-Elmer, 2020) in their role as medicines and in culinary use, such as Saffron's (*Crocus sativus* L.) costing in excess of €10,000 / Kg, (Kafi, Kamili, Husaini, Ozturk, & Altay, 2018), and others (Moore, Spink, & Lipp, 2012). Additionally the issues with toxicity in seeds was well established as demonstrated with seeds of *Hyoscyamus niger* L., and *Strychnos nux-vomica* L., know to pose risk due to their hyoscyamine and strychnine content respectively (C. Xiong et al., 2018).

Further, the toxicity of CHM was highlighted by a comprehensive eleven year survey of 1067 samples in a Taiwanese herbal manufacturing facility pointed to seeds in particular as a potential source of toxicity, with aflatoxins featuring highly (M.-Y. Chien, Yang, Huang, & Chen, 2018). C4's reference to Pyrrolizidine alkaloids (PA) are those intrinsic and potentially toxic that are mainly present in the *Asteracea*, *Boraginaceae*, *Fabaceae* plant families (Dharmananda, 2001), however PA are also known to be naturally occurring in high concentrations as found in the *Orchidaceae* family and more than forty-nine Chinese herbal medicines including *Crotalaria sessiliflora* L ., (CP: Ye bai he), and *Tussilago farfara* L . (CP: Kuan dong hua) (Peter P Fu et al., 2002).

The quotations selected were from the question 8 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 8 were; adulteration, authenticity, dishonestly, substitution and toxicity.

AKI 6.1.6.7 Opinions on quality risks at specific stages of the herbal supply chain

Posed as question 9, “do you think there are higher risks at specific stages of the herbal supply from Asia to the UK?”

Opinions on herbal quality risks at specific stages the supply chain divided opinions somewhat. Though general agreement emerged on specific risks occurring at certain stages of the supply chain, opinions on which stage was higher risk differed, and that they were influenced by external factors such as enforcement of import checks and willingness of suppliers to comply to regulations.

C4 thought that “*risks can occur anywhere along the chain*”, and makes the point that, “*herbs may be fine in the country of origin, for example, but be shipped in unsuitable conditions. Or there may be contamination at source. Or the product might be fine when it arrives in the UK but then be processed in such a way as to reduce quality, or only a very small percentage of it used but pharmaceutical products added*”. C3 agrees with this but feels that the import stage is critical, and failure is due to “*stringency of the import process in the UK fails to identify and filter out poor quality*”, whereas C2 identifies that it is upon the willingness of the supplier to “comply to GACP”.

These points are credible as China cancelled national adherence to GAP in 2016 (M. Zhang et al., 2021), C3 mentioned earlier here that the lack of effective testing in place at specific supply stages has affected the quality of herbs adversely. Importation checks, do occur randomly but it is sporadic and normally initiated

through the suspicion of illegal practices, specifically, in the case of the UK, under section 1.2.2 of the “Border and Protocol guidance, relating to agreement with international conventions such as CITES, the Convention on International Trade in Endangered Species of Wild Fauna and Flora, in controlling, “Wild Fauna and Flora section 1.2.3, Phytosanitary Controls Additionally, section 1.2.5 relating to medicines in general, if claimed or intended for “medical” use. (Secretariat, 2011), (Government, 2021).

The quotations selected were from the question 9 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 9 were; analysis, controls, false certification, honesty and incentive.

AKI 6.1.6.8 Opinions on licenced and unlicensed herbs

When asked about the emergence of quality problems in licenced and unlicensed herbs, posed as question 10, “so you feel that these issues affect only unlicensed herbs or are they also applicable to licensed herbs?. Participants’ thoughts on quality problems in licenced and unlicensed herbs was diverse. Ranging from full confidence to little influence of the licencing process to ensure herbal quality. However, opinions appear biased towards mixed reasons rather than polarised, “yes” or “no” feelings about licencing and herbal quality.

C2, C4 and C5 felt that licenced herbs were generally of better quality, as C2 stated, [poor quality] *“issues mainly affects unlicensed herbs*”. C2 and C4 both specifically referred to products that have received Traditional Herbal

Registration (THR) in the UK (Dickinson et al., 2019), an adaptation of the general EU directive 2004/24 EC which has mandated licencing of herbal products since 2011 (EU, 2004). C4 wished to emphasise that "*if there are any problems products*..[they would be]..*recalled.*", however also acknowledged that, "*there are problems in the unlicensed sector both in terms of OTC*..[over the counter]..*products and herbs*". C5, added "*in order to apply for license for the TCM products, there is requirement for auditing the manufacturer, so the problems are much less than the unlicensed herbs*".

C1 and C3 wholly disagreed with the others, both clearly stating their attitude in relation to licencing. In C1's case, that "*both unlicensed herbs and licensed herbs.*.[are affected]", and C3 "*given the fundamental flaws in the current licensing system, the problems that exist are not specific to whether herbs are licensed or unlicensed. Currently, having a license in the UK does not ensure quality".* Further adding in relation to suppliers that **"***entities are actually capable of operating without licenses at all*".

The quotations selected were from the question 10 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 10 were; ability, controls, and licencing.

AKI 6.1.6.9 Opinions on the scale of unlicensed Chinese herbs

Posed as question 11, "what main problems would you say unlicensed Chinese herbal medicines present?".

Answers to this question illustrated two observations, firstly that the question was perhaps poorly constructed and possibly not necessary, or secondly, it may indicate that opinions on this topic had already reached saturation at the point that this question was posed.

C3, did not respond to this question and, C4, noted "*same as* "previous" *answer*" to the opinions on licenced and unlicensed herbs.

C1 wrote "*price of unlicensed Chinese herbal medicines is cheaper*" and C5, "*contamination, substitution, and adulteration*", both repetitions of their earlier responses.

The quotations selected were from the question 11 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 11 were; adulteration, contamination, cost, financial motivation, quality control, and substitution.

AKI 6.1.6.10 Opinions on the scale of unlicensed Chinese herbs

Posed as question 12, "on what scale would you say unlicensed Chinese herbs exist?".

This multiple-choice response revealed a significant bias in opinion, that unlicensed herbs are available on a mainly large scale (C2 – C4, inclusive), with one respondent, C1 indicating they believed this was a medium scale issue. This

directly mirrored earlier opinions on what scale quality problems in general existed, including the same participant C1 answering similarly.

AKI 6.1.6.11 Opinions on effectiveness of legislation for quality problems

Posed as question 13, “how effective do you think legislation has been at dealing with Chinese herbal medicine quality problems?”.

When asked about the effectiveness of legislation, there was a general sentiment that legislation was lacking in effect, however there was an underlying thread of opinion that regulation could be effective if implemented correctly, as evident in the highly qualified responses to this question, in contrast to that for the previous question 12. There appeared perhaps a general sense of what was interpreted as frustration, that legislation could work, but was not effective in its current form.

C1, was the only participant with an unqualified response, simply stating that it is “*much effective*”. Whereas C4, disagreed with this expressing that “*we haven’t really had effective regulation”,* however highly qualified this opinion by adding, *“the introduction of the THR has given customer assurance about THR products bought over the counter but the market is still full of other unlicensed products which are at best effective, often ineffective and at worst dangerous*”.

C2, joked “*what legislation? I wish we had legally binding registration*”, then added, “*seriously though, any herbal practitioner supplier who meets GACP and GMP standards is far more likely to have dependable products compared to one*

that does not", which indicated the general tone of the participants on this topic. GACP and GMP, refer to good practice for collection, agricultural, collection and good manufacturing guidelines (M. Zhang et al., 2021). C5 stated that "*the legislation...*[is]...*only strict at controlling the licensed TCM products, but did not deal much about the unlicensed ones*", which perhaps expresses more about the inequitable application of legislation than its effectiveness, as asked.

C3 responded in a similarly nuanced manner, feeling it was "*commercially unfeasible to enforce strict licenses on individual herbs*", due to the complexity of Chinese herbal medicine practice as a "*diverse composition of several herbs selected from a repository of hundreds of different herbs*" while also believing potential exists for improvement, that "*current legislation needs to look towards other countries in which herbal medicine is part of the healthcare system*" where there were "*valuable lessons*" to be learnt.

The inconsistencies, variable levels of participation and voluntary engagement nature of GACP and GMP expressed by C2, was previously acknowledged by (M. Zhang et al., 2021) who detailed the many of different forms of GxP and difficulties encountered by those who have chosen to participate compliance to various degrees. (H. H. Fong, 2002) had earlier highlighted many the challenges related to integrating these guidelines while emphasising the necessity for improving enforcement of these guidelines, further recommending post-marketing quality assurance surveillance to verify that practical adherence, in addition to on-paper compliance.

C3's reference other countries who could act as good examples, included Switzerland who had stringent requirements from herbal medicines, since 1971 from when they considered similar to pharmaceutical medicines and therefore requiring a product licence and associated testing (Organization, 1998). Additionally Switzerland via the Swiss Federal Office of Public Health, reimburses the public medical products, through a system of compulsory public health insurance (Gächter & Tremp, 2019). Chinese herbal use is covered by an additional supplementary payment and is considered high quality due to the convention of batch testing all Chinese herbs to standards often higher those of the European Pharmacopeia (Complemedis, 2023). Germany too has a specific tradition with Chinese medicine, in 1991 as the first recognised TCM hospital was opened in Koetzting, Germany, in collaboration with Hospital in Dongzhimen, Beijing (Melchart in (Q. H. Xu et al., 2013), and was a primary historical influence on the development of the first modern Chinese Pharmacopeia(M. Fitzgerald et al., 2020). Orthodox biomedical physicians in Germany often prescribe and recommend natural medicines alongside pharmaceutical products (Joos, Glassen, & Musselmann, 2012) making it the largest purchaser in Europe for complementary medicine, (WHO, 2005), where Herbal Medicines have been regulated since 1989 and tested to pharmaceutical standards (WHO, 2019).

The quotations selected were from the question 13 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 13 were; improvements, legislation and regulation.

AKI 6.1.6.12 Opinions on non-quality CMP issues

Posed as question 14, “are there non-quality related problems with Chinese herbal medicine?”.

Although seeking opinions on non-quality related issues in an investigation of herbal quality may at first seem somewhat irrelevant, it did reveal several pertinent influences on CHM quality. It raised with most participants, the effect of education on the supply and prescription of CMP.

Though one participant felt there were no non-quality related issues, most referred either directly or indirectly to the influence of education on CHM quality.

The circular nature of the effect on quality issues could have on the practice of herbal medicine, and in turn the practice on herbal quality became apparent, C5 “*lack of TCM education, qualified TCM practitioners with real knowledge are hard to find, which lead to the result that Chinese Herbal Medicines are sometimes inappropriately prescribed*”, further reflecting that “*due to the lack of understanding of Chinese Herbal Medicine in UK, there are lot of herbs being banned for various of reasons, which lead the practitioners practicing without enough herbs*”. C2 mentions that reports of such events has led to “*some poor and misguided media coverage*…[which]…*has damaged the sector*…*more with medical practitioners rather than the public*”. Deaths from mistaken and unlicensed Chinese herbal usage use containing aristolochic acids and ephedrine have been confirmed leading to a ban and restriction for use only through prescription by general medical practitioners and under the supervision

of pharmacists (Government, 2021). Similarly, the use of Chinese herbs for skin conditions in the 90s led to negative sentiment media reports (Kane, Kane, & Jain, 1995).

C4 indicated that such events may not be due to herbal quality in the first instance, instead they may arise from "*lack of patient / public awareness about the need to get proper treatment from a qualified practitioner*", reflecting again to education. There has been a reduction in the number of courses in the UK where most of the participants reside, with closures of Lincoln University, Middlesex University and more recently the University of Westminster ceasing applications for degree course in Chinese herbal medicine (EHTPA, 2022). The regulation of herbal practitioner in the UK is on a voluntary basis, through registration following an application process several organisations such as the ATCM (association of traditional Chinese medicine and acupuncture UK) and RCHM (register of Chinese herbal medicine) which assesses applicants experience and education, not necessarily within a university accredited system. In return the practitioner agrees to adhere to a code of practice guidelines which warrants the recognition of their patients' treatments by insurance companies (ATCM, 2021), (RCHM, 2021).

Though C3, felt that damage to the perception and reputation of CHM was not only due those who were "insufficiently educated", but also "*poor quality of supply can only be propagated by entities which have an irresponsible disregard for patient welfare*", that it is not just those who are not aware of their *"irresponsible"* actions but also those who simply do not care about the consequences.

C4 also brought attention to the public that "*self-prescribed for serious illness'* without adequate knowledge, in part either knowingly or otherwise due to "*medical claims being made*" through *"mislabelling"* of products.
C5 and C3 reiterated their earlier feelings on lack of regulation, C3 in particular, "*regulation of online shops*", from which the public and potentially irresponsible practitioners could secure an unverified a herbal supply.

C1 was the only participant who felt there were no other problems to mention outside that of quality issues for CHM.

The quotations selected were from the question 14 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 14 were; ability, controls, dishonestly, education, false advertising, false certification, improvements, legislation, misidentification, mistakes and regulation.

AKI 6.1.6.13 Opinions on the scale of non-quality related CMP issues

Posed as question 15, "please give your thoughts on these including a sense of their scale".

When asked about the scale of non-quality related issues most participants did not respond to the question. The two who did, C3 and C4, felt that these were

“huge” and “big” respectively. C4 gave further thoughts on why this was the case, indicating that the regulatory agencies may not have the ability to be effective, with “*inadequate means for bodies such as the MHRA to deal with products bought on the internet*”, such as “*Amazon and eBay can continue to sell unlicensed herbal manufactured products”* which if “*taken down they are back up again in a different guise”.* This point was also expressed by legal experts in the United States who attest to herbal medicines that were removed from online sales platforms following warnings, then “reappear. They further verified the availability of counterfeit goods directly from Chinese online sources, that allowing such practices to continue on a global scale (Chow, 2019).

The quotations in this section are selected from question 15 paragraph of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 15 were; ability, controls, dishonesty, education, false advertising, false certification, improvements, legislation, misidentification, mistakes, online sales, and regulation.

The quotations selected were from the question 15 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

AKI 6.1.6.14 Opinions on human influence upon Chinese herbal medicine quality problems

Posed as question 16, “do people cause quality problems for Chinese herbal medicine?”.

Opinions on the human influences upon Chinese herbal medicine quality were clearly stated by those who responded to the question. C1, C2 and C5 simply replied “yes”, as did C4, with further explanation.

C4’s thought the motivating influence of human actions was that of cost**,** as “*patients want cheap products and practitioners want to buy these too*”, in addition to labelling products dishonestly to make higher profits, saying “*many high street CHM shops sell such poor quality products which don’t have proper labelling, for which they make medical claims and charge a lot of money*”. C3 chose not to respond this question, however it is evident from C3’s earlier response to question 14, they believed human thought and actions do play a part in affecting CHM quality, as they stated their attitudes towards CHM, education, and wilful disregard for consequences, among others.

The quotations selected were from the question 16 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

Codes formed from the participant responses to question 16 were; education, cost, dishonesty, false advertising, false certification, financial motivation, and labelling.

AKI 6.1.6.15 Opinions on the scale of human influence on Chinese herbal medicine quality problems

Posed as question 17 “if so, please give your thoughts including how big are these problems?”.

For the last question on the questionnaire those who had given shorter answers in the previous earlier question tended to write more information. Conversely, participant C3, who was highly verbose in earlier questions, (2, 4, 5, 6, 7, 9, 10,13 and 14) did not respond to this question nor questions 11 and 16. As did C4, who was consistently highly responsive throughout, but did not comment on the final question. This may be perhaps as a consequence of opinion saturation or other unknown factors related to the circumstance in which they completed the questionnaire. Whereas C1 who had given very short, monosyllabic “yes”, “no” or no answers in earlier questions 6, 8, 9, 13, 14, 15, expanded in their comments, as did C5.

When expressing thoughts on the issue of the scale that human influence played upon Chinese herbal medicine quality problems, participants gave highly qualified answers, most offering examples rather describing the scale of the issues, as asked.

C3 did not offer any answer, however C4 thought the scale of this influence was significant, C1, C2 and C5 believed it is increasing. C1 thought this was “*because most herbs are cultivate*[d] *today, the problem will become more seriously”,* interpreted here, “*as more herbs are cultivated*”, there will be more human involvement in cultivation perhaps imparting and increasing influence of

associated human problems. Nonetheless, even with modern farming methods in place, it has been estimated that still as much as 80% of Chinese herbs are collected from the wild, however this number is reducing with evidence of increased cultivation (X. Li et al., 2015).

While C2 thought the scale of influence is "*big*" and will also increase due to the people who "*cause/allow the adulteration, substitution and contamination*" both intentionally and unintentionally through "ignorance" or lack of knowledge. They also drew attention to variable standards of clinical practice for "*CHM practitioners who do not belong to a PA..*[professional associations]*..and who are not practicing safely, some CHM PAs do not have as high a standard as others*".

C5 though the scale of human influence on Chinese herbal medicine quality wasn't big, however did think it would increase and reflect negatively upon it, as the standard of education for CHM practitioners lowers. Observing that "*educational bodies in UK providing high quality TCM educations, but all closed their courses…more and more small scaled, unprofessional, so called TCM education service appeared on the market, poorer education means less qualified TCM practitioners*". Even if higher educational courses were in place C5 felt that "*some of whom even with no related knowledge at all as they are practising TCM from a working experience as sales*", were providing CHM services". C5 reiterated the lack of legislation.

The quotations selected were from the question 17 paragraph, of the participant transcripts, cases 1 to 5 inclusive.

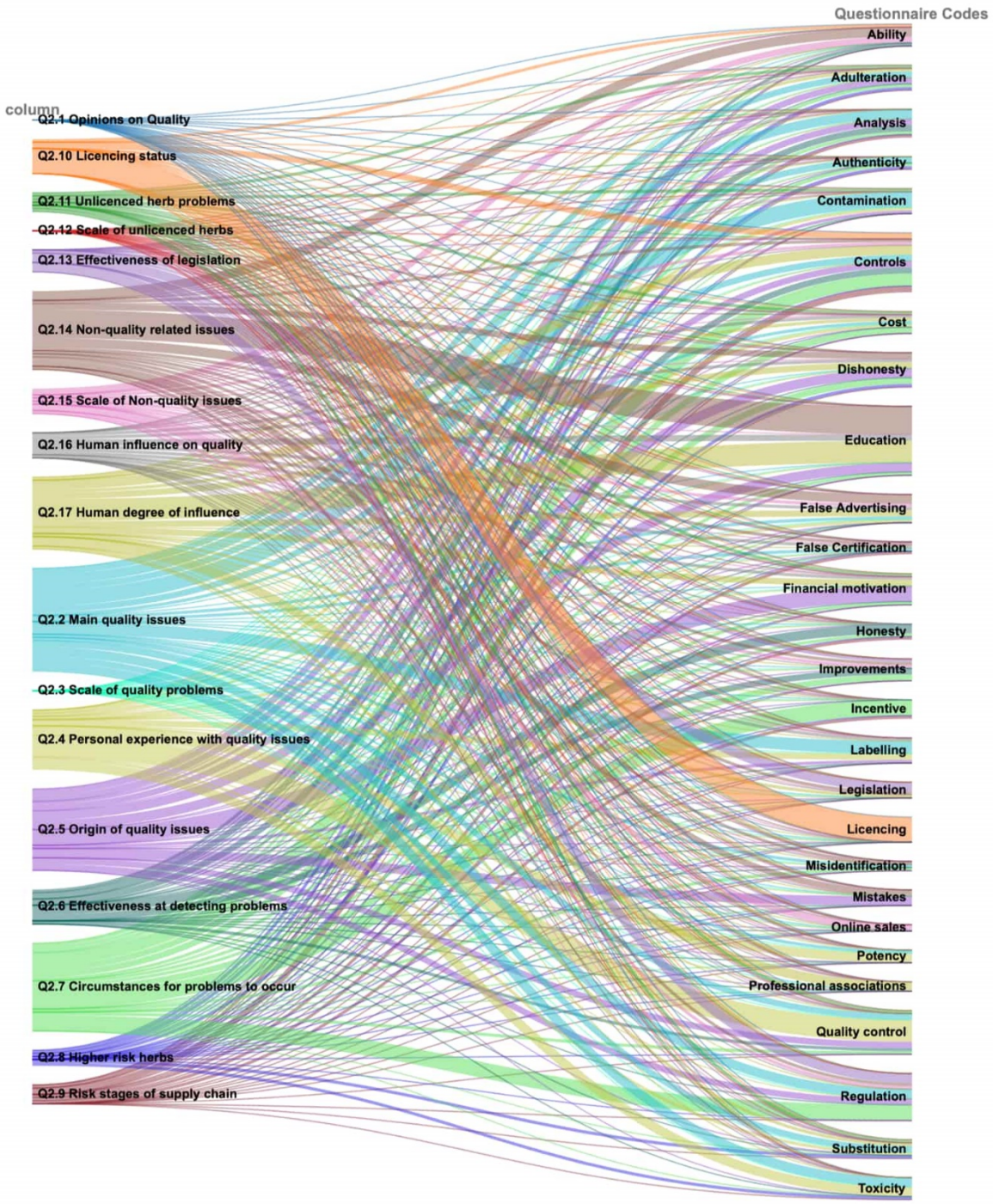
Codes formed from the participant responses to question 17 were; education, controls, cost, dishonesty, false advertising, financial motivation, legislation, professional associations, and substitution.

AKI 6.2 Thematic analysis of questionnaire responses

The preceding sections represent steps one and two of the thematic coding process, those of familiarisation and generating the initial codes. *Figure AKI 6.1* is an illustration of the relationship between these two steps, where each coloured strand represents an instance where a narrative element in response to each question, listed on the left axis, has been formed a code, listed on the right-hand axis.

FIGURE AKI 6.1 ILLUSTRATION OF THE RELATIONSHIP BETWEEN NARRATIVE ELEMENTS AND CODES FROM QUESTIONNAIRE RESPONSES

Each strand represents one narrative element in response to a question (left axis) that has been coded to a new code (right axis)



The proceeding section documents the subsequent three steps shows the formation of themes from codes, *Table AKI 6.5*, those of;

3 Searching for themes

4 Reviewing themes

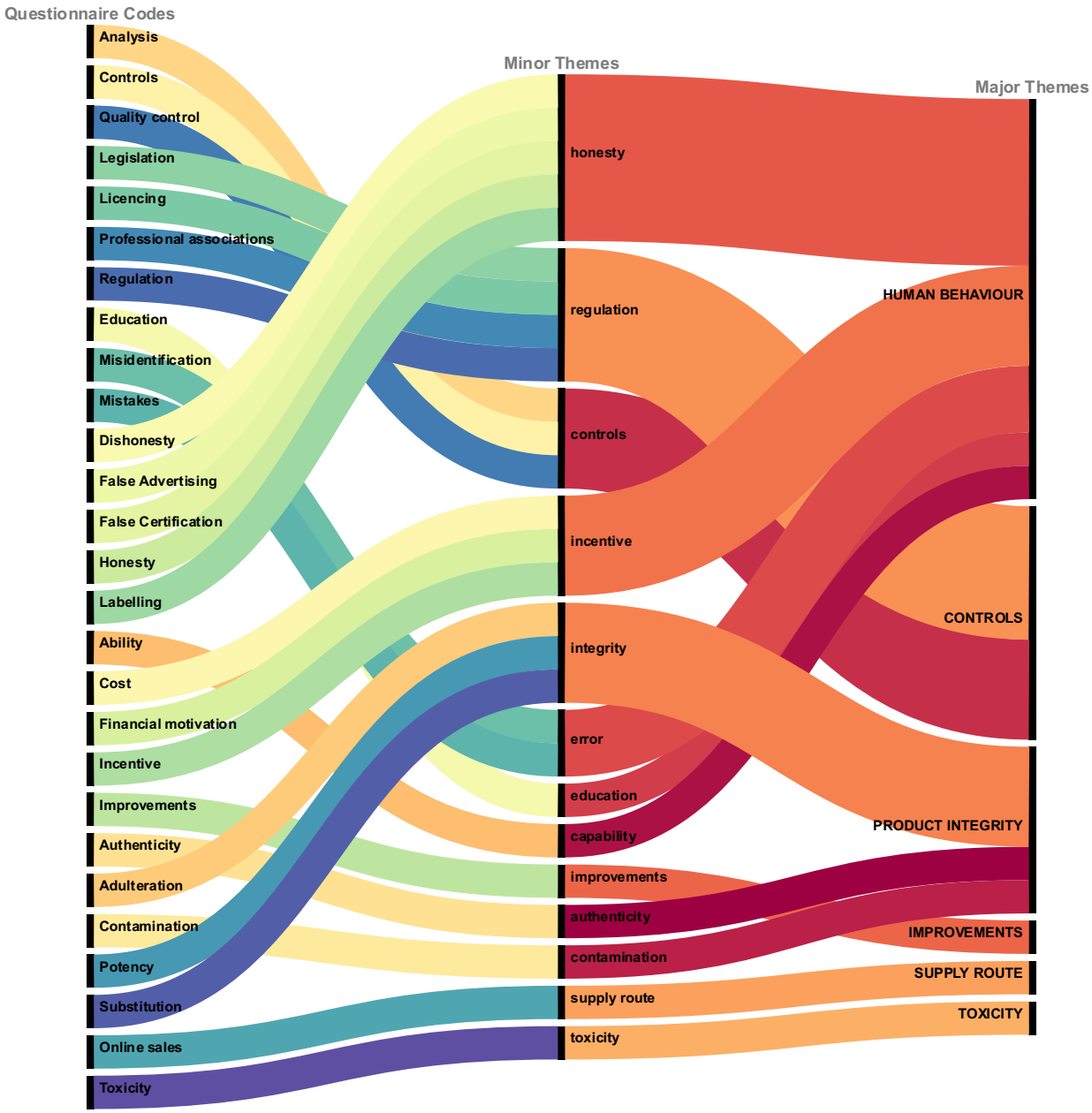
5 Defining and naming themes

The final step six, producing the report is shown in *figure AKI 6.2..*

TABLE AKI 6.5 STEPS 3 TO 5 IN THE THEMATIC ANALYSIS PROCESS FROM CODES TO THEMES FROM QUESTIONNAIRE RESPONSES

Initial codes	STEP 3 Searching for themes	STEP 4 Reviewing themes	STEP 5 Defining and naming themes (minor)	STEP 5 CONTINUED Defining and naming themes (major)
Analysis	*controls*	*controls*	**controls**	**CONTROLS**
Controls	*control*	*controls*		
Quality control	*controls*	*controls*		
Legislation	*regulation*	*regulation*	**regulation**	
Licencing	*regulation*	*regulation*		
Professional associations	*regulation*	*regulation*		
Regulation	*regulation*	*regulation*		
Education	*education*	*education*	**education**	**HUMAN BEHAVIOUR**
Misidentification	*human error*	*error*	**error**	
Mistakes	*human error*	*error*		
Dishonesty	*honesty*	*honesty*	**honesty**	
False Advertising	*advertising*	*honesty*		
False Certification	*false claims*	*claims*		
Honesty	*honesty*	*honesty*		
Labelling	*labelling*	*claims*		
Ability	*capability*	*capability*	**capability**	
Cost	*value*	*incentive*	**incentive**	
Financial motivation	*financial incentive*	*incentive*		
Incentive	*incentives*	*incentives*		
Improvements	*improvements*	*improvements*	**improvements**	**IMPROVEMENTS**
Authenticity	*authenticity*	*authenticity*	**authenticity**	**PRODUCT INTEGRITY**
Adulteration	*herb integrity*	*integrity*	**integrity**	
Contamination	*contamination*	*contamination*	**contamination**	
Potency	*herb integrity*	*integrity*	**integrity**	
Substitution	*herb integrity*	*herb integrity*		
Online sales	*online supply*	*supply route*	**supply route**	**SUPPLY ROUTE**
Toxicity	*toxicity*	*toxicity*	**toxicity**	**TOXICITY**

FIGURE AKI 6.2. STEP 6, PRODUCING THE THEMATIC ANALYSIS REPORT: ILLUSTRATION OF THE RELATIONSHIP BETWEEN CODES (LEFT) FORMED FROM QUESTIONNAIRE RESPONSES THEN FORMING MINOR THEMES (CENTRE), AND FINALLY MAJOR THEMES (RIGHT)



AKI 6.3 Emphasis of the key informant responses to the questionnaire

The themes formed both major and minor, were composed from a relatively higher or lower number of codes. Themes formed from a greater number of codes represent a greater emphasis in the key informant responses. Themes are underlined in the following text to differentiated from general terms.

The six themes formed from contributions to the questionnaire process in order from highest to lowest number of unique codes were; human behaviour, controls, product Integrity, toxicity, improvements and supply route, respectively.

The theme of greatest emphasis from the questionnaire process was that of human behaviour influencing the quality of CMP and secondly, the theme of controls, referring to controls intended to maintain CMP quality by minimising challenges of both human and natural origin to the integrity of the medicinal plants, and their products. The third theme of product integrity related to participants' descriptions of these challenges to quality, such alteration of the authenticity, potency, or label descriptions to a medicinal plant product through adulteration, substitution, or contamination that could impact its purity, safety or efficacy. The theme of toxicity formed from informants descriptions of how these challenges to product integrity could ultimately impart toxic effects on consumers, in addition to the natural and intrinsic toxicity of some medicinal plants. The theme of improvements represented the informants' collective contributions to improving the general problem of persistent CMP quality issues, and the that of supply route,

from descriptions of the different paths which herbs can follow from cultivation to consumer, including online sales.

The 14 minor themes emerging from the questionnaire process formed the six major themes. Three minor themes, those of toxicity, improvements and supply route, respectively, were of significantly different thematic content to remain differentiated as single major themes.

Two minor themes, controls and regulation were formed from thematically similar but comparatively diverse content. Participants sometimes referred to controls as laboratory quality control testing and others to regulation as the licensing of herbs and herbal practitioners.

The four minor themes that formed the major theme product integrity were related but more diverse than those that formed the controls theme. They included, authenticity, integrity, contamination, and again, integrity. Integrity emerged twice as a minor theme from different types of responses, that were highly related. One from participants descriptions of adulteration and the other from substitution. Adulteration describing the addition of undeclared or non-authentic material to a medicinal plant, and substitution where one plant is presented as another. However, in cases where there is a high level or complete adulteration with another plant or material, it is effectively a substitution, and were grouped under the major themes of product integrity. The minor themes of authenticity and contamination were also related but from conceptually different responses. Authenticity in more general descriptions of cases where one medicinal plant was erroneous or intentional exchanged for another, as in the case of substitution, whereas contamination derived from descriptions specific materials often in small

concentrations but sufficiently potent to affect the safety of herbs, such as heavy metals and a various toxins.

The most diverse major theme formed from the questionnaire responses, that of human behaviour comprised five disparate but related minor themes; education, error, capability, honesty and incentive.

They related collectively to human actions that affected the quality of CMP. Education featured highly, as both a detrimental influence on CMP and as a possible solution to quality problems. Detrimentally, in contributions describing where the absence of training, where it is insufficient, or not relevant specifically to CMP, and therefore, those handling medicinal plants could act inadvertently in a manner that adversely affected quality. Including when misidentifying the correct plant species, storing inappropriately, or conducting insufficient testing. Conversely, as a potential solution, participants suggested more widespread education and that which is more specific to Chinese herbs could somewhat improve and address the influences of human actions which effect the recurrent and persistent CMP problems that reach and affect consumers. The four minor themes error, capability, honesty and incentive also represented participant contributions around the effects of human behaviour on quality. Human error and lack of capability arising from the aforementioned insufficient knowledge and capability of those handling herbs in the supply chain. The themes of honesty and incentive, emerged from informants' accounts of intentionally dishonest and nefarious behaviour such as adulteration, and the incentive to conduct such actions, of gaining profit by increasing the value of cheaper herbal material in priority to supplying genuine and unadulterated CMP together with the positive and beneficial effects they could bring to consumers.

AKI 6.4 Summary of the questionnaire findings

In summary, the questionnaire responses revealed the participants' awareness of problems with CMP quality on a medium to large scale.

Opinions converged around a general insufficiency of the current quality control testing and regulation to detect and enforce current quality standards. There was agreement that measures in place to assure quality were not fully effective where incentive exists for dishonest and misleading behaviour practices such as adulteration and substitution, including the addition of dyes, fillers and synthetic active ingredients, and others that occurred. Participants attributed these occurrences in-part to the relatively agile nature of nefarious actor who for example sell CMP online, then if redressed, quickly restore sales through other online channels. Whereas the legislation process is generally a more gradual process, and both legislators and regulators may not possess sufficient information to effectively deal with such practices which consequently would reduce their ability to effectively deal with such problems.

Frequent references to education emerged in the participant responses, both the part which lack of education played in influencing the occurrence of quality issues and as a contribution to improving the current situation. The low scale on which herbal licencing was implemented also featured highly in responses. However, in reflection the prominence of this opinion is most likely a bias in responses elicited from the inclusion of a relatively high proportion questions related to licencing in three of the seventeen posed.

There was divergence of opinion around the circumstances in which herbal quality issues emerged. Some thought that financial incentive has influenced people's behaviour such as honesty / dishonesty such as in false advertising, while others refer to human error as a central influence in issues such as inadvertent misidentification.

Some themes formed during the questionnaire process also emerged during the subsequent interview process. However, the responses were more nuanced, qualified, and diverse as documented in the following *section 4.5.2, interview findings.*

AKI 7 Interview participant information sheet

INTERVIEW PARTICIPATION INFORMATION SHEET 参与信息表

AN INVESTIGATION OF QUALITY IN CHINESE HERBAL MEDICINE SUPPLY: The problems that exist and why they persist?

中草药供应质量量调查:存在的问题及其存在的原因?

Researcher(s): 研究员:主管 Martin Fitzgerald. **Supervisor:** Dr. Anthony Booker.博士士.

You are being invited to take part in a research study on the quality of Chinese herbal medicine. It involves identifying the quality problems with Chinese herbal medicines supplied mainly, but not exclusively to the UK. Many efforts have been made to control the quality of herbal medicine but problems still occur. This research focuses on why the quality problem exist and why they recur after measures have been introduced.

• 您被邀请参加有关中草药质量量的研究。 它涉及识别主要供应中草药的质量量问题，但不不仅限于英 国。 已经做出许多努力力力来控制草药的质量量，但是仍然存在问题。这项研究的重点是为什什么质量量问 题存在以及为什什么在引入入措施后它们会再次发生生。

This research is being undertaken as part of the researcher's studies for a PhD in Ethnopharmacology (Chinese Medicine) programme at the University of Westminster. The study will involve:

该研究正在作为威斯敏敏斯特大大学民民族药理理学(中医)博士士研究员研究的一一部分进行行行。 该研究将涉及到您:

An interview asking opinions on a number of topics around the quality of Chinese herbal medicines. This will take about 1 hour and an audio recording with notes will be taken on your responses. The notes will be anonymised with a code to obscure your identity. The audio recording and notes will be deleted by the researcher (Martin Fitzgerald) after retention as part of the research archive for a period of 2 years.

• 参与我的访谈，了了解您对中草药质量量的一一些主题的看法。 这将花费大大约 1 个小小时，并且会在您的回 复中录制带有备注的录音音。 这些笔记将使用用代码匿匿名，以掩盖您的身份。 研究人人员(Martin Fitzgerald)将作为研究档案的一一部分保留留 2 年年后，将删除录音音和笔记。

Please note: • 请注意:

• Your participation in this research is entirely voluntary. •您参与本研究完全是自自愿的。

- You have the right to withdraw at any time without giving a reason.
- 您有权在不不给出理理由的情况下随时退出。
- Withdrawal from the research is without prejudice.
- 退出研究是不不偏不不倚的。
- You have the right to ask for your data to be withdrawn as long as this is practical, and for personal information to be destroyed.
- 只要可行行行，您有权要求撤销您的数据，并且有权销毁您的个人人信息。
- You do not have to answer particular questions either on questionnaires or in interviews if you

  do not wish to do so.

- 如果您不不想这样做，您无无需在问卷调查或面面谈中回答特定问题。
- Your responses will normally be made anonymous, unless indicated above to the contrary, and will be kept confidential unless you provide explicit consent to do otherwise.
- 您的回复通常会以匿匿名方方式提出，除非非上文文另有说明，除非非您明确表示同意，否则将予以保密。
- No individuals will be identifiable from any collated data, written report of the research, or any

  publications arising from it.

- 任何整理理的数据，研究的书面面报告或由此产生生的任何出版物都不不会识别任何个人人。
- All computer data files will be encrypted and password protected. The researcher will keep files in a secure place and will comply with the requirements of the Data Protection Act including GDPR 2016/ 679 which addresses your personal data and its confidentiality.
- 所有计算机数据文文件都将加密并受密码保护。 研究人人员将文文件保存在安全的地方方，并符合数据保 护法的要求，包括 GDPR 2016/679，其中涉及您的个人人数据及其机密性。
- All hard copy documents, e.g. consent forms, completed questionnaires, etc. will be kept securely and in a locked cupboard, wherever possible on University premises. Documents may

be scanned and stored electronically. This may be done to enable secure transmission of data to the university's secure computer systems.

• 所有硬拷贝贝文文件，例例如 同意书，填妥的问卷等将尽可能安全地存放在一一个带锁的橱柜中，尽可能 放在大大学校舍内。 可以电子子方方式扫描和存储文文档。 可以这样做以便便能够将数据安全地传输到大大学 的安全计算机系统。

• Please notify the researcher immediately if you feel psychologically or physically uncomfortable during or after the research. 如果您在研究期间或之后感到心心理理或身体不不适，请立立即通知研究人人员。

- If you wish you, can receive information on the results of the research. Please indicate on the consent form if you would like to receive this information.如果您愿意，可以获得有关研究结果的 信息。 如果您希望收到此信息，请在同意书上注明。
- The researcher can be contacted during and after participation by email (m.fitzgerald@my.westminster.ac.uk).
- 可以通过电子子邮件(m.fitzgerald@my.westminster.ac.uk)在参与期间和之后联系研究人人员。

  • If you have a complaint about this research project you can contact the project supervisor, Dr. Anthony Booker by e-mail (A.Booker@westminster.ac.uk).

  • 如果您对此研究项目目有任何投诉，您可以通过电子子邮件联系项目目主管 Anthony Booker 博士士 (A.Booker@westminster.ac.uk).

AKI 8 Interview consent form

CONSENT FORM 同意书

Title of Study: **AN INVESTIGATION OF QUALITY IN CHINESE HERBAL MEDICINE SUPPLY:** *The problems that exist and why they persist?* **研究题目目:中草药供应质量量调查:**存在的问题及其存在的原因?

Lead researcher:首首席研究员: Martin Fitzgerald
I have read the information in the Participation Information Sheet, and I am willing to act as a participant in the above research study.

我已阅读参与信息表中的信息，我愿意作为上述研究的参与者。

Name:名称: _____

Signature:签名: _____

Date: 日日期:_____

This consent form will be stored separately from any data you provide so that your responses remain anonymous.

此同意书将与您提供的任何数据分开存储
你的回答是匿匿名的。

I have provided an appropriate explanation of the study to the participant

我已向参与者提供了了对研究的适当解释

Researcher Signature 研究员签名:

_____ Martin Fitzgerald

AKI 9 Interview tool

Interview

访问

Date / Time / Location

日期/时间/地点

Introduction

本次访谈旨在探讨有关向英国供应中草药的专家意见见。 特别(但不不仅限于)与质量量相关的问题。 在您的回复中，您可以想到任何进一一步的评论和想法。 它们非非常有价值且受欢迎.

This interview is designed to explore expert opinion on the issues in Chinese herbal medicines. Particularly (but not exclusively) around quality related problems.

The questions are semi-structured as prompts, however your personal opinions are most important and the discussion is intended to be open.

这些问题是半结构化的提示，但您的个人意见最重要，讨论是公开的.

There is room for any further comments and thoughts that come to mind during your responses. They are very valuable and welcome.

如果您在回答过程中想到任何进一步的评论和想法。 他们非常有价值和受欢迎.

1. Could I ask you about the nature of your work?

我可以问你工工作的性质吗?

positions? 工作岗位

area? 工作领域?

time? 你的经验长度?

expertise? 专业知识?

countries? 国家?

2. What do you think about Chinese medicine quality?

regulated and unregulated?

different supply chains?

3. What do you think about species of herbs being mixed up?

您如何看待被其他人人更更换的草药? 你有这些问题的个人人经验吗?

examples? 例子？

prevention strategies? *预防策略？*

4. What do you think about species of herbs being replaced with others?

您有过黄黄曲霉毒素的经验吗?

examples? 例子？

prevention strategies? 预防策略？

5. Do you have personal experience of these issues?

您对这些问题有亲身经历吗?

6. Have you had much experience with aflatoxins?

您认为关键问题是什什么?

7. What do you think the key issues are?

您认为最重要的中草药质量量问题是什什么?

8. Why do you think these problems continue despite control measures being in place?

尽管采取了控制措施，您认为为什么这些问题仍然存在?

9. Do you think that CHM quality could be improved? If not - why?

您认为 CHM 质量可以提高吗？ 如果不是——为什么？

If yes- how?

如果是 - 怎么样？

10. Anyone else you would recommend to speak to?

您会推荐与之交谈的其他任何人？

AKI 10 Interview participant anonymised transcripts sample

Sample of interview respondent data, four examples (cases 6 to 9, of total 15).

Case 6 interview participant response data

Interview Details:

Type: In person one to one Interview Language: English Location: London, UK

Date / time: 13/5/19 1.03pm Format capture: Handwritten notes

Question 1: Could I ask you about the nature of your work?

Question 1a: Positions?

Participant: Pharmacy degree and operations for Lloyds pharmacy, PhD medicinal chemistry

Participant: Lecturer [TEXT REDACTED] in medicinal chemistry

Participant: [TEXT REDACTED] director
Participant: Currently in consultancy at herbal medicines regulatory services

Question 1b: Area?

Participant: In the area of mutagenesis and anti-cancer compounds
Participant: Aflatoxin analysis, test development
Participant: Community cancer campaign

Question 1c: Time?

Participant: 6 years as a research scientist
Participant: Consultant pharmacist Llyod's pharmacy
Participant: 1997 moved into herbal medicine OTC
Participant: To date work for a German herbal company [TEXT REDACTED]

Participant: Then director of the [TEXT REDACTED] recently retired Now a consultant

Question 1d: expertise?

***Interviewer**: Experience over 10 years?* **Participant**: Yes, much more as I've said. Question 1e: countries?

Participant: UK, Germany, Tanzania

Question 2. What do you think about Chinese medicine quality?

Interviewer: regulated and unregulated?

Participant: It's a completely opaque situation. Estimation would be guesswork. We just don't know.

As things stand it is impossible to know what the quality situation is. It's impossible to differentiate regulated from unregulated.

Since as far back as I can remember, even in 1978 when section 12 came in it was a similar situation. [***interviewers note:***

https://www.legislation.gov.uk/uksi/1977/2130/made/data.xht?view=snippet&wrap=true]

Then you know, in 90's when TCM become more popular it was difficult to recommend anyone to see a TCM or other herbal practitioner. How would you know who's who?

Quality comes at a price. Some charge less to be competitive and make a living.

Then there was a focus on the efficacy, do they work? But you just can't have a tradition that lasts over two thousand years and not work. They worked historically.

But now? With competition for lower prices, maybe the quality has reduced. But how do we tell? We don't know.

This is why efforts to regulate the whole thing is important. But there is this thing with politicians, and they have been against regulation. The costs involved in meeting regulation would have to be taken up by companies. The regulation costs are not insubstantial. If I was in their position, would I try to enforce regulation try to enforce these costs? I don't know.

On one side was there really enough risk to warrant the effort to push all this regulation and all the costs with it? Probably not, but then we don't know from the situation, it's never been clear-cut.
But then there was the Aristolochia case and then the attention was resting on the practitioners' side after that.

But of course, we saw the problem with all of that was, that for herbalists to be integrated into primary care, they are not regulated in the first place. If they were it would have been easier and happened earlier. Still hasn't. How can all that work within the NHS system then? It can't really can it?

Basically Martin, if a CHM company doesn't wish to comply then how can we know about issues? Because for example even with the THR inspections

happen every two years for compliance. There are times in between that things can happen.

There is no incentive for CHM companies to do this, really only if they want to "do the right thing". So in some ways we have to look at things as if we were in a CHM company. Why would you want to take all that on. There would be cost to you, drawing attention, all that.

Question 2b: different supply chains?

[Interviewers note: this comes up naturally and covered in Question 6 below]

Question 3. What do you think about species of herbs being mixed up?

Participant: This is a significant problem, big problem.

Its deliberate sometimes but not always, you know that it can happen out of ignorance too.
Ineptitude, incompetence, not always intended.

Basically, it comes down to if the supply chain isn't regulated. No way you can control things. Things can be done on the spot anywhere along the way.
There is a demand so the focus will be on getting the supply delivered. That's it. The priority is on getting the supply done, the rest, well, who knows?

Question 3a: examples?

Participant: Remember the Black Cohosh situation? Kava kava was a problem
And of course, people had to stop taking St. John's Wort

But still it is purchased online, there isn't enough of it. There is the supply shortage of Kava because of demand. So the supply chain then becomes vulnerable and to things such as adding in other herbs.

The problem with that of course is to identify them, how much of that is in there? We don't know. Even when you have experts in their field, it's hard to identify herbs. This is a difficult thing. Even those good at this can't be good at identifying everything.

Question 3b: prevention strategies?

Well, really its costly you see. Like DNA profiling and testing. This has a cost. Not attractive always to put effort into prevention when you have to concentrate on delivering material to a market.

But that said, there are those who do. Look at Pukka herbs for example, they invest in sustainability and quality by principle. It's not an extra thing for them,

they had that intention to do this. So, it can work commercially to put all this as a priority. But they set out to do it that way.

Sustainability is a viable way to prevent things. They have SOPs in place for everything so that things aren't left to chance. Including visual checks etc., even in unregulated places they have procedures in place. Even their own standards as well as others. It can be done if the will is there.

Question 4: What do you think about species of herbs being replaced with others?

As I've said, there is deliberate action also.

Question 4a: examples?

I was approached by a company to look at some unlabelled products. If it isn't labelled, then. Is something really technically replaced? It's difficult to pin down.

Also, do these herbs have drugs in them? You don't know. You have to rely sometimes on reputation.

I've seen things like chondroitin sulphate and mannitol, more than a hundred times more than could be accounted for.

But also, there are manufacturing issues, like ginseng for example. It just has no real practical shelf life on its own. So what do they do? To be able to keep selling it. They do things to offset issues like these. Theoretically of course this would be regulated in the food space. By food standards. Food training should help all that. But how can it be practically enforced. Where would it be picked up? There is just so much out there. And then there is the whole other side, with bacterial spoilage etc.

Question 4b: prevention strategies?

Question 5: Do you have personal experience of these issues?

[Interviewers note: this already came up and covered earlier]

Question 6. Have you had much experience with aflatoxins?

Participant: Yes, much of all this we have seen before. Often simple testing, like bacterial nutrient testing, just using simple petri dishes. You use another petri dish control, but many things can be camouflaged. With more selective nutrition you can get more colonies appearing for things you want. But also underlying can be mutagenic substance can be present. More colonies be indicate more mutagens if done correctly, so complicated testing isn't always needed. Just understand what you are trying to test and have something to compare to.

Question 2b: different supply chains?

Participant: Chains of course can be regulated. Using testing in many ways, but you have to be realistic, you can't control everything. Even when the herbal teas took off in the market, and become more popular. We went on to test herbal stocks and found passion flower extracts that were way above spec levels.

Also you see this report here [report with data shown to interviewer]. This is an example of how regulation can work well. We were in action within one hour and communicated the issue up the chain. This really shows that spot testing is needed along supply chains. If we tested bulk material further back, we would have missed it. Only for checking the extracts at the end. In the end it was down to a humid summer and storage conditions. So even if you test and all looks well. It doesn't mean the product is good either. There are more factors involved that anyone can ever test.

Question 7. What do you think the key issues are?

Participant: Checks – but you can check at the finishing stage all the way back to the beginning. But you would really need to check an extract of every batch. It's not always possible.

Question 8. Why do you think these problems continue despite control measures being in place?

Participant: It's just down to simple morality to "do the right thing", or not. As I've said, Pukka has tapped into the commercial benefits of this. These values are human qualities. Their value focus is more on people.

Where there is opportunity to make money and there aren't checks things can happen. Even when things are in place to check, things can still happen. So it's people.

Question 9. Do you think that CHM quality could be improved?

Participant: Oh yes, as we've been talking about from the beginning. There are always ways to improve things, including good regulation, this could improve. We have proved it works when done well.

If there was more support for trade associations and PR for those doing the right thing. They would be more of them.

RCHM for example has the voluntary auditing system, but this is a cost to bear upon themselves for the companies. If consumers were made aware of the companies who are making these efforts perhaps the "doing the right thing" would be rewarded, perhaps.

Sustainability is making progress with various organisations in that area. This could be expanded to include efforts in being open about those who make efforts to be audited on their systems. Maybe that could help with the reputation side of things and convert to sales.

That is maybe one way forward.

Question 9a: If not - why?

No, things can be done.

Question 9b: If yes- how?

We've covered these, I think. Haven't we? Ok, is that OK?
You can contact me if there is anything else. No, nothing more to add.

Question 10: Anyone else you would recommend to speak to?

N/A not asked.

End Of Interview

Case 7 interview participant response data

Interview Details: Type: In person one to one

Interview Language: English Location: Bristol, UK
Date / time: 20/05/2019 11.30am Format capture: Audio recording

Question 1: Could I ask you about the nature of your work?

Question 1a: Positions? Question 1b: Area?

Interviewer: Testing, one, two, three. One, two, three. Participant, if you could please tell me about the nature of your work?

Question 1c: Time? Question 1d: expertise? Question 1e: countries?

Participant: Well, I'm a practicing herbalist, Chinese herbalist for 15 years. I also run an approved supply scheme for [TEXT REDACTED] which aims to improve the standards of supply of products for our members.

Interviewer: How long have you been involved in herbal medicine work?

Participant: I studied 15 years ago, and I started the [TEXT REDACTED] at the same time, and I've been working with suppliers for the last 10 years.

Question 2: What do you think about Chinese medicine quality?

Question 2a: regulated and unregulated? Question 2b: different supply chains?

Interviewer: Thank you. If I may ask, what do you think about the general quality of Chinese medicine?

Participant: It's improved in the time that I've been working on it. There are fewer herbal suppliers in the marketplace but the ones that are there are more serious about quality control issues. It's not compulsory to join the Approved Supply Scheme but we try and provide not just advantages in terms of selling product, having our Kitemark.

I would say all of them are audited by pharmaceuticals auditors, so there's a certain independent standard that is set, although the register determines the

minimum standards they expect to reach. We're about to increase those standards, which I'll explain in a minute.

Once the suppliers that are on our list, which are about five at present, have reached the certain standard, which on the first stage has been really recordkeeping. A lot of paperwork and training and SUPs, that sort of thing, which were lacking.

A lot of the other suppliers have dropped out of the marketplace. Even Tong ren tang has just dropped out because they didn't want to be involved in any sort of auditing at extra expense. It's a difficult market, there's not a lot of profit in it, and they probably decided there wasn't enough, but the ones that are left, are very happy.

Interviewer: Participant, you mentioned that you feel that the quality has improved in the time you've been involved. What specifically around the quality would you mention as

improvements?

Participant: Well, as I say, the first stage has been batch auditing. In other words, they are more aware of the need to control the flow of a batch that's imported so they can trackback in the case of adverse reactions. Storage, that sort of thing has improved a lot. The issues of storage, of particularly dried herbs, has greatly increased the risk of aflatoxins or pest infestations, that sort of thing.

The other thing that's improved is that the suppliers that are left are more serious about their quality of product that's coming in. It really has to come from the suppliers. There has to be not a policing because that doesn't really work. You have to have suppliers who really want to increase the quality and we do have those that are left. Without that two-way process, it doesn't really work.

You can get around auditors, but they see the auditing process as an educational process because they haven't had any training, officially in even distribution or storage or this type of work so they've been needing to have help. It's now they got the help and it's increased with their willingness to provide a proper standard of service. There are still issues though that need to be resolved.

Interviewer: Thank you. You mentioned that some suppliers have left. Do you know why they've left the market?

Participant: I think some of it is just Britain is not a very lucrative business for herbal a supplier. There just isn't enough product being sold for them. If you're interested in profit margins, it's not a very profitable country. Plus there are more restrictions on importing certain herbs which have come from the government. I would say the ones that are left are not actually entirely profit based. They are committed and they're passionate about what they do and that's important.

Question 3: What do you think about species of herbs being mixed up?

Question 3a: examples?

Interviewer: That's really interesting. In terms of species and herbs being mixed up, do you have any thoughts about that?

Participant: It's still an issue. Several reasons that happens is that the staff are not trained here in pharmacognosy properly. The labelings is still in pinyin, not enough Latin. It doesn't come naturally to the Chinese herbal industry, the use of Latin source species.

There is an educational process on that score which we are trying to address but they are tending to be aware of the ones which are problem herbs. As I was explaining, the next step in approved suppliers is trying to draw up a list of herbs which are commonly substituted. Provide a little training program for that so that in terms of the dried herb then there's more awareness.

It seems less of a competitive thing. There used to be an approved suppliers organization, which they tried to work together to try and deal with some of these issues but in fact it was too competitive, they wouldn't work together and there was fighting all the time. The register had to step in for our members to provide this neutral space in auditing and education that is not competitive.

We get more cooperation with the suppliers and they try to work together. They really need to have this independent umbrella. Not to control them, but to help and regulate their activities. At the moment, it's only the register that has provided that umbrella as a voluntary system. There's no auditing of suppliers done by the government and they never will.

They make sure they are not interested in doing that, so unless someone does it-- They are aware that we're doing this and they're happy with it.

Actually, are very happy we're taking that load and being conscientious about our supply. But it is a voluntary scheme and they don't have to join it, but we try and provide incentives. That's the way ahead. It's not so much a stick as carrots and sticks.

Interviewer: You mentioned that you feel that maybe education is the way forward when we're talking about this species mix up because of language difficulties and

identification difficulties. Do you feel that the education falls on the suppliers or other organizations?

Participant: No, no, it is up to them to make sure their staff are trained. That's one of the issues that we're talking about raising the bar now for standards. As I said, the register sets the bar that we want auditing on. The auditor produces a report to say, "Well, look, they're not meeting this standard." Now, when we

raise the bar, we change our minimum standards, and say, "Now we want you to check for this."

The areas that we're going to ask for now is that all their staff know exactly what's in their products. That's particularly with powders, for instance. Powders are now increasing. They have their own advantages and disadvantages, which we will talk about but they should know exactly how they're produced and they should know what their parent company is doing, and they should be able to know which herbs are problem herbs and be able to identify them.

This training has to be written down and they have to-- It's only good for them as well to know that stuff. That's going to come out in the next six months. But again, I'm going to work with suppliers to say, "Well, what do you think the problem herbs are? Why don't we have a little training day or something for new staff?" I've got lots of samples of good and bad herbs which I collect and we have got a sample museum here, which we're trying to increase all the time as soon as we hear about something. We need their feedback as well.

Interviewer: With this education, are there any particular species that you think should be focused on first that are commonly mixed up?

Participant: Some are not particularly dangerous, seeds which look very similar. Others are more dangerous. The one we're focusing on the moment is Wu Jia Pi/Xiang Jia Pi, Periploca, which is a dangerous substitute. The problem is there-- I mean I don't know the reason for it.

It seems to be that it's not a question of demand. It's a question of the Chinese people themselves have these ideas that it's more effective. They think, "Oh, they'll want Xiang Jia Pi because we think it's better." They're not aware of the health issues around Xiang Jia Pi. They just see them as Jia Pi and they mix them up because that's the problem with this pinyin system. Some of the problems come because that's how it is in China and it's not good enough for here.

The same goes with the heavy metals, pesticides. The standards are lower in China than here. We found that with the tea. They can't export tea because their standards are not good enough to meet the European standards. This is a more difficult issue because the testing is expensive. For this, we're working with the BHMA which they're launching they are launching their own scheme.

Actually, funnily enough, their scheme is less stringent than ours because they're playing soft. They're a bit further back. Their supplies are resistant and they have got the paperwork, all the things that our ones have slowly over the years seen the value in doing. It makes their life easier. Initially, it makes your life more difficult, so you

have to see the benefits. They're more involved in testing, so we may have to discuss things with them.

Question 3b: prevention strategies?

The powders themselves are in some ways safer because they're tested. They have big factories. In a way, they're taking over the ground of dried herbs in many cases. In China also. Quality assurance issues are different in that you can't see the herbs so you can't do your own pharmacognosy. You're very much reliant on this company which is situated in a far off land. You're reliant on their pharmacognosy, which is probably better, but I don't know. We're now insisting that we have evidence that they have a pharmacognosist on board in China.

This is our only way of getting around this. I think if they don't have the skills here where you can't. We don't want to be testing herbs all the time in the UK, so we need more assurance from the parent company back in China. Their auditing schemes, their GMP. Most of these big companies have GMP. We need more information about this. We don't know whether we can trust the Chinese GMP. The government doesn't seem to be very happy with it. Is that true? Can we have GMP without having a pharmacognosist? These distributors don't know this themselves. They need to know this. We all want to know what's going on with GMP in China.

I think the Australians are happier with it than we are, the Chinese GMP. That's an area that you could help with through your contacts as to-- They have something called COA, Certificates of Analysis on exporters. What does that involve? How stringent is it? Do all herbs that are exported have to have it? This data is useful for us.

The only other thing is to send an auditor out to these companies, which we think is another way of doing it. It's worth it for the company to take a British auditor out there. We can't set that up. The distributor would have to.

We haven't got to the stage we're insisting with our suppliers but it's coming up that way that they take more responsibility for their own supply. At the moment, they've be dealing with staff training and stuff and SOPs. It's the next step and any help you can give us on that back in China-

Interviewer: Definitely.

Participant: -about GMP and about exporting.

Question 4: What do you think about species of herbs being replaced

with others?

Interviewer: We've mentioned about species being mixed up but then sometimes they find that one species has been intentionally replaced by another.

Participant: Well, I see that as the same problem really. Why are they substituted? Like I say, sometimes it's just they look similar and sometimes they think they're better. The main ones are the expensive ones, the ginsengs. I think we're a little bit more aware in this country than we used to be. We used to be a soft touch I think for exports but I don't think that's-- Particularly with these new suppliers, they're not just trying to sell product to maximize profits, in which case they'll buy the cheapest on the market. Some of these suppliers, the Di da herb sources. They're taking more care now. I don't see that fakes as such are such a big issue any longer.

Interviewer: Would it be fair to say then, given what you've mentioned previously, that perhaps the way forward is through moral conscience and responsibility from suppliers in a

more broad sense, rather than just direct legislation and focusing on that?

Participant: Well, no, they're both needed. They're both needed. They have to be audited independently or else it doesn't mean anything. The audit team has to be based on something which is realistic. There's no point in just coming up with a load of, "Well, you need to do all these tests," or whatever, and the guy's out of business because it's expensive and it's a borderline business.

The register has a place and it's always aware of how realistic you have to be. That's why we set the bar reasonably low. You could have just gone for the top and then they would have all dropped out and had one supplier. That was never our aim. No, I wouldn't like a heavy-handed approach from the government based on pharmaceutical industry. That would be the death knell. At the same time, they need some support and they need more information. I think it's going the right way.

Interviewer: Participant, based on the support you feel they need, does it include finance? Does it include training? Does it include [crosstalk]?

Participant: I don't think it needs money put into it. It just needs educational work really. I guess you could say that involves a bit of money but it's not huge. I think the price of herbs is going to be a big issue. If you start to increase that, then it becomes more like Switzerland where you have all these tests and things. Then the herbs are three times expensive, but then they have an insurance policy that they can join that pays for it. You can't compare one country with the other because they have different things going on here.

We're trying to protect our members and the public. That's our main thing. I think you could easily put all these suppliers out of business fairly quickly because they are on a margin.

Interviewer: It's a kind of fragile situation?

Participant: It's a fragile business to be in, definitely. There's less herbalist training now as well so the market's going down. There's restrictions on them already about selling to acupuncturists, to not making up patents. They've lost the whole market there from not selling patents. That was very lucrative for

them. They've been pushed back all the time by legislation so more legislation is bound to have a negative impact on them as far as I can see.

It's not as though it's totally unregulated but it is a voluntary system at the same time. It's the best thing you could have. The same goes for ASR practitioners. I'm in two

minds about it to be honest. Voluntary regulation's okay as long as people know what they're doing and are serious. That's my--

[00:20:01] [END OF SECTION AUDIO 1]

Question 5: Do you have personal experience of these issues?

Participant: A whole raft of other things on there and it tends to put the price of everything up. I don't know if it improves the quality that much but that's my personal opinion. Some people disagree that SR would be a really good thing. I'm not convinced.

Interviewer: Based on what you've mentioned do you think the Swiss route would be a good option for UK and the rest of Europe, or do you feel that we need to go more in the conscience-of-supplier direction?

Participant: No, we can't do the Swiss route. The insurance, people aren't going to pay that level of insurance that will include herbal medicine and they're only allowed to use certain products. I certainly don't want to go down the Swiss route. The Australian system seems to be the best. They acknowledge the herbalist. They regulate the supplies a bit. They allow for Chinese GMP.

I'd like to be able to say, "Well, look, this is a GMP exporter. We can have faith in that." What else can you say? We can't do full GMP in this country of any of these herbs. It's too expensive, we don't have the skills, don't have the turnover of the product, and it's very small-scale stuff.

Interviewer: Do you feel that, looking at the Australian example, Australian route might be an option for us?

Participant: Yes, that's the one that I find the most sensitive and realistic to this country. The herbalist there has got some sort of statutory regulation. They haven't resisted that, so that does give them a certain standing which legally--

We still have this silly position of not being able to order herbs for patients and they have to come to our premises and have them made up. We don't have ability to control certain drugs or use certain herbs because they're deemed to be a little bit dangerous and therefore-- The Australians have got more-- Because they've got more of a profession, they can have their supply chain more professional too.

Interviewer: Do you feel that's a question of numbers, that there's just a bigger market?

Participant: In Australia? No, it's just their attitude. They're more Asian in their thinking. They're very pacific. Europe's just very stuffy. It's just like MDs and doctors and it's just very, very traditional.

Interviewer: It seems more restrictive?

Participant: Yes. Definitely, yes.

Interviewer: You mentioned earlier about the patent herbal medicines. Do you think there is much of a danger or a safety issue with these?

Participant: Yes, there were heavy metals. There were toxins in there from Long Dan Xie Gan Tang for instance. The pill. They definitely had aristolochia in them. Yes, they were dangerous products.

At the same time, if the acupuncturists were better trained they could order these patents through suppliers as capsules, but they're not allowed to because the supplier isn't allowed to make up the capsule. It's the manufacturer, so that's where it all comes in.

The whole division between the distribution and manufacturing is a very gray area as to what scale it becomes manufacturing. We're not wanting to push this area because it might come down on the wrong side. [chuckles] In effect I think they should be allowed to do certain things that they're not. It's a difficult line to draw for the Register as well because some of the law doesn't make any sense.

It's not even safe to allow a practitioner to make up capsules in their unknown dispensary, with small equipment which is probably not very hygienic, unregulated, unaudited, is okay. Some supplier who's got the professional - and they have from the past - £7,000 stainless-steel capsule maker, audited by the pharmaceutical agency - is not allowed. It doesn't make sense. That's a situation we're in.

Interviewer: Is this do you feel a question of common sense or is the question of-?

Participant: It's safety.

Interviewer: Safety.

Participant: Yes, it's safety. It's safer to give an order to a supplier with a professional machine that's been cleaned, than a practitioner, because they're allowed to do it in their dispensary. It doesn't make sense.

Interviewer: Again, this is back to then would you feel, from what you've mentioned earlier, that actually, again back to focusing on having the suppliers take on more of the

responsibility, being audited more, being--?

Participant: Well, no that's not a question of auditing. They have the equipment and they have the skills to do it. It's the law. The law is ridiculous around that area.

Interviewer: It's more the regulation?

Participant: The regulations and if we were to get more regulated, it would get worse, not better, as far as I can see because it'd be less and less that was allowed under manufacturing. What we want is being allowed to form a form of regulation for us herbal suppliers which is more realistic.

Interviewer: More suitable, Participant?

Participant: More suitable for safety never mind anything else. ***Interviewer: Safety.***

Participant: We're only interested in safety. That's the situation we're in.
Interviewer: The legislation that's in place at the moment, you mentioned if there was

more of that it would create more problems than solutions or be more difficult.

Participant: If it's heavy-handed, yes. It tends to be what you can't do rather than what's possible. You would definitely have to look at the impact on the supply.

Female Speaker: Hi.

Interviewer: Hi.

Female Speaker: I'm finishing my shift now.
Interviewer: [laughs] Finally off. Bye-bye.

Participant: In Portugal, they just decided that the suppliers weren't safe and they just closed them all down. That's the heaviest hand you can think of. It seems to be it's a very hard area for the government or MHRA to get their head around. They've got one or two people. That's all. I think they're quite happy with what we're doing and I think it should just be in the voluntary sector.

Participant: Yes.

Interviewer: More voluntary.

Interviewer: Self-regulatory.

Participant: Yes, but with some auditing. Then it's a question of education. We try and make our members, when they buy, when they use the pre-supplies-- We can't enforce it but we try and say, "Well, I've been advised to check with the insurance company that they may not be insured," and they're not.

Interviewer: I see.

Participant: These are the carrot and stick things. This is the way to go.

Question 6: Have you had much experience with aflatoxins?

Interviewer: You mentioned earlier about some safety issues with heavy metals and so on. In particular do you have any experience with aflatoxins?

Participant: I haven't myself, no. I guess now we've improved the storage of herbs in the UK, that's where most of it would come in.

Interviewer: More on the storage?

Participant: Yes, on the storage. that's where it comes in, isn't it, on poor storage? as you improve the supply, that becomes less of an issue. Those heavy metals I think they are a problem. I don't know what to do about that to be honest. At the same time people aren't taking massive amounts of herbs at any one time.

Participant: No, we haven't got our head around this one yet. [chuckles]
Interviewer: There's more work to do. [laughs]

Participant: Yes. It's a question of how expensive would it be. This should go back to GMP in China. Their standards of heavy metals, aflatoxins should be made very clear and they should have certification. It's not really a British problem. It's a Chinese problem.

Interviewer: It's a Chinese problem. [laughs]

Participant: That's a quote.

Interviewer: Yes.

[laughter]
Participant: What can you do? We're such a small country with limited resources.

Interviewer: It's true.

Participant: We don't even know how it's produced. I think China is aware of the problem but can they anything about it?

Interviewer: That's interesting. Can they even do something about [crosstalk]?

Participant: Yes, yes. That's where the supplier's responsibility is, to choose the supplier which is not the cheapest but the best. They know that. They know them.

Interviewer: Participant, in terms of these issues we've spoken about today, do you have any personal experience with anyone or other of these issues?

Participant: Well, I've never had a huge adverse reactions from a patient or poisoned a patient if that's what you mean. I obviously have personal experience in that I teach pharmacognosy [laughs] so I see what's coming in. I'm a bit disappointed to hear that something like 50% or 60% of Wu Jia Pi is the incorrect one. That's experience from ordering from suppliers and seeing what they're selling. I do certain

scans myself and I haven't been impressed by that particular one. Also Bei Mu I think is a problem being exploited in the wild.

Participant: Bei Mu. **Participant:** Fritillaria.

Interviewer: Bei Mu? Interviewer: Bei Mu. Interviewer: Ah, yes.

Participant: Fritillaria cirrhosa. If you examine it you find there's some, a lot of them, are closed, they haven't been flowered, so they're not ecologically sound.

Interviewer: Ah.

Interviewer: There's serious interest. I suppose maybe its my just experience, but it's just what I've seen. I won't use it. I will only use zhe bei mu. I teach the students for that reason as well. They need to also be aware of the sustainability issues. These are big issues, I mean they're massive issues, and we're a long way from China. I'd just like there to be more information.

Interviewer: More information is needed?

Participant: Yes. For me, yes.
[chuckling]
Participant: Most of us, "What's going on?"

Question 7: What do you think the key issues are?

Interviewer: Just closing, what do you think - you've touched on some of them during the last half an hour, 40 minutes - if you were to summarize what the key issues are for

Chinese quality and supply?

Participant: Making sure you've got the right species, number one. To do that we have to have people that can recognize the right species, that they know how to write it down in Latin. These are all educational issues. Pharmacognosy is number one as far as I can see.

The quality of it, from what I see they're fairly well stored and looked after, these herbs now. The big issue really is once it leaves the supplier, what is the member doing with them in their dispensary? That we haven't really got any auditing for. There's no point blaming China and blaming suppliers if our own members don't know what they're doing.

That to me is what I try and do here, trying to get that standard up because in any herbal course it's not included unless they come here and do this two-day course. That's really been really remiss in the past just to send a member out with no herbal dispensary training or pharmacognosy training. [chuckles] Look at yourself before you blame others.

Interviewer: I'm sure there's a Chinese proverb for that somewhere.

[laughter]
Participant: Just translate that into Chinese [crosstalk].

Interviewer: Directly.

[laughter]

Interviewer: Just before we close, do you have any other comments or thoughts or suggestions that you feel generally relevant to Chinese herbal medicine quality, supply,

solutions? Just anything you want to add in terms of information today?

Question 8: Why do you think these problems continue despite control measures being in place?

Participant: I think there's a misunderstanding about Pao Zhi and that needs to be taught or we'll lose it. The suppliers don't stock enough Pao Zhi products and our members can't do it properly. It affects clinical effect of the formulation. Although a product may be Pao Zhi form and it's important, it's not labeled as such. You take Pao Zhi This ethnopharmacology journal I got.

Interviewer: Yes?

Participant: This is quite a recent one. The dangers of and danger with He Shou Wu. Hepatic toxicity of Polygonum multiflorum. This is looking at why the raw herb is toxic. Basically we should never use it in the raw state. You should always put-- In fact, I've heard that most of it is processed. However, they don't actually state that. The suppliers don't say, "This is processed." An ignorance about it, ignorance culturally, and its clinical importance and it's important in terms of lists.

Question 9: Do you think that CHM quality could be improved?

Question 9a: If not - why?

Question 9b: If yes- how?

I've been pushing for lists. Pao Zhi lists. That's one of the other things I'm trying to work on, otherwise we'll lose that. There's not a big market for it unless both the members know about it and order it. They don't order it then they won't supply it.

Interviewer: It has to come from the members to—

Participant: The members have to say, "I want this in a Pao Zhi form. Is this the right--?" Then the suppliers have to say and have to know whether it is or not and they have to know their products. Everyone has to know more about

their products, from member upwards, and then maybe go back, and then the supplier has to say to their supplier, "What testing have you done on it?"

Everyone needs to go back. The member has to say, "What testing have you done?" The supplier has to say, "What testing have you done?" Everyone has to be more demanding. Just to say, "Well, this is the supplier's issue." I just get one of my supplier's salesmen and then the supplier says, "Well, this is what they sent." It's like, "No, let's push back on China and get some more information."

If they can't provide it, that's what the new audit's going to put through. If you can't answer these questions, you should be able to answer them. Put a bit more on feedback going back. We need more information as to what is happening and what's possible in China.

Interviewer: Education and communication in two ways?

Participant: Demand.

Interviewer: Demand—

Participant: Yes. That has to come from the grassroots, from the members-
Interviewer: From the members.

Participant: -yes, as well. **Participant:** All right. **Participant:** That's fine.

Participant: Okay. **[00:18:17] [END OF AUDIO]**

Interviewer: Thank you, Participant. Interviewer: Appreciate that. Interviewer: Thanks very much.

Question 10: Anyone else you would recommend to speak to?

N/A not asked.

End Of Interview

Case 8 interview participant response data

Interview Details:

Type: In person one to one

Interview Language: English

Location: London, UK

Date / time: 21/05/19, 10.35am

Format capture: Audio Recording

Question 1: Could I ask you about the nature of your work?

Interviewer: Participant, if I may ask about the nature of your work in general and your background, please.

Participant: Okay. Let's start from the beginning. I got my degree in chemistry, a PhD in Medicinal Chemistry and Biochemistry. I then worked at the [TEXT REDACTED] as a researcher and genetic therapist. I've got quite an unorthodox research background with a lot of access to analytical quality work as well. I worked in academia for about-- gosh, about seven years, then had enough and so decided to retrain. I did a degree in Herbal Medicine at the College of Phytotherapy, in Western Herbal Medicine, I should say, so a four-year degree course BSc (Hons). Then an MSc in nutrition after that.

Question 1c: Time?

I've been working as a western medical herbalist ever since then. I qualified in 2006. I've been qualified now for 13 years in July.

Question 1d: expertise?

I'm currently President [TEXT REDACTED], which is, as you know, one of the professional associations that overseas herbal medicine in the UK. I'm also Chair of [TEXT REDACTED], which looks at the whole of the herbal medicine industry, both practitioners, industrial suppliers, herbal practitioner suppliers, et cetera, and very much interested in quality safety issues there. I'm also co-Chair of the [TEXT REDACTED] which again is looking very much at quality, but more concentrating the quality of training and of keeping the quality of practitioners up. A sort of different quality assurance around the whole board from supplies to practitioners to the whole industry. It's kind of interesting.

Question 1e: countries?

UK stuff, and Europe…mainly.

Interviewer: It's quite a broad range.

Participant: It is. It keeps me from being bored, I would say.

Question 1a: Positions?

Interviewer: ***You span the whole range from the theoretical academic to the practical, all the way up to the research side, you touch on that. Looking to expand it to an educational role, so that's quite the broad range.***

Question 1b: Area?

Academic and herbal practitioner

Participant: Yes. I've still got two busy practices, herbal medicine practices. I work three days in London, and three days in Epping where I lived I still do research papers as well. I published a research paper a couple of months back on a meta-analysis of tea, cardiovascular disorders. I'm just about to publish a new paper on herbal teas, mint, spearmint, ginger, looking at some of the clinical studies of those, meta-analysis of available data on those as well. I try to keep my fingers back in the research line of things as well as in other things as well.

Interviewer: ***It's quite broad, and I think there must be a clone somewhere. It's impossible that one person can do all of that. Participant, in terms then, more specifically around the Chinese herbal medicine area, could I just get your opinions and thoughts on what the current situation is?***

Question 2: What do you think about Chinese medicine quality?

Participant: I think things are much better than they were. The RCHM The Register of Chinese Herbal Medicine has their approved supplier's scheme. I think that's been a pretty successful model that was initially started by Tony Booker and then has been expanded further by the RCHM Emma Farrant. I think it's a really good model that has really improved the quality of the supply chain in obviously, in the approved suppliers. Of course, the issue is with that, not all suppliers have to belong to that, so there are non-approved suppliers, and they can basically do whatever they want. Obviously, as far as possible, the RCHM members are encouraged to use the approved suppliers, which I think means they know they're getting high-quality stuff. They're getting stuff that actually has been identified as being the correct stuff so it's more efficacious and less risk of adulteration, substitution, et cetera, so toxicity issues reduced.

It's a great design, the RCHM Approved Suppliers List, and certainly, it's one that has been adapted in the BHMA. We've got the herbal practitioner supply section now. I think all the members of the RCHM approved suppliers, they supply us from western medicine, Ayurvedic medicine as well all together under one umbrella. They are looking to address quality there generally and ensure safety, identification, et cetera.

Question 2a: regulated and unregulated?

I think that the Chinese herbal medicine sector has improved its game greatly. I think there are some really, really good quality suppliers out there, but I think there are some suppliers who aren't as good as well, so there's a mix of them. That's a bit of an issue. If we've had statutory regulations, which of course, is off the cards now, it would have meant that we could have automatically installed standards into all our suppliers that had to meet certain standards. Now, that's out the window, we haven't got that tool anymore which is why it's important what the RCHM is doing, what the BHMA is doing, to try and independently and voluntarily improve standards as far as we can do.

This doesn't apply to Chinese herbal medicine, but for the western sector, certainly, some research that we did a couple of years ago with the BHMA onto western herbal medicine products, Echinacea product, we've found that from practitioner's suppliers, from good practitioner's supplies, 30% to 40% of them didn't actually meet label requirements. Some didn't contain the herb that they

said they did, another species, or sometimes nothing at all, occasionally wrong plant part used and things.

Even within the practitioner's supply industry, there is a great deal of room for improvement. That's certainly for the western side, and I know it's the same for the Chinese herbal medicine side as well. Things are improving, there is little interest from the practitioner's suppliers to work to improve the qualities. They're being very proactive and affable and helpful and communicating and being collaborative, which I think is the first step forward really.

Interviewer: ***The collaboration aspect, you feel is key. Would you feel, for example, if we had statutory regulation, the regulation route would have been a better route, or do you think the collaboration voluntary route is a better route, or do we need both?***

Participant: Ideally, both would have been better. With the regulation, it gives the legal push behind doing this. At the moment, we rely on the companies voluntarily wanting to pay to do this, which, it's not cheap. It's not a huge amount, but it's not cheap either. They could be using the money elsewhere. They have to be willing to do that. If it'd been a legal requirement, they would have to had done it that anyway, so it would have been easier. I think it's much better to try and get people to do things voluntarily if they can because then they're involved in it, and they're going to want to do it. I think collaboration is important for everything, but it's difficult with herbal practitioner's suppliers. It's such a small area anyway. There's obviously a lot of competition.

It's hard to get that collaboration going on because they're obviously directly competing, but there's a lot they can actually do to complement each other. That's what we've been doing, helping people to see that if they can't get one product, they can probably ask somebody else where they get theirs from or buy it from somebody else rather then risk getting poor quality herbs from a cheaper source because they can't get the one they want. They can actually ask around and ask other companies where they're kind of getting it. I think it does improve the quality of the whole supply chain. That's a crucial thing I think, collaboration.

Interviewer: ***It raises the general quality level***

Participant: Yes, absolutely.

Interviewer: ***That makes sense. You mentioned that there isn't a whole lot of them there at the moment. Do you think that's down to adversity and resistance to the current legislation and the legislation that's gone through the European directive, or do you think it's a financial, commercial economic issue, or is it both?***

Participant: I think everything. It's a combination of everything. Obviously, with the statutory regulation, everybody was working towards herbalists being statutory regulated, in which case our profile would have risen greatly. We would have had more students entering in universities to get qualifications because there's an assured job at the end. Therefore, there would have been a knock-on effect that could increase the number of herbalists who would require more medicine, and it would have been a sort of boom boom growth area for the whole herbal medicine industry. With the lack of statutory regulation, of course, that's all collapsed, so the promises we had, all the structures they put in place have now just gone.

The whole idea provision 2 report was that we had to have BSc (Hons) qualification in herbal medicine. That was all put in place with five, six, seven, eight different universities around the country. Of course, when that disappeared, the courses collapsed, Westminster, Middlesex collapsed up north and of course, Westminster are closing their course in herbal medicine in four years' time as well. That's a huge shame. We've gone from quite a good plethora of university courses in both Western, Chinese, and Ayurveda medicine to there being one BSc (Hons) in herbal medicine. You got the Northern College of Acupuncture doing the herbal medicine course. You've got a couple of new ones coming up that EHTPA is developing that are non-university, but still level 6 standards. Ayurveda, there's absolutely no courses at all in the UK.

Interviewer: ***It's gone.***

Participant: Gone. When Middlesex closed their course, that was it. It's a really distressing situation, and obviously a lack of students entering the area, so, therefore, a lack of people buying things from practitioner suppliers. It's tough for them. There is an increased financial pressure on the suppliers to make sure they have got the good quality products. They're having to do testing now. They're having to test them for aflatoxins, and in the majority of cases for Pyrrolizidine alkaloids, for microbial contaminants, possibly things like tropane alkaloids and ochratoxins, that sort of thing. A whole range of different things, and of course, that costs time and a lot of money, it's not cheap. The PA tests are about £230-odd each for one batch. It's a lot of money, it has to be a liquid chromatography mass-spec machine because it's only such small amounts they're in, so it's really very very specialist and very expensive. There's a huge push to get high-quality medicines, but practitioners aren't always happy to pay the price for that. It's a balancing act that the companies know they can't charge too much, but they also need to make sure they've got the quality there, so it's a balancing act.

Interviewer: ***It's a tough one.***

Participant: Even education I think to show practitioners that actually it is worthwhile paying more if you could be certain that what you're getting is the right herb, is properly dried or processed, so it contains the active compound and doesn't have any contaminants in it. I can go anywhere and buy cheap herbs, but if they don't do what they say that they do, don't work or got a toxic, they're not doing much good for the patient are we really? Certainly, I use an expensive company in my practice, but when I changed which was about 15

years ago, I noticed an immediate change in patient outcomes, and they're happy to pay for that. I'm absolutely certain the herbs I use are what they say they are.

Interviewer: ***They really are the thing.***

Participant: They are the thing, and certainly in Western herbal medicine usually we tend to use tinctures. With tinctures it's-- these other companies, they can be very variable with the batches, so one day you can get a clear tincture pearl yellow, next day it could be black and treacly. Batch variability is always worrying isn't it because it should be identical. The company I use, I bought stuff this afternoon but I'm using an Australian company called MediHerb.

Interviewer: ***Oh, MediHerb. Yes***

Participant: They're all HPTLC tested, and they're all very, very high quality.

Interviewer: ***Would they be considered as pharmaceutical testing almost?***

Participant: It's GMP standard, absolutely. They're prepared really, really well.

Interviewer: ***All batch traceable, batch surveys.***

Participant: Batch traceable, yes. Everything is there and it's all tested, and that's why I use. They're expensive but you can buy a batch-- to compare a batch two years ago with a batch from today, and they're identical.

Interviewer: ***Completely traceable.***

Participant: Chromatography fingerprints, and it's really good. They are natural, they're not processed any way other than the normal extraction process. Not concentrated or fiddled around with to get levels of active compounds up. They just use good quality products that they know are coming from good places, usually organic, as you say good supply chains, they know where they're grown, how they're grown, how they're stored, or how they're stored in their warehouses. The supply chain, as you know, it's just absolutely essential. As you say, you need to know what happens from seed to storeroom. If you don't know that, you don't know the whole picture of what's going on, and where things can go wrong.

Interviewer: ***You feel that's crucial.***

Participant: Absolutely crucial. That's why I think the work that Tony is doing on that, the work that Pukka is doing on that as well, they're doing a great job there with working with farmers in India to get quality of supplies up there is absolutely essential. I think it's absolutely so necessary, and things like pyrrolizidine alkaloid contamination, we know now, that the main issue there is really batch industrial farming which lets these things get in. When things are growing on a smaller scale, hand-weeded, farmer checks it out. Contamination goes right down because you can spot the weeds and take them out.

As you know the main contaminant is ragwort which is, well it was Senecio jacobaea, it's now Jacobaea vulgaris but anyway. One plant will contaminate a whole hectare of field of herb to higher than standard MPA levels, so just one plant can do it, which is kind of scary, isn't it?

Interviewer: ***It's really scary actually. You mentioned earlier about the fact that often, the practitioner isn't either aware of the quality of what they're getting, or is focusing on the price. As a practitioner, what's your feeling about ordering herbs, looking at prices, looking at quality and your peers, do you feel that there's a general awareness about quality? Are practitioners selective?***

Participant: Practitioners have got selective memories.

Interviewer: ***Selective memories.***

Participant: No. I think a lot of practitioners, particularly newer practitioners will tend to go for cheaper products, so that they cannot charge their patients too much money, and can make a tiny profit themselves. Even more experienced practitioners-- a lot of practitioners won't use the MediHerb ones, or not use all MediHerb ones because they say they're too expensive. They can't pass the cost on. As I said to you, I think the issue is, patients will pay more if they can be assured something is good quality. I always talk about this with patients and say why this costs more. You could probably get it cheaper from a herbalist, but I am certain what I'm supplying is what it should be whereas another herbalist cannot possibly say that, they can't be 100% certain. There's a lot of either deliberate or accidental ignorance I think in herbal practitioners generally. They don't want to be aware of things, or they just don't know what questions to ask. I think partly, we need to concentrate more on training courses on going through quality issues, showing the advantages of things like HPTLC.

Interviewer: ***There is an interruption and have to move location, recording starts, about 6 minutes later.***

Participant: Is that recording?

Interviewer: ***Education.***

Participant: Education meeting. Training herbalists to know what questions to ask. On university courses, you need to make sure that they know to ask-- they know about things like HPTLC, HPLC, even Thin-Layer Chromatography. Even organoleptic testing is useful. They need to know what questions to ask the suppliers because if they don't know that, they don't know what questions to ask, so how do they know they're getting good quality stuff?

Education I think is really important, so education of both the suppliers to make sure they're actually getting the right products, but the education of the practitioners to make sure they know to ask the suppliers to make sure they're

getting good quality products. The other thing is to educate the public to make sure they know to ask to get good products because with herbalists, we have voluntary regulated and independent unregulated herbalists, different standards, so the public has to know the difference between them as well.

If you go and see a freshly-qualified PA member herbalist, they're going to charge more than somebody who's perhaps independent, has got the same costs. You're paying for quality. It's a bit like going to-- I don't know, I'm trying to think of like a backstreet doctor or going to somebody on Harley Street. There's a difference, you pay extra but you get a better outcome, better service generally I would say. Arguably, there's cases that may not happen, but generally, that's the case.

Interviewer: ***Economics and value play a big part in all of that in terms of the testing, in terms of practitioner selection, and viability, and the phase you're at as practitioners you mentioned earlier. Perhaps at the beginning, as a new practitioner, you may not have the luxury of choosing very high-quality products. That's an interesting point.***

Participant: Yes, you may not have the knowledge, you may not have the finances, or the contacts to know because in training you tend to use initially what the college or university was using in their clinic. They may not necessarily be the best ones. It's a fascinating area I would say.

Question 3: What do you think about species of herbs being mixed up?

Interviewer: ***Education is key. Then moving into, you've touched on it earlier, one of the key problems in Chinese herbal medicine is mixing up these species. I just wanted your thoughts about that. Is it down to education? What is it down to actually?***

Participant: Well, I think it's a compilation of everything. It can be ignorance sometimes. Obviously, if you've got two herbs that look the same. For example, this is for this afternoon, I'm giving a little talk to the students.

Question 3b: examples?

Interviewer: ***Yes, I'm looking forward to that.***

Participant: I've got two herbs here. If you look at them, they look vaguely identical.

Interviewer: ***Wow, I couldn't determine those.***

Participant: Yet, anyway, to tell is by smelling. If you smell that one here, you'll know straight away. You can see that this has got a--

Interviewer: ***It's quite aromatic.***

Participant: Lemony. It's lemon balm.

Interviewer: ***Is that lemon balm?***

Participant: Melissa officinalis.

Interviewer: ***That's beautiful. I've never seen it like that good-looking before.***

Participant: Fresh out my garden this morning. Whereas this one here looks very, very similar. You can understand this has been picked and dried and it would be very hard to tell the difference but absolutely no smell at all.

Interviewer: ***[crosstalk]***

Participant: This was actually supposed to be Scutellaria baicalensis, so Huang-Qin. I've got seeds from a reputable source of Huang-Qin, grew it, it wasn't. This is not Scutellaria baicalensis, it's Scutellaria altissima which is a different different than the other one, much easier to grow. It's one area where I actually bought this from a reputable supplier, got the seeds. If I hadn't have known A, to check it, send it to Kew for double-checking, I could have been harvesting the root of this and using it as a herb and when it's absolutely useless, it has no medicinal use, so you see, that's an issue.

Interviewer: ***That's a very big issue.***

Participant: I've had the same issue as well with getting from previous approved plant suppliers things like Eleutherococcus senticosus. I got seeds given to me of that. I bought some seeds of that. It wasn't Eleutherococcus senticosus, it was one that's used in Chinese medicine, the other--?

Interviewer: ***Was it Periploca sepium?***

Participant: No. What's it?

Interviewer: gracilistylus?

Participant: Yes, gracilistylus. It was that, not that, and okay, they're kind of vaguely interchangeable but slightly different.

Interviewer: ***And toxic.***

Participant: Look, the problem is they look exactly the same.

Interviewer: ***They look so alike.***

Participant: Only was I knew was when it fruited. The fruit is totally different. I guess the other's from the senticocus. Then you can see the different there, but the leaves look, unless you know to look very carefully there are slight differences, they look pretty much identical.

Interviewer: ***Yes, they both have five leaves***

Participant: Yes. I got them growing together in my garden. You can just see how similar they look. A lot of it can be ignorance, so both plant suppliers, seed suppliers sending out wrong products. Another thing, I was given seeds of Panax quinquefolius which is used in Chinese medicine, American ginseng, and it wasn't. It was another member of the ginseng family, it was Aralia californica, California Spikenard which is used herbally in America. It's Ginseng family. It's not American ginseng but superficially, it looks very similar because it's got the same leaf structure in its early life. It's only when it gets older, it changes.

Question 4: What do you think about species of herbs being replaced with others?

There is either seed suppliers are obviously being given the wrong seeds because these are cheaper alternative ones. They don't know. If you're given a seed, you can't tell, and particularly if it's similar species or similar genuses, the seed is going to look very, very similar, so how do you tell? If you grow it and it has its seed leaf and its first true leaf, the first true leaf looks right, "Hey, that's fine." It's only if you grow it to maturity and then it fruits and then flowers, you can actually see what's going on there.

Question 4a: examples?

Question 5: Do you have personal experience of these issues?

I know some suppliers do use these plant suppliers to actually grow crops. You can see immediately, there can be an issue there directly with inadvertent substitution going on there. There is ignorance, and particularly when you've got species that look very similar, it's very, very hard to know. It's a big issue. I think things are complicated in Chinese medicine because you have accepted changes in your formulae, so there are species and in genuses you can actually change things around. If this one isn't available, you can send us instead. Of course, that led to huge issues with things like Mu Tong. Mu Tong?

Interviewer: ***Mu Tong.***

Participant: When there was the whole mix up of clematis and aristolochia and the other species, and of course, then the aristolochia toxicity and kidney

failure, et cetera, in the Netherlands. It's more complex I think in Chinese medicine because you are allowed a degree of substitution depending on what's going on there. I think, even then, that there is still, in some plant species, substitution that's either deliberate by growers or inadvertent, using cheaper things.

From Tony's work with turmeric, there's adulteration of that either with adding extra colors to make it look better, the turmeric, or mixing other things in there to make it go further when turmeric itself, the price is increasing because of its importance and due to crop failures. There's deliberate financial substitution of herbs and that's a big issue. That's in Western, it's in Ayurvedic, it's in Chinese, Tibetan, Unani. It's in all the traditions, that if there's a cheaper herb, some people try and use it. Certainly in the work we did on echinacea, at the HMA. There was a lot of times where there's one echinacea, echinacea Angustifolia, narrow-leaved coneflower. It's much harder to grow and much more expensive compared to Echinacea purpurea which is the broad-leaved purple kind of coneflower, much easier to grow, it's much cheaper.

The medicinal properties of the echinacea Angustifolia is slightly better. It's one that tends to be used. If you can afford it, it's the best one to use, but a lot of the products, both over-the-counter tablets on the public sector and by herbal practitioner suppliers, when you actually buy an echinacea Angustifolia, a lot of times they're getting Echinacea purpurea. Not too much an issue because their properties are pretty similar, but from a legal point of view, it's fraud because you're paying for something that actually isn't what it says it is on the label. It doesn't make much difference to outcomes, but it's just a slight issue there.

Interviewer: ***There's a human factor there around value and choice and economics and all of that kind of thing?***

Participant: Yes, absolutely. The problem is that herbal medicine generally is a very low-earning sector. The growers don't make much, suppliers don't make much, herbalists don't make much, therefore, there's always a push to keep prices down as much as possible as you said earlier.

Interviewer: ***It's a kind of narrow margin.***

Participant: It's a big issue. It would be great if we had the pharmaceutical backing in a sense because they've got so much money, but it wouldn't make any difference if they had had support there, but of course, they're not interested and we wouldn't want them involved anyway, to tell the truth. It would be good to have pharmaceutical standards imposed, in many ways, apart from the expense wise, but it's just not going to be done without a regulation. We've seen some degree of the quality put in by the THMDP, the THR licenses. There are various products there. There's only one Chinese THR isn't there? Obviously, they are basically regulated in the same way as a medicine is, so the same degree of pharmacovigilance and stability and things. That's been good for the public generally, but it's underused and unknown.

Interviewer: ***It's not well known and again, you mentioned earlier about the cost aspect of it, and the THR process is very expensive and-***

Participant: Do you know how much it costs?

Interviewer: ***I'd actually like to know exactly.***

Participant: It costs massively, all the data, stability data, toxicity, mutagenicity, £80,000 to £100,000 per license for a herb.

Interviewer: ***Per license.***

Participant: Yes. It's a huge, huge, huge undertaking for a company to do that. Think of something like Vogel's or Potters that have got 20, 30 products, that's a lot of money they've invested in doing that.

Interviewer: ***Then in Chinese medicine, of course, one formula could have 12, 14 components.***

Participant: Exactly, and of course, the problem then, is stability data, the more herbs you've got, the harder it is to show convincing shelf stability, so if you've got more than three or four herbs, it's almost difficult. Saying that, there's a Tibetan THR product, I think it's got 22 or 24 different herbs in it, and they've managed to get convincing stability data for that, which I find quite amazing, actually.

Interviewer: ***It's quite difficult actually, isn't it?***

Participant: Yes, it really is amazing. The MHRA was extremely surprised that they managed to get good data on that. It can be done, it's just very difficult.

Question 4b: prevention strategies?

Interviewer: ***It's quite difficult. You mentioned earlier about the fact that the pharmaceutical industry has this financial backing whereas maybe perhaps lower profit margins in the herbal sector. Do you have any feelings about, you touched on it, but do you have any feelings about if we just got the drug regulation models, API, active pharmaceutical models, and post those on the herbal sector, do you feel this is a viable route, in terms of perhaps getting rid of the suppliers who are non-compliant, who are not interested? Or would it just kill the complete market do you feel?***

Participant: I think if it wasn't instigated straight away, the whole market would collapse, they couldn't afford it. I think it's the best model to use because I think we need to show chemical analysis just so everything is of the right quality, so there's no contaminants. I think long term, herb medicines are medicines, so we need to have a comparable safety activity profile to a pharmaceutical drug.

Otherwise, patients are going to learn more, Google is fantastic now for putting these out. Patients are going to want to know things, they're going to learn more, they're going to ask questions, and great, I think that's brilliant. Patients

should be asking questions, and they're going to be pushing for, "Is this product, the right one? Prove it to me." We do need to show that. Now that's the BHMA are encouraging that gradual move for all our individual company members to move towards a good level of quality management towards GDP, but it's a slow step. Lots of the big companies are there, the smaller companies aren't, and to try and put that high limit for them, high bar straightaway would make it financially inaccessible and they would fall apart.

Interviewer: ***Complete death knell altogether.***

Participant: Yes, a death knell. It has to be slow, steady steps, gradually climbing up towards a drug standard, definitely, but that's the goal, I think.

Interviewer: ***That's the goal.***

Participant: Of course, a lot of practitioners don't like that because they think then, we're moving towards the pharmaceutical side of things, which we're not. We're just ensuring standards, that's all.

Interviewer: ***On the safety side in particular.***

Participant: Safety, efficacy, It's safety, efficacy, and quality, those are the three things that we've got to prove, and we can't at the moment.

Question 7: What do you think the key issues are?

Interviewer: ***That's the key point. You mentioned earlier that, one example you gave is the variability of natural products. One tincture can be done and also you mentioned that perhaps we could use the pharmaceutical API and drug quality model for herbal medicines, but do you feel that the current drug testing regulation approach would need variations or changes to fit the herbal model?***

Participant: Definitely.

Interviewer: ***If you feel that, do you think that is one of the reasons why we have so much friction in the herbal market to compliance. Is that a factor, do you feel?***

Participant: I think it probably is Martin. Yes, I agree. Obviously, it's easy. If you've got a single isolated drug, it's easy to show you've got that and you can make a preparation, batch standard all the way through, no variability at all, absolutely fine, herbs aren't like that. They're multi-phytochemical many multiactivities. Any herb has at least 10 to 20, or 30 active compounds, yes, you can identify one or two key ones that probably have a major effect, but we all know that those are just the tip of the iceberg. It's the other ones that are actually complementing those, without the other ones, you don't have the same effect-- I'm losing my train of thought.

Interviewer: ***Actually, good train of thought, just in terms of applying the pharmaceutical model directly on variable products.***

Participant: Okay, and we have-- so the issue there, that a lot of herbal products will have varying concentrations, ratios of active compounds, depending on where they're grown, the weather, the soil, what time of year they're harvested. That's something that's obviously nature, we can't control that, there's going to be natural variability there. If you're trying to say that tincture of hypericum, has to have 15 milligrams of hypericin, otherwise, it's going to fail, well, if you have a bad year, and the levels of hypericin are slightly down, the whole batch could fail in the whole UK or the whole of Europe's crops. There has to be a range of active compound for herbal medicine, so the drug model doesn't work exactly, we have to adapt it.

There's another issue, of course, even with herbal medicines, within that, there's chemotypes, chemokines, so there's variability in active compounds, essential oil content, in that. We know that's a problem as well, in a lot of different herbs there's variability. We can't be too prescriptive and rigid in applying the drug model to herbal medicines, because herbal medicines are naturally more variable. That was one of the problems with the traditional herbal registration. We had to look into that and say, "Yes, the pharmaceutical model is good, and that's what we're aiming towards, but it has to be a different model because we have to allow for variability, the stability is not going to be the same as an isolated compound in an inert tablet, it's not the same. You've got a granule or a dried herb or a tincture, it's a different pharmaceutical preparation.

Question 8: Why do you think these problems continue despite control measures being in place?

Interviewer: ***How aware do you feel where the regulators are, of the difficulty with variability in natural variation? Do you think there is an awareness there of that?***

Participant: The MHRA is extremely supportive, as much as it can be within that, they've done everything they can to help. The problem is the variabilities, the allowed variabilities are in the EU law, or if there's Brexit, it will be in UK law, so there's not much they can do outside of that, but they're supportive in helping companies to find ways around issues, if there is a variability or a stability issue that's causing issues.

Sometimes it's a simple thing as you might know the active compound. The active compound, it may not be the best one to monitor long term, so you find another one that you can use and monitor that and that gives the stability you need in order to have the pharmaceutical level license put towards it. Sometimes it's just thinking out of the box a little bit, and that's what the MHRA has the experience because they've worked with so many different things. They can advise the suppliers of ways of doing things to get the results, to ensure the quality, efficacy. They don't ever cut corners, I'm not suggesting that, but they

can make sure that they can help the supplier reach the product that they need to reach.

Interviewer: ***That's good to know actually, I wasn't aware of that.***

Participant: They're very supportive, the MHRA. There's a lot of misunderstanding and demonizing of the MHRA within the herbal medicine arena, particularly by practitioners, they think they're overseeing them and trying to limit them, they're not. The MHRA is under the control of the Department of Health, so it's the Department of Health that puts all the issues through. The MHRA, the poor thing, is left to follow it up and do it, so the MHRA is actually not the bad guy.

Interviewer: ***Caught in the middle of it all.***

Participant: They're caught in the middle, and they are extremely supportive of herbal medicine. Off the record, they were extremely supportive about such a Statutory Regulation for Herbalists. They were all in favor of it, even the heads there when I spoke to them. On record, they said they were. It was the Department of Health that wasn't because the cost of regulation, so it's purely, again, a cost issue, unfortunately.

The MRHA does a great job, I really stand in awe of what they do but they're only human. They haven't got the money, the resources, time to do everything they should or could, it's impossible. Herbs are a small part of their remit lteratlly has lost a huge amount of their income because obviously, the European Medicines Agency had to move to the Netherlands. They've lost a third of their income.

Interviewer: ***Actually, I hadn't thought about that, that there's a financial implication of that.***

Participant: The NHS lost a third of their income, they also had to move from Victoria, the offices, because the UK Government had released the Canary Wharf buildings for the EMA for like 10, 15 years. They had to pay to move to these buildings because otherwise, they'd be a huge billion-pound loss. EMA is having difficulties with all the Brexit as well. It's things that aren't talked about or known about, unfortunately. Let's not even talk about Brexit.

Interviewer: ***I think I need a new hard drive and a couple of power supplies.***

Participant: I could rant on that for a long time.

Question 9: Do you think that CHM quality could be improved?

Interviewer: ***There's about seven minutes left. We're doing well. I can tell you a real progress because you've already touched on practically everything I wanted to touch on. You've touched on the mixed-up species, you've touched on the PAs and aflatoxins, et cetera as well. Just in the last six, six and a half minutes roughly. Just taking a step back given the fact that you have been in the industry for a long time, you've been on the practitioner side, regulation, and education side. Taking a step back from it all. Let's say we're about 70 years old having a whiskey and***

Question 9a: If not - why?

Question 9b: If yes- how?

Participant: [laughs]

Interviewer: ***we're reminiscing, what should we have done?***

Participant: Wow, gosh. No regrets. No. Oh God, it's what-- Ideally, we should be more aware as an industry as a whole from an earlier time about the issues with adulteration and substitution and contamination. The PA issue hit us with absolutely no warning at all. We were absolutely caught off guard in the whole industry. Europe or Germany had known about it a couple of days earlier but they hadn't shared anything with us. It wasn't their fault, it just didn't-- There was no communication between the different institutions which they're paying.

Interviewer: ***Communication?***

Participant: Exactly. Which is partly the UK's fault rather than Germany's fault quite frankly. I don't blame Europe at all, I think the blame is with the UK, not with Europe at all. Ideally, we should have had better. I guess, using a pharmaceutical term, pharmacovigilance, from an early time. The problem is we couldn't have done because there was no enthusiasm from suppliers to do that. With that, we needed something like the PAs to actually show there was a public health issue, that then really kickstarted, fired up the suppliers to actually make changes, both the suppliers to the public and suppliers to the practitioners as well, and raise the awareness within the herbal medicine sector.

If we had thought to do that before it would been great, but I think nobody would have really ever considered it, and I said, the problem with PA testing is so expensive. If you've got this nebulous thing that could happen, are you going to spend £250 per batch getting it tested? No, you're not quite frankly, are you?

Interviewer: ***It's not going to happen, no.***

Participant: Hindsight is brilliant, but unfortunately, we don't have foresight. Ideally, yes, we would have been more careful. We would have checked quality, we would have-- unfortunately, things like the Aristolochia issue caused a huge,

huge amount of damage to Chinese medicine, unfortunately. It was unnecessary. It was a mistake in one country with inappropriate substitution. It wasn't done maliciously, it was an honest mistake, but it led to major health life altering effects for patients, and it is detrimental to Chinese medicine. It did-- not irreparable but long-term damage and I think we're still in that issue now.

A lot of people still think Chinese medicines are unsafe or unregulated. That's in the public sector but even in the western herbal medicine sector. Not in my professional association but in another major Western Practitioners' Association they're very anti-Chinese herbal medicine because they say it's unsafe and it's dragging down the quality and the public view of herbal medicine, which is so unfair. Makes me absolutely rabidly mad.

If we had a clean bill of health in western herb medicine it'd be great, but we are equally in the same issues. In fact, we've done less than the Chinese medicine sector has done so it's just so inappropriate to say that the Chinese medicine sector-- the herbal medicine sector is to blame for this, it's not true at all.

Interviewer: ***Even within the herbal community there's fractions and so on?***

Participant: There's huge fractionation. Even with pyrrolizidine alkaloids, there's two practitioner associations that are still allowing their members to use herbs that naturally contain pyrrolizidine alkaloids, which is absolutely beyond belief. Again I can just see the media issue there if that comes out.

Interviewer: ***It's a ticking time bomb.***

Participant: Yes, it is a ticking time bomb but that's another issue to deal with. If we'd known about the quality issues, if we'd known about the contamination issues, if we'd known about the mold issues, drying, aflatoxins, pyrrolizidine alkaloids, the aristolochic toxins, all the other various mycotoxins, bacterial things, it would have been good, if we had time to actually gradually put this into place, rather than having to put a lot of the things into place suddenly with a huge financial cost to the companies. Which is why a lot of the companies couldn't keep up and some of the smaller ones closed because they couldn't keep up anymore with what was necessary for them to do.

If we had had more time we could actually have brought in more slowly and done things there, ideally. As I said, in practice, I'm not sure it would have happened because you wouldn't have that enthusiasm from the companies.

Interviewer: ***Unsurmountable obstacles?***

Participant: In a sense. Like anything you need something major to happen in order to make things change unfortunately which is sad. We have learnt lessons, and we're moving forward. We are looking at a range of different contaminations, we are looking at the adulteration, substitution things. Different people are looking at different things. Kew is doing a fantastic thing which you probably know they're doing. They're looking at, I'm not sure it's public knowledge, you might know about it, but they're digitizing the whole Chinese herbal medicine. From Mass Spectrums, you've heard about that?

Interviewer: ***Yes, I heard from "person's name".***

Participant: I think brilliant, absolutely brilliant. You've got proof of what the mass spec should look like of an authenticated specimen. It was so brilliant to do. That's going to be so good for safety, quality issues going on.

Interviewer: ***Even to know where we are, you got the point.***

Participant: Things are moving forward, there are positive things happening, but there's still a lot more to be done. It's interesting. Certainly, I, when I started out, thought that one of the issues with Chinese medicine was the fact that some of the suppliers, particularly in China were supplying poor quality things. Having talked to a number of like Phoenix, et cetera, and Herbprime, in Korea, aren't they?

Their pharmacovigilance is way superior to us, to what we're doing in the UK. I've actually learnt a lot, and it's very easy to come into the whole area with prejudices, which you hear from other people, and then you see actually what you've been taught or told is actually wrong. That actually, there's a lot of work being done in China to ensure quality, and the money is really being pumped into it in a huge way because it's such a major part of their heritage and financial culture. It's important for everything there.

They're doing such a lot to make sure that the prestige of Chinese herbal medicine is kept up high, but we need to make sure that we do the same here, even though we get a lot of our supplies from the Chinese suppliers. We have to make sure that smaller companies that aren't, aren't letting the whole sector down.

Interviewer: ***Finally, is the future bright? Is it a dark future, is it a bright future, or is it a variable future?***

Participant: I'm not a betting man so it's hard to know. When it comes to it, there's a lot of interest in herbal medicine, all different modalities, but particularly there's a lot of interest in Chinese medicine. A lot of obviously good quality research is coming out now. There's a lot of research been done the past but it's been variable quality, but a lot of the research coming out of China now is very very very very high quality so it's really transforming the research about herbal medicine. I think there's going to be a lot more interest in Chinese herbal medicine in the future. If we can show that we're working towards quality, safety, efficacy, then we're going to get the public involved even more. I think it's a brilliant way forward because the NHS, as we all know, is not going to be able to survive as it is.

Interviewer: ***Good point.***

Participant: We won't be able to get money from the NHS or referrals from the NHS but what we are doing voluntarily and perhaps totally involuntarily is we are propping up the NHS. We are seeing people with self-limiting conditions so we're saving a lot of money to the NHS because their people aren't going to hospital or are not seeing their GPs, et cetera, et cetera. We're saving actually billions to the NHS. It's not recognized at all but moving forward we need to

make sure it is recognized perhaps by the public more than anything else and make sure the Department of Health knows more about it.

We're looking at some point doing some work seeing in an average sort of herbal practice, seeing patients, what sort of difference that actually makes saving wise to GP time and thing. Stopping people who are going with a cough or a cold or backache or something like that. I think there's a lot of interest in herbal medicine. I think there's a lot of media interest in herbal medicine, very positive, not negative interest. I just think we need to continue to work to show what we're doing and to raise the awareness of herbal medicine generally. I think it's interesting times. My only concern is getting new students in to keep practitioners in the supply chain.

Interviewer: ***We think of the herbal supply chain but the chain is bigger. It's from seed to consumer to consumers. You need all of the people in the middle.***

Participant: That's it.

Interviewer: ***Wherever you pick the middle to be in the circle.***

Participant: Exactly, and you need to make sure quality is assured at all the different points within that whole line there otherwise if one area is weaker, the whole thing will just collapse.

Interviewer: ***The bicycle chain breaks.***

Participant: Absolutely.

Interviewer: ***Participant, that's fabulous I really appreciate that. You have no idea how valuable that is to me.***

Participant: [laughs]

Interviewer: ***Thank you. Is that all, Participant?***

Participant: That's all from me.

Interviewer: ***Thank you.***

Participant: If you have any other questions when you listen to this and contact me.

Question 10: Anyone else you would recommend to speak to?

Participant: Mmm… have you considered [TEXT REDACTED] ?

End of Interview

Interview Details:

Type: In person with 2 observers

Interview Language: English

Location: Taichung, Taiwan

Date / time: 11/9/18, 12.30 (time estimated)

Format capture: Handwritten notes

Question 1: Could I ask you about the nature of your work?

Question 1a: Positions?

Professor [TEXT REDACTED] University, since 2001

Head of college [TEXT REDACTED]

Question 1b: Area?

pharmacognosy of TCM

Question 1c: Time?

More than 35 years

Question 1d: expertise?

TCM and education

Question 1e: countries?

All over the world, America, mainland China, Japan, all over Europe and many more.

Question 2: What do you think about Chinese medicine quality?

Question 2a: regulated and unregulated?

This is a big problem and not new. Practices such as this have been conducted through all of history. This is one of the reasons that the Pharmacopoeias exist. So we can define what is regulated and what is not.

Even so there are many unclear areas that cannot be well defined. It's complicated by long history sometimes which conflicts in opinions, and languages. For example in Taiwan indigenous herbs were recorded in Japanese language though their origins are from Taiwan. It wasn't until later that it was translated to Chinese then only 15 years ago into English. So they may be errors there. It's likely that we don't even know about some of them.

If you consider that the Taiwanese pharmacopeia has about twelve-thousand plants, over three volumes, these are ones that have been studied and well described. But some have not and even the ones we have studied, even with the best available knowledge. Some has been lost, some may contain errors. If we think that way we can look out for mistakes and new things. There are

corrections of pharmacopeia all the time. We must see these as working documents that will change.

Here we have done a lot of work to verify the information in the new pharmacopeia without much funding, we pay for most ourselves and takes a lot of time. We try to make it part of students, like postgraduate mainly for their academic advantage, so not all the work is directly for pharmacopeia but we can integrate it into the research. Sometime I have done this work myself and my colleague here [text redacted] has been working with me for many years. It's a big effort, costs a lot and not much support. We look for external funding, I am not sure if we can keep doing it. Maybe we will have to rely more on the Chinese pharmacopeia for the next time. Maybe this will be the last edition of the Taiwanese one. We will see.

different supply chains?

Yes, we will talk about that more in a presentation later, but there are so many, you know about my book?

Question 3: What do you think about species of herbs being mixed up?

[Interviewers note: talks to assistant, askes to turn on the projector]

You can look in that, book, and things like Bupleurum in Taiwan is different from its name in the macroscopic form.

[interviewers note: researched later: Bupleurum “kaoi” is native to Taiwan but since 1963 the Chinese Pharmacopeia describes the “official” as B. Chinese DC, Taiwanese Pharmacopeia 2nd edition p52.

Question 3b: examples?

Yes I will include these in our presentation

Question 3c: prevention strategies?

We want to educate people at the university and also through workshops and seminars. The main contribution is in the Pharmacopeia. If we have good standards we can prevent a lot of things. We will cover some things about this today.

Question 4: What do you think about species of herbs being replaced with others?

Yes, we will talk about it soon.

[Interviewers Note: participant talks to assistant. We need to turn it around, its upside down. Turn it around]

But the adulteration is a big problem, like with Magnesium sulphate, its heavy. It can increase the value of the herbs because it weighs heavy. Its added in. The “jia zhong fen” .

[interviewers note:加重粉].

It can be caught with the simple ashing tests, the total ash content test. There are about sixteen herbs commonly adulterated with this. But also Barium Sulphate, barium sulphate is used more with Hong Hua, very expensive. Can be big money.
You know about the starch?

[Interviewers Note: participant talks to assistant to get someone to fix the projector].

The starch is heavy but you can test easily, it doesn't dissolve in the alcohol. But there are more tests for these things. The hard ones are the drugs added. You know we looked at 19 crude herbs from the Chinese Pharmacopeia and 10 of them contained drugs.
Since 2010 the Chinese Pharmacopeia added decoction pieces with very detailed instructions for preparation at this stage. 1985 was the first English one.

2004 was the first Taiwanese pharmacopeia, we raised the sulphate levels to 500ppm you can catch the herbs with the sulphates added. But we also looked at the heavy metals and pesticides which need to be checked. Herbs are commercialised now, its different from the classical times and the times of the wild herbs. You have to check for effects of industrial production. Even production not related to TCM can enter the TCMs.

The Korean regulations in 2008 only were at 30 ppm for sulphates. But the Chinese in 2011 (SFDA) proposed 400ppm, for commonly fumigated herbs in particular and the 150ppm for the ones not commonly fumigated.

But they left some of the flowers on the herbs that are used for food. The left these as exceptions, so you don't have to test these. So the herbs could fail but the parts can still be used as a food.

[Interviewers Note: participant talks to assistant and other helper to get the projector working and thanks them]

I have the slides here you can see them in a minute. [Interviewers Note: participant talks to assistant, bringing up a presentation on a screen]
Taiwan in 2006 set 400ppm for sulphates, but for the twenty five most commonly used herbs. We had to put in colour in the pharmacopeia at this time. For things like, to see the colour TLC and HPTLC plates.

You will see we have conditions, like extraction conditions for the tests. Absorbance maximum and minimum. [starts reading from a presentation verbatim for some time, presentation attached]
Key points from presentation noted hand notes:
Single granule extracts accepted and used commonly in Taiwan, for a long time but is only recently accepted in PRC and used, compound formula still not popular. There are 301 formulas and 353 single extracts accepted by the Taiwan National health insurance. They are about 3:1 concentrated

The Taiwan Health insurance is well established since 1995 and TCM is central to its function. All aspects rom presrctiptions, payments and insurance are all integrated.

Question 4a: examples?

Question 4b: prevention strategies?

Question 5: Do you have personal experience of these issues?

List of herbs more likely to be adulterated with Magnesium sulphate – required to do testing since 2009. These generally are herbs with a loose texture.

Coptidis Rhizoma

Polyporus

Tetrapanacis Medulla

Atractylodis Macrocellalae Rhizoma Alpiniae Katsumadai Semen

Stemonae Radix

Scutellariae radix

Dictamni Radicis Cortex

Cimicifugae Rhizoma

Aucklandiae Radix

Clematidis Radix

Belamcandae Rhizoma

Atractylodis Rhizoma

Salviae Miltiorrhizae Radix et Rhizoma Placenta Hominis

Amomi Fructus

Lonicerae Flos

Saposhnikoviae Radix

Carthami Flos

Test for Magnesium sulphate can used barium chloride

Hong Hua when Barium sulphate added makes the colour much brighter and fresher and considerable bulks up the herbs.

The first picture given is with adulteration the second without, *Figure AKI 10.1*.

FIGURE AKI 10.1 CHINESE MEDICINE HONG HUA CONTAMINATED WITH BULKING AGENT BARIUM SULPHATE

The pharmacopeia has botanical origin, description and identification but this needs experience to really be useful.

Many photos needed to be replaced / in the pharmacopeia because of misidentification

16 examples given of photos were given (permission not given for reproduction of photos). Some CMP are shown in *Table AKI 10.*

TABLE AKI 10 EXAMPLES OF MISTAKEN ENTRIES IN PHARMACOPIEAS

Original	Corrected entry
Hua juhong,化橘紅 *Citrus grandis* (L.) Osbeck	Huazhou juhong, 化州橘, *Citrus grandis* (L.) Osbeck var. *tomentosa* Hort.
Shanzha, 山楂, *Crataegus* *pinnatifida*	Shan Lihong, 山里红, *Crataegus* *pinnatifida* Bge. var. major N. E. Br.
Qian niu zi, 牽牛子, *Pharbitis nil* (L.) Choisy	Yuan ye qian niu, 圓葉牽牛, *Pharbitis* *purpurea* (L.) Voigt
Huang pi shu, 黃皮樹, *Phellodendron chinense* Schneid.	Huang bo, 黃蘗, *Phellodendron* *amurense* Rupr.
Yu jin, 溫鬱金, *Curcuma wenyujin* Y. H. Chen et C. Ling , Wenyujin	Guang xi e zhu, 廣西莪术, *Curcuma* *kwangsiensis* S.G.Lee et C.F.Liang
Jiang huang, 薑黃, *Curcuma* *longa* L.	Peng e zhu, 蓬莪术, *Curcuma* *phaeocaulis* Val.

Some photos were understandably almost indistinguishable such as those for 大棗 and 花椒 but other such as 地骨皮 / 枸杞 were markedly different

Sulfur Dioxide limits for the following commonly fumigated 25 herbs was set to 400 ppm:

Achyranthis Bidentatae Radix、Puerariae Radix、Gastrodiae Rhizoma 、Asparagi Radix、Trichosanthis Radix、Bletillae Rhizoma、Paeoniae Alba Radix 、 Paeoniae Rubra Radix 、 Atractylodis Macrocephalae Rhizoma 、Dioscoreae Rhizoma 、 Lilii Bulbus 、 Ginkgo Semen 、 Longan Arillus、Mume Fructus、Lycii Fructus、Crataegi Fructus、 Jujubae Fructus 、Codonopsis Radix 、 Angelicae Sinensis Radix 、 Chuanxiong Rhizoma 、Anemarrhenae Rhizoma 、 Kaempferiae Rhizoma、Nelumbinis Semen、Tremella Fuciformis、Euryales Semen

The limit for other herbs:150 ppm。

Question 6: Have you had much experience with aflatoxins?

The Aflatoxin Limit was set in 2016 for some herbs of higher risk including: Arecae Pericarpium 、 Ligustri Lucidi Fructus 、 Corni Fructus 、 Piperis Fructus 、 Corydalis Rhizoma 、 Citri Reticulatae Pericarpium 、 Astragali Radix、Hedysari Radix、Platycladi Semen、Quisqualis Fructus、Arecae Semen、Hordei Fructus Germinatus、Cassiae Semen、Polygalae Radix、Coicis Semen 、 Pheretima 、 Scolopendra 、 Hirudo 、 Scorpio 、 Bombyx

Batryticatus、 Ziziphi Spinosae Semen、 Persicae Semen、 Sterculiae Lychnophorae Semen、 Citri Reticulatae Pericarpium、 Armeniacae Amarum Semen、Cyperi Rhizoma、Glycyrrhizae Radix et Rhizoma、 Scrophulariae Radix、 Belamcandae Rhizoma、 Jujubae Fructus、 Anisi Stellati Fructus、 Foeniculi Fructus、Crataegi Fructus、Lycii Fructus、 Nelumbinis Semen、 Saposhnikoviae Radix

The total aflatoxin limit is now 10 ppb (including aflatoxin B1、B2、 G1 and G2)，The limit for aflatoxin B1 is 5 ppb。

Question 7: What do you think the key issues are?

Weight additions,

Fumigation,

Misidentification

Contamination like from pesticides

The general limit for pesticide residue is under review

Question 8: Why do you think these problems continue despite control measures being in place?

There are a lot of controls

Herbs for national use can only come from GMP – factory based systems not small local suppliers.

Before marketing, TCM Herbal Preparations must be licensed from DOH after documents examined by CCMP and products analyzed by BFDA.

Manufacturing factory must be GMP compliant.

GMP Companies: 103 (2015)

(All pharmaceutical factories were GMP since 2006)

Licences: 19,532 Prescription Drug:7,311

OTC Drug: 8,176

Qualified Herbal Store Runners:13,500

40 TCM herbs should have TLC verification

At least half of the prescription ingredients should provide TLC verification

Marker constituents used as reference standard if available

Blank test required

They continue because,

“The quality control of TCM herbs is much more difficult than that of active pharmaceutical ingredients in western medicines because many environmental factors will affect the quality of TCM herbs. “

Question 9: Do you think that CHM quality could be improved?

Question 9a: If not - why?

Question 9b: If yes- how?

“Good preparations only comes from TCM herbs with good quality and the authenticity of TCM herbs is the first point of concern for quality” presentation p 101

You can look in our museum in the tour, I will give you a tour. Have you already been to see it?

Question 10: Anyone else you would recommend to speak to?

[interviewers note: This question was asked while in the lift and interrupted by a person entering]

You can look at Zhong Yongxun’s presentations on the CMU website. You can find out more about all this.

[interviewers note: Reference given in conversation to;
Zhang Yongxun

Weight powder
It is reported that Magnesium Sulfate is a small white oblique or oblique columnar crystal,
Odourless, bitter taste, easily soluble in water, and relatively dense. Chinese herbal medicines,

After the decoction pieces of traditional Chinese medicine are soaked in an aqueous solution of magnesium sulfate, the magnesium sulfate will
Adsorbed to the inside of Chinese medicinal materials and Chinese medicinal pieces. "Aggravated medicinal materials
After drying, the weight can increase at least 20%, more can increase a few Times. Not an insider, it's hard to tell. "A person from Bozhou City
The drug dealer, who did not want to be named, told reporters, “The market in Bozhou
Most of the magnesium sulfate sold comes from Shanghai, Lianyungang, Dalian and Qinghai
Island’s chemical plant, one of the brands also exports, this product
The brand has the highest price and is the most difficult to distinguish after use. "According to a reporter's investigation,
At present, the price of magnesium sulfate on the market in Bozhou City is 30-38 yuan per bag.

Bags of 100 kg, converted into one kg is 6 gross money around.
"Even if it is 10 yuan a kilogram of medicinal materials, use weighting powder to increase the weight.

After doubling, 60 cents per kilogram of magnesium sulfate will be sold at 10 yuan, and you will know once you count
How much illegal profit can be made. "The drug dealer said, "The huge profit is The direct reason for illegal drug dealers to use aggravating powder. "

End of interview

AKI 11 Summary of key contributions from interview participant responses

AKI 11.1 Opinions on quality

Posed as question 2, “what do you think about Chinese medicine quality?”

Several diverse opinions emerged from participants with fundamentally differing perspectives around how herbal quality is defined, tested, and controlled. Views on their use as medicines varied by expertise, ethnicity, and residency.

It brought to light opinions about herbal quality and differences in views between Chinese and British participants.

AKI 11.1.1 Variable definition of quality

Case	Key contributions
C11	*“good to treat patients”*
C12	*“different areas to grow herbs and different seasons. They can be used differently. North and South, East and West all can be different”*
C18	*“..we need a definition about quality. Because herbs quality is not simple, say, like a TV quality. They are all nature growing in the field.”*
C19	*“I think good quality is difficult to maybe to specify what is good quality”.*

Fundamentally different views on herbal quality was apparent from the interviews in general, typified by a group of senior Chinese medicine professors in Beijing,

China, Cases 11 to 13 inclusive (C11-13), who when asked about their thoughts on Chinese medicine quality immediately replied with a question, “how do you mean about quality…what do you mean”.

When asked again, “I mean in terms of how good or bad the herbal material in China and exported abroad”. “Do you think the materials, the herbal materials are good?”, they again asked “Good for what?”.

The contributions were interpreted as, that quality characteristics of herbs vary greatly and are influenced by many factors, so asking about quality in general is not particularly specific, and that in their view it is linked to intended use. Or otherwise stated, quality needs to be defined before it can be further discussed. Therefore the concept of quality is highly-relative, and variable.

AKI 11.1.2 Quality defined by standards

Case	Key contributions
C17	“*generally speaking, the quality of traditional Chinese medicines could basically meet the requirements for current clinical efficacy*”, however qualified this by saying, “*on the other hand, from the perspective of foreign demand for traditional Chinese medicine, their quality requirements are basically met as a whole*”

C17, a senior professor of Chinese medicine in China, felt that efficacy was a measure of quality. Interpreted in context of the full interview as “good quality herbs” impart clinical effect, however when exported, what is supplied as good quality is whatever is requested as a whole. In the case of Europe and the UK this would in general relate to the European and British Pharmacopeia standards respectively.

AKI 11.1.3 Quality is specification dependent, including cost

Case	Key contributions
C15	"*Chinese medicine could be very high quality and could be very poor quality depend the country*", "*good quality in the country like Taiwan, Japan, Korea, Hong Kong, but then it could be a very poor quality like England, or the other country*..[with]..*no regulation*".
C16	"*different specifications lead to different prices...we produce the Chinese herbal medicines according to the standard requirements of our clients. If he asks for higher quality, we will improve our quality and deliver the Chinese herbal medicines according to his requirement*"
C17	*"The quality of Chrysanthemums planted in different places is very good, but you must plant them according to their own growth characteristics. If you don't plant them according to their own growth characteristics and apply excessive chemical fertilisers, they will grow too fast and the accumulation of the effective ingredients must be different. In addition, if you use some technical measures to make them grow too fast, the quality will certainly not be good".* *"The best Angelica Sinensis grows in Mingxia county, Gansu province. It has been so good since ancient times, and it also grows in the high altitude area there. In Anhui, it does not grow naturally, and the planted one "cultivated" is not as good as that grown in minima county, Gansu province. For example, liquorice, which is a harmonising Chinese herbal medicine, has the efficacy of clearing heat and detoxification. It grows in the north of China, from northeast, Inner Mongolia to northwest. When in central China, it's not the natural growth and distribution area of the liquorice. You can plant it but the quality will be totally different"* *"…even though there are laws and state control, there are still problems, because it's a commercial issue."*

C15, a Chinese national who owns a herbal supply company in the UK, shared an insight into the variation that exists with the quality of exported herbs, and it depending on what quality specification an individual country requests. C16, a Chinese national and senior manager of herbal manufacturing company in China, supported this opinion in that, indicating that what level of quality is requested is what will be supplied and costed accordingly. C17 offered a number of highly qualified examples of quality variation that challenge the natural integrity and add variability to CMP quality.

These contributions collectively illustrated the many natural factors influence quality and that perhaps, when taken in context with C16's opinion that quality is related to cost, then if cheaper herbs are requested these may be cultivated where it is feasibly cheaper, and perhaps outside areas well known traditionally and viewed "not as good" quality. C17, believed similar to C16 that quality is led by cost, "A reiteration of financial interests influencing selective quality.

AKI 11.1.4 Herbal quality perspectives have changed

Case	Key contributions
C14	"*From the beginning, nobody cared about the quality, now more and more people realize that is essential*". "*At the beginning, they realized that medicine is essential for people's life. They were doing very carefully. They really care about the quality". "They haven't realized that's big margin in TCM industry because after several years of introduction to TCM, introduction of Chinese medicine to Western countries. As soon as some more businessmen involved in TCM industry, and then, they just ignore the key issue of quality". "After more and more business evolved in TCM and more and more businesswoman or businessmen look for the margin, they don't care about the quality. They want the quantity.. people have instincts. They haven't got any, how to say, the responsibilities. Then they think margin and profit is more important for them rather than the awareness of the people's life. I definitely think the quality is much better in the past*."
C18	"*I quite believe it's getting better and better and under control, under regulations*", and that more regulation has positively influenced herbal quality. However they qualified this by mentioned that "*from China, public opinion they will say the good quality herbs go into the Taiwan, Japan, and Europe. In Japan they have high standard, so you will see that the top quality or better quality are going to Europe and Japan. In general, UK's herbs quality is better*". , "*…for quality, number one, of course, we need to see it's authentic herbs", "secondly, we need to think about purification. No dust no other metals in", "third one, about how they process herbs"..[then].."..how they're packing. How they store, the conditions...how they transport*"
C19	"*300 years ago, the medicine seems to have a better efficacy compared to today. At that time, most of the herbs are collected from the wilds. I think no pesticides was invented at that time. They do not have to get big ones to make more profit*".

C14, a Chinese national working at a senior level in a Chinese herbal supply company emphasised in an extended explanation, the shift in view of quality with commercial influence. Interpreted here as, this participant feels that earlier, before large scale commercialisation of Chinese herbal medicine, it was seen as

an essential part of people's daily lives and not a so much as a commodity. Then when the opportunity to make large profit presented with foreign exports, the focus was more on meeting supply demand rather than it's suitability as a medicine as a priority. C19 reference to "Big ones" interpreted here as larger herbal specimens for more profit, in agreement that herbal medicine quality has inherently changed over the years. C18, the Chinese national and a supplier, in disagreement that the general quality of herbs has declined, is an additional expression of supplied quality is dependent on local standards. Further adding that feeling that quality is about basic authenticity, purity, and good handling care along the supply chain.

Although it is not possible to verify the above reference to the quality of herbs 300 years ago, certainly contemporary chemical fertilizers and pesticides were not available. Trading and commerce has been long practiced, but it was not until the relatively recent "opening up" that commercial activities in China saw their greatest historical development. In the 90s there was a 49% increase in the use and supply of herbal medicine (E Ernst, 1998), (David M Eisenberg et al., 1998). Mainland China overtook the USA in the year 2000 as the world's greatest medicinal crop grower (676,000 hectares, 2.6 million tonnes per annum), it placed Chinese medicinal plants (CMP) as the most prevalent medicinal plants globally. (NSBC, 2018), (FAO, 2020, p. 7), a trend predicted to continue (Bekkers et al., 2021). The traditional location in which herbs are grown is still considered an indicator of quality for specific herbs. The Chinese term "Dao di", is used for such areas of land used traditional and favoured for specific herbs, "dao" officially used by the Tang dynasty government in the early CE 600 to demarcate ten

administrative districts and in later times indicate most appropriate growing areas for particular CMP. Regions of areas of superior location were recorded in earlier herbal classical texts such as the Shennong Bencao Jing from the second century BCE (D. Lei, J. Wu, C. Leon, L. F. Huang, & J. A. Hawkins, 2018; Y. Yuan & Huang, 2020).

AKI 11.1.5 Different perspectives on quality at different parts of supply chain

Case	Key contributions
C8	"*practitioners, particularly newer practitioners will tend to go for cheaper products, so that they cannot charge their patients too much money, and can make a tiny profit themselves*",
C19	"*where you are in the system, whether you're a practitioner, dispenser, supplier, or whether you're involved with research or new drug. For example, the farmers cultivate the plants. What's the next, stakeholders want those with a good look. Normally, they do not do the, let's say, the chemical detection at the transaction of this step, from farmer to the stakeholders or manufacturer or something. They do not do that detection, that chemical detection, but they can evaluate the quality by the appearance of herbs. To get the herbs with a good appearance, fertilisers, and pesticides already applied*". "*If the farmers sell their dark gojis to the middleman then they will get a lower price but the dark ones are from safety sides it's better*",

C8 as an ethnic British herbal medicine educator felt that even at the end of the supply chain practitioners can influence supply quality. As practitioners favour cheaper herb purchases, it can influence herbs selected by suppliers, and yet further back the supply chain to the cultivators.

C19 felt that different views people hold at different of roles at various supply chain steps influence quality, and therefore quality is dependent on the people in the supply chain, in addition to natural phytochemical variability. Interpreted here as, dependent on where stakeholders are in a supply chain, different attributes are prioritised, for example from farmers to other stakeholder they may judge quality by the appearance of the herbs, which may have been enhanced with chemicals. Practitioners, dispensers and suppliers will have different ideas and demands for quality at different stages of the supply, all of whom can influence quality. Further emphasising the point that stakeholders demands within a supply chain may not always be oriented towards best quality, but instead towards what appears good to sell well.

AKI 11.2 Opacity between perspectives along the supply chain, influence quality

Case	Key contributions
C7	"*quality assurance issues are different*..[in formulations such as granulated herbs].. *in that you can't see the herbs so you can't do your own pharmacognosy*"
C8	*"you need to know what happens from seed to storeroom. If you don't know that, you don't know the whole picture of what's going on, and where things can go wrong*".
C6	"*it's a completely opaque situation. Estimation would be guesswork. We just don't know*". Even on a basic level, "*it's impossible to differentiate regulated from unregulated* [herbs]".
C7	"*we all want to know what's going on with GMP in China", adding "you're very much reliant on this company which is situated in a far off land*".
C10	"*the doctor or assistant can know the suppliers personally or through family, but many these days, they don't. It's different from the old times*". "*the people who have the fake things can be in another country or far away from the market so they don't care about the people who take it. They don't know them, they will never see them or their relatives*".
C14	"*when they made into granules, how can you what species they have been used. You can't tell straight away, you can't tell no matter whether you are experienced, a professional practitioner, you still can't tell it".*
C15	*"I don't import the raw herb because we don't think we have a right knowledge or test equipment can check the quality*".
C18	"..*the lack of this knowledge or information. That's partly missing when you introduce Chinese medicine to the UK or to Europe*." C6 further adding that *"in 90s when TCM become more popular it was difficult to recommend anyone to see a TCM or other herbal practitioner. How would you know who's who?*"
C20	"..*market surveys to see actually try to systematically quantify the quality of TCM herbs in Europe. We feel this has not been done*".

C10 noted that supply chains becoming longer and distant over time has impacted connection and communication between people. Furthermore, as people's perspectives on quality may vary along the supply chain and there may not be mutual awareness of the others. C6 a British senior regulation consultant stated this has developed to the extent that he believed that regulators' perspective is that the Chinese herbal medicine quality situation is highly opaque. C8 believed that there are clear implication of these factors. Interpreted as; barriers to basic knowledge collection exist and quality issue may arise due to lack of basic awareness of problematic quality issues. Further, an inability to access information from those involved across the complete supply chain can impact quality and create possible problems. Or alternatively expressed, the opacity arising from siloed knowledge, the views and perhaps actions they inform could affect herb quality.

C20 expressed that efforts have not been sufficient to study TCM quality in the supply chain as a whole. C10 a Chinese national and Chinese medicine senior professor re-emphasised. Whereas C7, a British national in involved in regulation thought that cultural and geographic distance between China and UK / Europe contributed to opacity by obscuring information about herbal quality.

Opacity was also linked to cultural distance which could affect perceived herbal efficacy, such as C18's opinion that we are currently the Chinese herbal education and professional associations situation is not yet well-developed in the UK.

C14 highlighted that opacity arises from the influence of the manufacturing process the different herbal formulations it produces,

Responses indicted that opacity could be fostered by a lack of resources in addition to siloed knowledge along supply and China's cultural and geographical distance, an opinion held by C15 and further supported by C7.

AKI 11.3 Opinions on barriers to understanding of herbal quality

Case	Key contributions
C6	"*the practitioner just trusts all their supply because they're..*[from an]..*approved supply, but then once you look deeper, if you look at the quality, I always make complaint when the auditor come to us. They should check the quality not just check there, because we have better herbs. Everyone can make them very clean and shiny when you come to auditor, that's only the paper and document, it's not the quality and the safety*" "*..like ginseng for example. It just has no real practical shelf life on its own. So what do they do? To be able to keep selling it*". "*Often simple testing, like bacterial nutrient testing, just using simple petri dishes. You use another petri dish control, but many things can be camouflaged. With more selective nutrition you can get more colonies appearing for things you want. But also underlying can be mutagenic substance can be present*". "*in the end it was down to a humid summer and storage conditions. So even if you test and all looks well. It doesn't mean the product is good either. There are more factors involved that anyone can ever test".*
C7	"*Wu Jia Pi / Xiang Jia Pi, Periploca, which is a dangerous substitute. The problem is there, I mean I don't know the reason for it*". C8, related that, "*I've had the same issue as well with getting from previous approved plant suppliers things like Eleutherococcus senticosus. I got seeds given to me of that. I bought some seeds of that. It wasn't Eleutherococcus senticosus, it was… gracilistylus*". "*powders themselves are in some ways safer*",

Case	Key contributions
C8	"*they're multi-phytochemical many multiactivity. Any herb has at least 10 to 20, or 30 active compounds, yes, you can identify one or two key ones that probably have a major effect, but we all know that those are just the tip of the iceberg. It's the other ones that are actually complementing those, without the other ones, you don't have the same effec*t"
C9	"*for example in Taiwan indigenous herbs were recorded in Japanese language though their origins are from Taiwan. It wasn't until later that it was translated to Chinese then only 15 years ago into English. So they may be errors there. It's likely that we don't even know about some of them*". "[The]..*Taiwanese pharmacopeia has about twelve-thousand plants, over three volumes, these are ones that have been studied and well described. But some have not and even the ones we have studied, even with the best available knowledge. Some has been lost, some may contain errors. Bupleurum in Taiwan is different from its name in the macroscopic form*".
C14	"*those kinds of, the testing report or analysis report can be duplicated, can be adjusted*". "*it doesn't mean if I provide a very comprehensive and very good testing report means, which imply my product has got very high quality. That's not the case*". Giving the example of, "*menthol, Bo He in it, you smell. It's not taste like oil, but it's artificial. Artificial oils that they accept from the procedure*".
C17	*"in general, the quality of the Chinese herbal medicines will be affected in the whole process of transportation, storage and clinical practice..*".

Case	Key contributions
C19	"*primary compound but that's not very scientific for a medicinal plant product with thousands of chemicals inside*".
C20	*Bai Fu Zi which technically according to Chinese Pharmacopeia was sourced from something called Typhonium giganteum Araceae. But all my experiences of actually examining material in TCM clinics here in the UK in herbal dispensaries is labelled Bai Fu Zi, is that none of it is actually Bai Fu Zi, but in fact which is Fu Zi, a species of aconitum possibly coreanum. Of course any species of coreanum is a POM species*..[prescription only]..*a medicine and that's apart from anything else, it is illegal for anybody to dispense that unless one is a registered pharmacist*". "*Wu Jia Pi, Xiang Jia Pi…Xiang Jia Pi, the Periploca TCM material…it contains cardiac glycosides which the other one doesn't have, therefore there's a dose difference in between using one rather than the other*". "*once they know what the laboratory criteria are for testing, they'll quite easily find ways around it and as we know they're very sophisticated attempts intentionally to dodge many of these formal KPI standards*". "*I personally feel that they*…[the tests]…*are so basic chemically as to be almost useless because the industry to meet can easily meet many of the standards, The bar's been set too low on the chemical front*" "*adulteration of Codonopsis roots, Dang Shen, with American ginsenosides, they're known to pass off the Codonopsis, as the much more expensive and valuable American ginseng*",

Participants from different perspectives felt that in addition to variable definition of quality, and opacity there are other barriers to capturing a more complete understanding of quality, including inadequacies in current regulatory systems.

When C6 was asked if they felt that current auditing processes are more based on documentation and systems rather than assessing the “real quality” they affirmed their opinion. C14 also attested that even if auditors inspect documentation, it may not always be a reflection of the herbal material’s quality, as documentation can be easily altered without further checks.

Furthermore, as regulators assist in the creation of and rely on pharmacopeias as a primary reference for quality, the integrity of such documentation can directly affect herbal quality. C9’s contribution highlighted the errors in “official” reference documentation / texts, a Taiwanese Chinese national and senior Chinese medicine professor was verified as *Bupleurum* “kaoi”, native to Taiwan but since 1963 the Chinese Pharmacopeia describes the “official” as *Bupleurum chinense* DC. (Taiwanese Pharmacopeia 3rd edition, p 431.) C9 supplied documentation substantiating sixteen other examples in photographic form of the herbal material in the pharmacopeia should be corrected. Considering that the Chinese Pharmacopeia forms a central reference for formation of the European Pharmacopeia monographs errors or inaccuracies it is of concern have potential to influence quality standards. C20, a British senior researcher described number of additional examples of such errors.

Three participants, C7, C8 and C20 independently identified one CMP which exemplified a number of CMP quality issues, that of CP: Wu jia pi 五加皮, *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu. which is commonly known to be misidentified, and adulterated with other substitutes, including a cardiotoxic CMP, CP: Xiang jia pi 香加皮, *Periploca sepium*. However, why this occurs and is not yet full explained. (Foster, 2016; Hosbas Coskun S, 2022). The confusion

apparent with this Wu ji pi issue prompted further study and consideration in the next chapter of this thesis.

This examples illustrated that even when accurate pharmacopeia controls in place, they may not be effective as herbs may be substituted in the supply or by practitioners.

Even when the pharmacopeia references are accurate and reliable, C19, highlighted that as many factors affect the myriad of phytochemicals within plants, these tests may not be a fit for purpose to determine herbal quality. C8 thought this is because analytical chemistry based testing is somewhat reductive, often focusing on single chemical markers.

Participants felt that even if the Pharmacopeia monographs could be developed further to determine herbal quality that they would still not be fully effective as they could be easily subverted. C20 believed KPI, or key performance indicators for analysis tests such as concentrations of key active ingredients found in pharmacopeial contents tests can be falsified (Mudge et al., 2016). C20 added that even if there was complete compliance to current standards, the criteria is not sufficient to ensure common quality problems will not recur.

C14 agreed with this, and that the nature of tests efforts can contribute to the content of the product being test results being with active ingredient appearing higher than otherwise with the addition of active compound mimics (Miloua, Ortuño, Navarro-Fuster, Beléndez, & Pascual, 2022), (Booker et al., 2016), (Dugo, Mondello, and Dugo, 2000). C6 described the objective nature of

interpreting test results and how they could be justifiably assessed to favour a unrepresentative result outcome. C20 identified further examples previously substantiated by other researchers (Kum, et al, 2016 and 2021).

Respondents suggested that even if product is of good quality and testing is done in a compliant manner, it does not necessary guarantee quality. Influences on natural products such as herbs are handled, transported and stored can further degrade after testing, which cause toxins to grow, with C6 describing such an incident of where aflatoxin developed. C17 agreed that herbal quality is the sum of many factors combined and is affected by each step of the entire supply chain.

While some respondents spoke more about the detrimental impact of growing supply chains and manufacturing on quality and its assessment, C7 felt that even though variable handling of CMP in supply chains can contribute to quality issue there are also some benefits. Processing occurs under more rigorously controlled conditions than whole piece dried herbs for decoction, and this can destroy some contaminant bacteria and mycotoxins (He et al., 2020)

AKI 11.3.1 Stated standards may not reflect or ensure quality

Case	Key contributions
C10	"*even when this doesn't happen the quality can be low. Who knows, maybe you can have the right herbs but because the quality is not taken care of, maybe it's as bad as the fake. Who knows*".
C15	*"this report had to provide by third party, not the supply, some supply really odd they change the. They copy the other company test report makes a fake*"

Continuing from the previous section relating to barriers to understanding quality, including issues with documentation in the form of quality certification. Some believed (C15 and C10), that even if such barriers were overcome they would not necessarily lead to better herbal quality and specific challenges to herbal integrity would remain.

AKI 11.4 Opinions on specific challenges to herbal integrity and quality

Case	Key contributions
C6	"*fillers such as chondroitin sulphate and mannitol*" [adulterants at].."*more than a hundred times more than could be accounted for*" "*Remember the Black Cohosh situation?...So the supply chain then becomes vulnerable and to things such as adding in other herbs*"
C7	"*heavy metals, pesticides*" "*dried herbs*…[there is a]…*greatly increased the risk of aflatoxins or pest infestations*"
C8	"*mould issues, drying, aflatoxins, pyrrolizidine alkaloids, the aristolochic toxins, all the other various mycotoxins, bacterial things*" "*pyrrolizidine alkaloids, for microbial contaminants, possibly things like tropane alkaloids and ochratoxins*"
C9	"*magnesium sulphate, its heavy*". [..which can add weight and therefore value]. "*Barium sulphate is used more with Hong Hua, very expensive. Can be big money*" "*we looked at 19 crude herbs from the Chinese Pharmacopeia and 10 of them contained drugs*".
C18	"*Chi Shao only wild, no cultured available at the moment. If they don't have enough wild, so what's going to happen?*".
C20	"*they're setting up new markets for products and the herbs, but I can see no evidence for where the herbal material is actually going to come from. The wild material and it's going to be further depleted*" "*Yin Yang Huo which is the Epimedium, which is sourced from five species of Epimedium. All of that, with the exception of I think of one in recent years is still coming from the wild, so very difficult plant to grow commercially because it's so slow growing. That's why it hasn't been brought into cultivation*".

While there were several diverse opinions around challenges to defining and assessing herbal quality, overlap occurred on some specific quality issues of contamination C8, C7 and intentional adulterants C6

C9, also referred to the addition of herbal fillers to add weight to herbs, Specifying that (Foster, 2011), however other adulterants, such as biochemical drug additives are not so readily apparent (CBI, 2020).

Issues such as financially motivated substitution of herbs and scarcity was brought up by participants. C6 referred to a situation arising from the use of Black cohosh, *Actaea racemosa* L., (CP: Sheng ma), used for menopausal symptoms, in the 90s and early 2000s when it rapidly because one of the most used plants. This led to widespread overharvesting and substation with *Actaea asiatica* (Hara et al., 2006).

Participants C18 and C20 believed that excessive demand on herbal supplies and its consequent scarcity is could motivate similar substitution as previously reported in the literature (Cunningham and Long, 2019).

C20 further Referring to the five *Epimedium* species *brevicornu, sagittatum, pubescens, wushanense, koreanum* (Bensky, et al., 2004), (Guo and Xiao, 2003).

The quotations in this section were selected from responses to question 2 and are listed in the respective question 2 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to question 2 were; adulteration, aflatoxin, apathy, authenticity, business focus, change, CHM is complex, contamination, cost, dishonesty, education, fake documentation, herb care, incentives, inertia, labelling, legislation, misidentification, mistakes, opacity, perspective, processing, purity, pyrrolizidine alkaloids, quality definition, reasons, regulation, scarcity, siloed knowledge, substitution, substitution acceptable, supply chain, sustainability, synthetic drugs, toxicity, traditional practice, trust, and understanding.

AKI 11.4.1 Opinions on herbs being mixed up

Posed as question 3 “what do you think about species of herbs being mixed up?“

When asked about inadvertent herb substitution due to mistaken mix-up, participant responses, in reflection revealed that the question may not be well composed. As evident from the responses referring to intentional substitution and traditional accepted substitution practices rather than the intended. Respondents expanded and detailed points relating to the next question 4, that of substitution sought for this question. Therefore, coding for this and the next question are blended where some responses given to the next question are included here and vice versa. Some insights around the types of substitution and why this may occur were gained from both questions.

Opinions around inadvertent substitution mainly centred around difficulty with identifying plants due to their visual or naming similarity, others referred to human error from lack of understanding about herbs. Perspectives around cultural and legal interpretation of what constitutes “inadvertent” mix-up also arose.

Case	Key contributions
C6	"*even when you have experts in their field, it's hard to identify herbs. This is a difficult thing. Even those good at this can't be good at identifying everything*". "*if it isn't labelled, then. Is something really technically replaced? It's difficult to pin down*"
C7	"labelling is still in pinyin, not enough Latin. It doesn't come naturally to the Chinese herbal industry" whereas the Chinese respondent C14 confirmed, "*sometimes I can't read the botanical*..[Latin]..*names*"
C8	"*aristolochia toxicity and kidney failure, et cetera, in the Netherlands*" [..substitution can be].."*deliberate sometimes but not always, you know that it can happen out of ignorance too. Ineptitude, incompetence, not always intended*". "*there is ignorance, and particularly when you've got species that look very similar, it's very, very hard to know*"
C10	"*Even if you know your herbs and are trained it may be not enough – have a look at the different quality of Bei Mu* [*Fritillaria cirrhosa* D.Don].
C14	"*the cheaper one to replace the expensive one. That is a very common cases for a mixed, species mixed up*".
C17	*it's more complex I think in Chinese medicine because you are allowed a degree of substitution*" "*safflower and saffron can be replaced by each other. They are alternative. There were many traditional Chinese medicines that could be replaced in ancient times*".
C18	resource "*like Chi Shao and Chi Shao only wild, no cultured available at the moment. If they don't have enough wild, so what's going to happen?*",

When asked about herbal substitution, most (C10, C6, C8) felt it occurred on a significant scale, whereas others C8 referred to the potential severity of the issue, such as the case of *Aristolochia fangchi* Y.C.Wu ex L.D.Chow & S.M.Hwang, Chinese pinyin (CP: Guang fang ji) where it was used in place of *Stephania tetrandra S.Moore* (CP: Han fang ji) when over hundred cases nephrotoxicity occurred with the occurred (Vanherweghem et al., 1993). Also pointing out that substitution can arise from human error and lack of training.

C6 also drew attention to situations where even competent trained individuals could make inadvertent mistaken substitution. C8 agreed with this general sentiment, when considering which actions could affect the authenticity of used herbs and their formulas. C10 demonstrated an example of this shown in in *figure AKI 11.1.,* where *"they are all Bei mu and will pass the tests, but the quality is very different*".

FIGURE AKI 11.1 HERBAL SUBSTITUTION EXAMPLE BEI MU IN INTERVIEW, CASE 10

Researchers note: Bei Mu herb pieces on the top are same price as the whole pile on right.

C10 "*Flatter not good*" (on the right) — also they are "*washed whiter"*, 珠贝 zhu bei "*shape too pointed not round*". [On the..] "..*left you can see some grew above ground some below. Some like a human navel, others spilt like a half moon shape and others straight line from top to bottom*". *"Triangular and rounder are better. Also smaller, better quality but people often like to see the white big ones*"

C10 "*The can come from different regions like mainland China, Zhejiang is sweeter and moisten lungs but the Sichuan ones are more bitter, very strong for phlegm and hot lung things*".

C14 emphasised the financial motivation behind herbal substitution, that such practices are deliberate where use of. Mixing unauthentic herbs with those intended specifically for a formula could affect its purity and function.

Participants related influences on herbal quality are more complex that perhaps fully acknowledged, such as cultural differences in language and accepted practices (C7). C8 and C17 offered insights into what they believe constitutes herbal "*mix-up*", an unacceptable substitution by one, may not be considered such by another. The complexity of herbal practice is apparent in the accepted substitution within contemporary CHM, where practitioners compose herbal prescriptions with specific modifications to traditional formulas to better suit a patient's treatment (Stefanovic & Yongping, 2002). Practitioners use Safflower (CP: Hong hua) for indications where pain is presenting as a result of blood stasis, in Chinese medical terms through its "*warm and acrid*" nature. Whereas saffron (CP: fan hong hua) is recommend for use for indications where pain may be arising from an underlying blood deficiency or where redness such as in the form of rashes present, in Chinese medical terms through its "sweet and cool" nature (Bensky, Clavey, and Stõger, 2004, p. 629).

C18 emphasised that the practice of substitution is needed and will likely increase as limited wild resources are depleted, also evident in the use of scarce or illegal Chinese animal ingredients (Cheung et al., 2021). However resistance to change is apparent as their use continues (Ellis, 2013), (Xing et al., 2020).

The quotations selected were from questions 2,3 and 4 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to the topics of herbal misidentification and substitution in coded to question 3 were; adulteration, authenticity, CHM is complex, cost, fake documentation, inertia, labelling, legislation, misidentification, mistakes, opacity, perspective, purity, substitution, reasons, scarcity, substitution, substitution acceptable and understanding.

AKI 11.4.2 Opinions on deliberate herbal substitution

Posed as question 4 “what do you think about species of herbs being replaced with others?”

Coding for this and the previous question were blended where some responses given are included where insights around the types of substitution and why it occurred were given, which also informed the previous question 3.

Case	Key contributions
C7	"*Wu Jia Pi, Xiang Jia Pi something like 50% or 60% of Wu Jia Pi is the incorrect one*"
C10	"*this is why is it's important to control things. You know they can take advantage of the people*"
C11	"*of course, if the doctor wants to use one*…[substitute]*…or the other he can choose*".
C14	"*Tao Ren is more expensive than Xing Ren*"
C15	"*I remember I read an article in the newspaper says about four, five, six years ago in Korea the custom, they reject seven-tonne raw hook from China, they reject because the safety but then all these seven-tonne come to UK*"
C18	"*the other herbs like Wu Wei Zi because these are now much cheaper Nan Wu Wei Zi than Bei Wu Wei Zi so if buyer buys it, I don't want Nan Wu Wei Zi. [The dried fruit of northern and southern varieties of Schisandra chinensis (Turcz.) Baill.], so now Nan Wu Wei Zi it's good quality, but never bring in China, people will prefer to Bei Wu Wei Zi, like Ge Gen [Pueraria lobata (Willd.) Ohwi], like Chai Hu [Bupleurum chinense DC.] because these are like Bei Chai Hu [Northern Chai hu] and Nan Chai Hu [Southern Chai hu] different price*"
C20	"*adulteration of Codonopsis roots, Dang Shen, with American ginsenosides, they're known to pass off the Codonopsis, as the much more expensive and valuable American ginseng*"

This issue of acceptable substitution was again raised by participants in response to this question 4 as it had to question 3. Financially motived herbal accepted substitution and the complexities of choosing herbs in CHM formulas featured in many responses to this question. C18 offered multiple examples, and C14 that relating to the seeds from *Prunus persica* (L.) *Batsch* and *Prunus armeniaca* L., respectively. Again illustrating the complexities of CHM practice when choosing herbs for prescription.

Financially motived non-accepted substitution was demonstrated by C10 who presented three samples of *Ophiocordyceps sinensis* (Berk.) (CP: Dong chong xia cao), two collected from the wild and another a convincing fake, to encourage intentional misidentification of the medicine, *figure AKI 11.2.* "Each single piece is about 500TWD" [interviewers note: about £13 in April 2021].

FIGURE AKI 11.2 HERBAL SUBSTITUTION EXAMPLE OF DONG CHONG XIA CAO IN INTERVIEW, CASE 10

C10, "*The one on the right is fake, some worms glued together and some earth and things added. The best quality one on the left is from Tibet, but looks not attractive. In the market people will pay ridiculous prices for these because maybe someone they know has cancer and they will do anything to try to find a cure*".

Both C20 & C7 referred to *Eleutherococcus nodiflorus* and *Periploca sepium* as an example of unknown or undetermined substitution, claiming that it mistaken due to similar Chinese name. This warranted further exploration and is detailed further in chapter five, the "EN study".

Substitution of different quality herbs was brought up again by C15, referring to *Uncaria rhynchophylla* (Miq.) Miq. Ex Havil. Even though the participant did not verify this and checks in English for such an report was not found, the possibly that this could occur was demonstrated in earlier responses to interview question 2, where cases of different quality herbs sent to different countries was described was described by C15, a supplier who manages a herbal company. An example of adulteration to circumvent testing legislation was given by C20, and is credible as reported in the literature (Kum et al., 2016 and 2021),(Chen et al., 2012).

The quotations in this section were selected from question 3 and 4 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to topic of substitution in both questions 3 and 4 were; authenticity, change, CHM is complex, cost, inertia, labelling, legislation, misidentification, mistakes, perspective, purity, reasons, scarcity, substitution, substitution acceptable, and understanding.

AKI 11.5 Personal experience with herbal quality issues

Posed as question 5 “do you have personal experience of these issues?”

The question specifically around personal experience of quality issues elicited a number of examples from respondents, in addition to those already detailed in response to earlier questions 1, 2 to 4 inclusive.

Case	Key contributions
C6	"*chondroitin sulphate and mannitol, more than a hundred times more than could be accounted for*"
C9	*"flowers on the herbs that are used for food. The left these as exceptions, so you don't have to test these. So the herbs could fail but the parts can still be used as a food*". "*weight additions, fumigation, misidentification, contamination like from pesticides*"
C10	*"But they know a lot the old doctors know a lot from the experience and patients getting better or not. The old doctors can see. But the new ones, I don't know, I don't know if they know their patients. The old doctors know the grand-parents, the parents, their children, sometimes even their children. You know the doctors and families come to them can have hundreds of years relationship"*
C14	"*Menthol, Bo He in it...artificial oils that they accept from the procedures. When you doing the testing, you can't see it, you can't see that ingredients in it*".
C20	"*He Shou Wu is cultivated in China*, [due to large demand as one of the most commonly used Chinese medicinal], *a significant amount is entering trade from wild plants. Because Polygonum multiflorum*, [He shou wu], *sourced plant is so difficult to identify, we've seen mixed but widespread quite commonly encountered mixed batches of He Shou Wu in TCM wholesalers across China*"

C6, C7, C10, C14 and C20 personally observed the use of undeclared herbal sources, and indicated there will likely be more inertia in moving from the use of wild to more widely available and cultivated sources (Leon & Lin, 2017, p. 154).

C7 referred to the aforementioned *Eleutherococcus nodiflorus* (CP: Wu Jia Pi) substitution with *Periploca sepium* (CP: Xiang jia pi). Through "*experience from ordering from suppliers and seeing what they're selling*".

C9 drew attention their experience seeing herbs fail quality tests but other parts of the herb being used as food. This is possible where no medical claims are made for the herbal parts used (Shaw et al., 2012), (E. Commission, 2020). C9 a professor involved specialising in CMP identification with experience referred to several personal observations of substitution when testing herbs including, Listing seventeen examples of weight additions including the aforementioned *Carthami Flos* (CP: Hong hua), *Lonicerae Flos* (CP: Jin yin hua), *Cimicifugae Rhizoma* (CP: Sheng ma) and *Salviae Miltiorrhizae Radix* among others. Adding twenty-five further examples of sulphur dioxide fumigation such as, *Paeoniae Alba Radix* (CP: Bai Shao), *Dioscoreae Rhizoma* (CP: Shan yao), *Lilii Bulbus* (Bai he) *Ginkgo Semen* (Yin xing), *Crataegi Fructus* (CP: Shan zha).

C10 mentioned that relationships in the supply have changed, obscuring how effective herbs that are prescribed, therefore if herbs of different quality or substitutes are prescribed, their relative efficacity and therefore quality levels or replacements may not be captured by those prescribing the herbs.

The quotations in this section were selected from question 1,2 4 and 5 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to the topic of personal expertise of herbal quality issues posed as question 5 and in arising in response to questions 1, 2, and 4 were coded as: change, contamination, cooperation, cost, dishonesty, education, fake documentation, inertia, labelling, legislation, misidentification, mistakes, reasons, regulation, siloed knowledge, substitution, substitution acceptable, traditional practice, trust, and understanding.

AKI 11.5.1 Opinions on experience with aflatoxin

Posed as question 6: Have you had much experience with aflatoxins?

Six out of the fifteen interview participants were aware of aflatoxin toxicity in herbs, mainly in the area of education (three), with additionally one in supply, one in regulation and a further one in manufacturing. However, two participants involved in research, C19 and C20 were not aware of the issue.

Case	Key contributions
C6	*"it comes down to if the supply chain isn't regulated. No way you can control things*"
C7	"*the issues of storage, of particularly dried herbs, has greatly increased the risk of aflatoxins or pest infestations, that sort of thing*". "*this should go back to GMP in China. Their standards of heavy metals, aflatoxins should be made very clear and they should have certification. It's not really a British problem. It's a Chinese problem"*.
C8	as "*mould issues, drying, aflatoxins, pyrrolizidine alkaloids, the aristolochic toxins, all the other various mycotoxins, bacterial things*".
C14	"*aflatoxin is a dangerous issue to cause cancer*" and added that "*now people starting to be aware of that issue*"
C16	"*the products as corydalis tuber* [(CP: Yan hu suo)] and *Platycladus semen* [(CP: Bai zi ren)], *etc. don't have the problem of aflatoxins at first before the shipping. But due to the temperature and humidity in the process of transportation, aflatoxins may also become a problem*"
C20	"*I may well have encountered it but not being aware of it because I've not been measuring it*".

Though Chinese and British ethnicities were represented almost equally in response to this question, it was four residents in the UK, except for one Chinese, who accounted for all of the participants aware of aflatoxins.

Some such as C7 and C8 drew attention to supply chain conditions which can create the conditions for aflatoxins to develop.

C6 had tested for aflatoxins and detected them in CMP, however C9 had the most experience of the participants in testing for aflatoxins, who identified thirty-six specific Chinese medicinals susceptible to aflatoxin growth, many of which were fruits and seeds including, *Corni Fructus* (CP: Shan zhu), *Piperis Fructus* (CP: Hu jiao), *Lycii Fructus* (Guo qi zi), *Platycladi Semen* (Bai zi ren), *Arecae Semen* (CP: Bing lang), *Ziziphi Spinosae Semen* (CP: Suan zao ren) and *Persicae Semen* (Tao ren), and others.

However, C7 believed that the onus of responsibility should lie at the origin

One Chinese professor C11, after being informed of the aflatoxin issue suggested that it would simply be a matter of better logistics, where "*herbs could just be transported more quickly*".

C16, in a response to a later question 8, said that CMP such as corydalis tuber (CP: Yan hu suo)] and Platycladus semen (CP: Bai zi ren), do not have a problem of aflatoxins at first before the shipping. But due to the temperature and humidity in the process of transportation, aflatoxins develop" as described by other researchers (Kumar, et al.,, 2021).

The quotations in this section were selected from question 6 and 9 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to question 6 were; aflatoxin, purity, pyrrolizidine alkaloids, supply chain and toxicity.

AKI 11.6 Opinions on key herbal quality issues

Posed as question 7: “What do you think the key issues are?” Many of the participants when asked about what key quality issues referred to authenticity and purity problems with herbs.

Case	Key contributions
C6	“*you can check at the finishing stage all the way back to the beginning*..[of the supply chain]. *But you would really need to check an extract of every batch. It’s not always possible*”.
C7	“*making sure you’ve got the right species.. and*…[also to ensure that herbs would be]…*well stored and looked after*” “*no herbal dispensary training or pharmacognosy training*”, and added that “*there’s no point blaming China and blaming suppliers if*..[UK practitioners]..*don’t know what they’re doing*”.
C8	“*PA* [pyrrolizidine alkaloids] *issue*”. “..*it’s easy. If you’ve got a single isolated drug, it’s easy to show you’ve got that and you can make a preparation, batch standard all the way through, no variability at all, absolutely fine, herbs aren’t like that. They’re multi-phytochemical many multi-activities*” “*we are seeing people with self-limiting conditions so we’re saving a lot of money to the NHS because their people aren’t going to hospital or are not seeing their GPs, et cetera, et cetera. We’re saving actually billions to the NHS. It’s not recognized at all but moving forward we need to make sure it is recognized perhaps by the public more than anything else and make sure the Department of Health knows more about it*”. “*my only concern is getting new students in to keep practitioners in the supply chain*”.

Case	Key contributions
C9	"*weight additions,* *fumigation, misidentification, contamination"* and "*pesticides*".
C10	"*contamination*" "*fake*" [herbs] that "…*quality can be low. Who knows, maybe you can have the right herbs but because the quality is not taken care of, maybe it's as bad as the fake. Who knows*". "…*we can't expect things to be the same as before, we are in a changing time…from the old to the new. We are in the middle of this…All the growing is different now. They are growing them in different regions. Before it's all more local, not big like the factories*".
C12	"*we can check the pharmacopeia, to check if there are any quality problems. In the pharmacopeia we can check about the quality*".
C14	"*in the last few years for example..his prescription* [Chinese medicine practitioner prescription] *was very successful at working on patients issues, condition and he had got good results, the same prescription…after several years later, he found his prescription wasn't working properly, exactly the same prescription and he was wonder why because the quality of the herbs has been dropping down*". "*you have to educate people and to be aware of the importance of the quality for the herbs they are eating, they are taking because the herbs they are taking for their health*" "*some patient also care about the price..*[who sometimes say]..*Oh, your prescription is too expensive*".
C15	"*the quality system…they need to change*".

Case	Key contributions
C16	"*we should look at the varieties. Different varieties may have different problems. It doesn't mean that all varieties have the same problems*"
C17	"*…we can't expect things to be the same as before, we are in a changing time…from the old to the new. We are in the middle of this…All the growing is different now. They are growing them in different regions. Before it's all more local, not big like the factories*". *the quality and efficacy of traditional Chinese medicine is more or less whether the clinical treatment matches the characteristics of the inherent efficacy of the traditional Chinese medicine*" "*there's also the difference between cultivated and wild herbs*"
C18	"*I think people who make this regulation really need to understand the herbs because this is like agricultural products growing in the field is not manufactured…I think the people who involve regulations has to understand, has to be expert*"
C19	"*if the value chain is reasonable, is a sustainable one, by which the stakeholders can get enough profits, if they invest properly, then that's a win-win result*"
C20	"*there are different concerns about TCM, herbal quality that arise at different stages along the supply chain*" "*we know that the Chinese government have invested very heavily the last 20-30 years in so called modernisation and standardisation of* CMs [Chinese medicines]". "*Unfortunately the paperwork associated with these standards, has not always been reliable. The enforcement of all the paperwork, again, checking some paperwork can only be done from say, the source, or by the Chinese government, or the regulators there*". "*say between the…health regulators in the West and health regulators back in China….Personally, there needs to be a much more open dialogue about how they can come together and work together, particularly when they're working towards their own Pharmacopeia standards*"

Convergent opinions emerged around deficiencies in current standards to account for the natural diversity and variability of CMP. C16 felt that this inherent variation has not been fully considered in quality assessment, agreed by C8 in noting the inherent complexity of natural plants, who thought that C18 suggested that those involved in regulation may not fully appreciate or allow for this natural variability.

More divergent views emerged on what were the key issues in herbal quality such as those expressed by C20 who thought they vary depending on the role and perspective of the person involved. Whereas C12 a Chinese professor, thought that quality issues should be viewed strictly from one perspective, that of adherence to pharmacopeia requirements.

C20, a Chinese researcher also has a different view from C12, as expressed in the echoed in the previous sections, feeling that even if herbal quality tests meet pharmacopeial testing level certification it may not be reliable measure of quality. C10 also disagreed with C12 believing that even if current quality standards were met that it does not necessarily indicate a level of high quality herbs.

C20 thought that key herb issues centred around cooperation and better alignment of quality goals, Understood here as the participant expressing perhaps that Chinese and European goals in the form of standards for herbal quality many not be the same, there may be unexpressed dialogue or information on both side of the geographical and cultural span which could benefit from further mutual engagement. In general opinions converged around a general

sense of progression and change, that gaining knowledge of and getting to grips with herbal quality is a continual process and that this is occurring as the quality of the herbs are also changing.

Education as a key issues was raised by some participants, including C14 who further expressed that patients may not be aware of the presence or extent of such of herbal quality issues. Suggesting that education is key issue in herbal quality. C7 a UK based, British participant involved in regulation said that education is critical to quality and that it is not a responsibly of the Chinese to train British practitioners. C8 further added that though awareness of the value herbs and that which its practice adds could be raised through education, however also highlighted the dwindling number of students and university courses available to students seeking to qualify in Chinese herbal medicine practice in the UK (EHTPA, 2022).

A general sentiment is apparent among some participants that current quality assessment systems are somewhat incomplete and require improvement. Suggesting that regardless of quality standards and efforts further back in the supply chain, the correct ordering, clinical verification of herbal identity in addition to correct handling and storage could have a considerable bearing on the quality of herbs by the time they reach patients. If then perhaps herbs are grown sustainably and equitable distribution of profit among those with a vested financial interest in the supply chain, then this could result in at least a somewhat more stable quality herbal quality. This would foster an environment where there was

less motivation for actions towards individual gain, such as deceptive practices to for short-term profit.

The quotations in this section were selected from question 7 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to question 7 were; change, contamination, cooperation, cost, dishonesty, education, herb care, incentives, inertia, legislation, misidentification, motivation, perspective, purity, pyrrolizidine alkaloids, quality definition, reasons, siloed knowledge, substitution acceptable, supply chain and traditional practice.

AKI 11.7 Opinions on why quality issues persist

Posed as question 8: “Why do you think these problems continue despite control measures being in place?”

Most responses to why herbal quality issues persist in context of the control measures in place, formed two juxtaposed strands of opinion, those of reasons related to both inertia and change. Thought at first seemingly opposed, when considered further, appeared to represent inertia associated with the relatively less agile development of analytical tests and legislation that arose from testing and regulating more well defined and standardised biomedical drugs, adapting to the variability and new challenges which the wide-scale introduction of CMP posed.

Case	Key contributions
C6	"*right and wrong, and that it is "just down to simple morality to "do the right thing", or not… these values are human qualities. Their value focus is more on people*". *"there is a demand so the focus will be on getting the supply delivered. That's it. The priority is on getting the supply done, the rest, well, who knows?*"
C7	"*I think there's a misunderstanding about Pao Zhi,* [traditional preparation techniques], *and that needs to be taught or we'll lose it. The suppliers don't stock enough Pao Zhi products…it affects clinical effect of the formulation. This is quite a recent one. The dangers of and danger with He Shou Wu. Hepatic toxicity of Polygonum multiflorum. This is looking at why the raw herb is toxic. Basically, we should never use it in the raw stats. In fact, I've heard that most of it is processed. However, they don't actually state that. The suppliers don't say, "This is processed"…*[there is]*…an ignorance about it*"
C8	*"herbs are a small part of their*..[regulators]..*remit laterally has lost a huge amount of their income because obviously, the European Medicines Agency had to move to the Netherlands. They've lost a third of their income*" "*the NHS lost a third of their income, they also had to move from Victoria, the offices, because the UK Government had released the Canary Wharf buildings for the EMA for like 10, 15 years. They had to pay to move to these buildings because otherwise, they'd be a huge billion-pound loss. EMA is having difficulties with all the Brexit as well. It's things that aren't talked about or known about, unfortunately*" *it's a simple thing as you might know the active compound. The active compound, it may not be the best one to monitor long term*"

Case	Key contributions
C9	"*there are a lot of controls..*[for]..*herbs for national use..[*which]..*can only come from GMP – factory-based systems*" *"The quality control of TCM herbs is much more difficult than that of active pharmaceutical ingredients in western medicines*" *The quality control of TCM herbs is much more difficult than that of active pharmaceutical ingredients in western medicines because many environmental factors will affect the quality of TCM herbs"*
C10	"*you know, it's the money Martin. People can take a risk and make the money. Mainly the money. People from some small villages have nothing. By doing small things they think are harmless, or don't care about. They can change their whole lives. In some way it's hard to blame them, maybe they don't know about some harm. Some of it is harmless, just the herbs won't work well. It's the people's minds, how they were brought up. Also, maybe if they know they will be caught it would be different. It's hard to get caught with some things*"
C13	*"doing research and improve things more and more*".
C14	"*I experienced in the beginning people, the quality of it is really good but why the quality dropped down gradually. At the moment you can see lots and lots of fake things, fake herbs and fake things. Everything is fake. Why people have to do that only for profit or what's the reason behind that*". C17 agreed with this when asked why problematic issues persist, "*Why? Because business is all about profit, right?*"
C15	"*it's not that difficult because in Taiwan, in Japan, Hong Kong, they already have so many mature systems to check the quality, so I think simply if they want to do it, it's not that difficult*"
C17	"[herbs are]..*affected by the ambient temperature. For example, the wolfberry, a product very likely to absorb water, is to be exported…you have to dry it sufficiently and pack in vacuum package. But once you open the package and expose it to the air, and if you don't test it in time, it will absorb water again. Your delay will lead to its regained moisture*"

Case	Key contributions
C17	"*the market has a transitional process, and it will be standardised gradually according to the Pharmacopoeia, now if a Chinese herbal medicine does not meet the requirements of the Pharmacopoeia, it will be judged as counterfeit medicine. If such counterfeit medicine is inspected by the drug administration authorities, it will be deemed as an illegal act and the party concerned will be punished by law. Our market supervision*..[in China]..*is also very strict; however, in the process of supervision there must be some problems. It takes time to improve. The current market supervision is much better than that in the past. In the past, when the market economy was just beginning while the market supervision was not standardized, there were some fake and poor quality Chinese herbal medicines, which were quite common*".
C18	*"the lack of this knowledge or information. That's partly missing when you introduce Chinese medicine to the UK or to Europe. They do understand it because they think that some key ingredient, they check them, but they don't understand because…they know fully the whole forest and not the seed. The whole system need to add something as it really make sense of the quality of herbs*". "*Some people did the research, quite interesting, produced in Shandong is a higher ingredient* [active single compound]…*the Huang Qin, but not best to result in the prescription, rather than using low I always heard a high percent, it doesn't mean effective because you don't need it high, you just need it reasonable. You want a high—because of western medicine said*, "*I want high*..[active compound]..*ingredient*".
C19	"*let's say the*…[focus is on]…*primary compound but that's not very scientific for a medicinal plant product with thousands of chemicals inside*".

Participants thought that the inertia to change legacy legislation for variable plant entities such as CMP, created difficulty. C9 thought that which were predominantly developed for industrial and drug production purposes. However others felt that this inertia is a natural part of market adjustment and though

current controls may not always seem effective, they are improving and will eventually adapt and adjust to the attributes of CMP given time.

C17 thought that currently that inertia to adapt legacy legislation is related to constraints including financial support. C8 expanded the point, some focused on the inertia associated with legacy legislation. Other participants contributed to views related reasons for simultaneous inertia and change, in the form of (lack of) understanding. European regulators may assume that they already possess a sufficient understanding of Chinese herbal medicines but may not. Particularly as pharmacopeial tests typically detect one or a small number of active phytochemicals to establish the content or potency of a herb, however there are different concepts of quality, C8 adding that using markers in tests for active ingredient content may be somewhat over-simplistic. C13 supported this view in for a more complete understanding of herbs is necessary to ascertain its quality. Some participants felt that herbal quality issues persisted because knowledge of traditional preparation methods has not been communicated to the West.

Though many opinions emerged relating to inertia, change, understanding and financially motivated influences, some participants had other views. They believed that these opinions or unsuitable quality controls are not the main reasons why problematic quality issues persist, and instead felt that it is more closely related to incentives presented to people and the resulting human behaviour. Including the often-mentioned profit motivation as just one in a combination or sequence of incentives.

C15 noted that the knowledge around controlling herbal products already exists, that But that incentives for behaviour which could improve people's quality of life without consequence, including profit, motivate people's actions, as reiterated by C10.

One participant C6, related different types of incentives and actions may result at different stages of the supply chain there resulting in different types of behaviour which influence the persistence of herbal quality issues.

The quotations in this section were selected from question 8 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to question 8 were; authenticity, business focus, change, CHM is complex, cooperation, cost, dishonesty, education, fake documentation, herb care, incentives, inertia, labelling, legislation Misidentification, mistakes, motivation, opacity, perspective, processing, purity, pyrrolizidine alkaloids, quality definition, reasons, regulation, scarcity, siloed knowledge, substitution acceptable, supply chain, sustainability and understanding.

AKI 11.8 Opinions on improvements

Posed as question 9 “do you think that CHM quality could be improved?

Opinions on how the general Chinese herbal quality in general could be improved were mixed. They centred around creating incentives towards better quality through education, to motivate behaviour where “honest” and more “responsible” practices are encouraged, as already demonstrated in sustainable herbal supply chains. Views were expressed that reducing the influence that herbal cost has on quality and adapting legislation towards more cooperative could be beneficial.

Some also expressed, as they did in response to earlier questions, that an increased general awareness is necessary around the specific and more variable demands of CMP compared with often more discrete and standardised pharmaceutical products. So that changes quality control testing and legislation could be made, while the herbal market is currently still in transition. Implying that this could perhaps support an easier and more gradual adaptation to the importation of Chinese medicine, and its practice.

Other participants thought that improving traceability of herbs from source to patient would reduce problematic herbal quality issues and suggested that implementing technological improvements which were not previously available.

Case	Key contributions
C6	"*if there was more support for trade associations and PR for those doing the right thing. There would be more of them*"…"*if consumers were made aware of the companies who are making these efforts perhaps the "doing the right thing" would be rewarded*" "*sustainability…*[that this]..*could be expanded to include efforts in being open about those who make efforts to be audited on their systems. Maybe that could help with the reputation side of things and convert to sales*" "*regulation, this could improve. We have proved it works when done well*"
C7	*"Pao Zhi* [traditional preparation methods for Chinese herbal medicine] lists. *That's one of the other things I'm trying to work on, otherwise we'll lose that. There's not a big market for it unless both the members know about it and order it. They don't order it then they won't supply it*" that "[herbal medicine supply]…*it's a fragile business to be in, definitely. There's less herbalist training now as well so the market's going down. There's restrictions on them already about selling to acupuncturists, to not making up patents. They've lost the whole market there from not selling patents. That was very lucrative for them. They've been pushed back all the time by legislation so more legislation is bound to have a negative impact on them as far as I can see*" "*we try and provide incentives. That's the way ahead. It's not so much a stick as carrots and sticks*"
C7	, "*everyone needs to go back…"What testing have you done?" The supplier has to say, "What testing have you done?" Everyone has to be more demanding. Just to say, "Well, this is the supplier's issue." I just get one of my supplier's salesmen and then the supplier says, "Well, this is what they sent." It's like, "No, let's push back on China and get some more information*."
C8	"*my only concern is getting new students in to keep practitioners in the supply chain*" "*there's a lot of work being done in China to ensure quality, and the money is really being pumped into it in a huge way because it's such a major part of their heritage and financial culture. It's important for everything there*" "*they're doing such a lot to make sure that the prestige of Chinese herbal medicine is kept up high, but we need to make sure that we do the same here*…[in the UK]…*even though we get a lot of our supplies from the Chinese*

Case	Key contributions
	suppliers. We have to make sure that smaller companies…aren't letting the whole sector down" "*there's two practitioner associations that are still allowing their members to use herbs that naturally contain pyrrolizidine alkaloids*"
C9 **C9**	"*we need to educate more, and the patients too. If they know more they can check themselves if they are not getting the right herbs*" "*before marketing, TCM,* [traditional Chinese medicine]…*Herbal Preparations must be licensed from DOH*, [department of health]…*after documents examined by* CCMP, [Committee on Chinese Medicine and Pharmacy], *and products*…[then] *analysed by* BFDA, [Bureau of Food and Drug Analysis]. *Manufacturing factory must be GMP compliant*" that "*good preparations only comes from TCM herbs with good quality and the authenticity of TCM herbs is the first point of concern for quality*"
C10	*we can't expect things to be the same as before, we are in a changing time. Getting used to a new way. From the old to the new*" "*use the technology like the smartphones. People have smartphones everywhere; they can take photos check online. The information can be compared. We didn't have this only a few years ago*"
C11	"*The pharmacopeia is improving so we can check more and more things about quality*"
C14	"*I think first of all is education. You have to educate people and to be aware of the importance of the quality for the herbs…. It's a primary issue you have to look at*"
C15	"*they've*…[China has]…*been through 80-70 years this poor quality to now…we don't have to start it from the low level. We can learn, we can share in their mature experience, that may be saving in a quick way. Interviewer, "Adopt the system that…[*already]…*works*?" *"the first thing is asking a supply have to keep original bottle to deliver not allow the private label*"
C16	"*just better education and follow the rules*"

Case	Key contributions
C17	"*new problems are found, then new solutions are required*" "*when the market regulation is not fully in place and the state has not yet enacted certain laws, some Chinese herbal medicines will have some quality problems, but this gradually will be less*"
C18	*"sometimes, you need to fry it a bit, like dang gui, because…Dang Gui without frying…cause diarrhoea… we have a dang gui, but for other sensitive people, we use a chao dang gui. We fried…*[it]*…for them, building that education*" "*Western pharmacist and China needed lots of communication to bridge the gap, to understand…*[in]*…our time…a modern time*, [to understand]*…what's going on*"
C19	"*the focus*…[of current regulation]*…is on safety rather than more general quality and the regulations maybe too simplistic*" "*I think to solve this, all this problem is to optimize the value chain, the supply chain of herbal medicines. This quality control is not the- to control is not a good solution. Just to, how do you say? Get the stakeholders better profit when they provide good quality of herbal medicines*"
C20	"*my feeling is that we need to have a more interdisciplinary approach to many of these traditional research methods that have been used so far*" *A sustainable supply of the herbs and the conservation of the germ plasm not just the species, but the germ plasm of all the species involved. I feel there is an acute shortage of efforts that China to conserve the plant material*" "*as the Pharmacopeia approaches or tend to be rooted in their own very traditional, conventional methods. It's like turning the Titanic around on many of these well-established systems. We need to find new ways of making more sensitive standards and quickly*" *"What we want is being allowed to form a form of regulation for us herbal suppliers which is more realistic*" *Well, you need to do all these tests," or whatever, and the guy's out of business because it's expensive and it's a borderline business."….*

C7 thought that education of traditional preparation methods could incentivise people to purchase better quality products, C8 felt (as expressed in previous sections) that education was critical. C18 a Chinese supplier, felt that it was through cooperation, exchange of knowledge and education within China that improvements could be achieved.

Whereas C8 a British educator, thought that mainly improvement is needed outside China. C6 believed that herbal quality could improve by through incentivised support and attributing more attention to those maintaining herbal quality.

C6 and C20 felt that it was by learning and highlighting the successes in legislation could benefit from the lessons learnt by those who have greater expertise with Chinese herbal medicines. C9 synopsised such a quality system, in Taiwan, that has already solved many of the problems with CMP quality more recently encountered outside China. (Kaphle, Wu, Yang, & Lin, 2006)

However some there was an overall sentiment that that regulatory change was too slow and that reducing inertia inherent in the tradition of European legislation could be beneficial, expressed by C20 and C10. C17 also wished to draw attention to the transitional nature of improvement, and that it should be done in an informed, and as reiterated by C20 "*sensitive*", manner.

C7 also emphasised that both incentives and controls are needed in-tandem for sustainable improvements.

Other strands of participant opinion around herbal quality improvements were mixed, however they generally related to reducing opacity in the supply chain, by establishing good quality at source and maintaining traceability through the supply. C10 thought that the integrity of herbal products and their care throughout a supply chain could be easily monitored by implementing newly available technology.

The quotations in this section were selected from question 9 paragraph of the participant transcripts, cases 6 to 20 inclusive.

Codes formed from the participant responses to question 9 were; aflatoxin, change, contamination, cooperation, cost, education, herb care, incentives, inertia, legislation, motivation, opacity, processing, pyrrolizidine alkaloids, responsibility, scarcity, supply chain, sustainability, traceability and understanding.

AKI 12 KI Master Table, analysis of specific examples by key informants

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 17	Accepted substitution	Saffron	Traditional accepted substitution of safflower for saffron and vice versa	Traditional knowledge	Accepted practice	Acceptable practice as per Pharmacopeia	Analytical surveillance / regulation
Case 16	Accepted substitution	Radix et rhizoma rhei.	radix et rhizoma rhei. Technically hcan be legitimately substituted with Rheum palmatum L. and Rheum tanguticum Maxim.ex Balf.	Commonly known / Accepted practice	Accepted practice	Acceptable practice as per Pharmacopeia	Not considered a problem by manufacturer
Case 20	Adulteration (analytical potency enhancement)	Codonopsis roots (Dang Shen)	Codonopsis roots, Dang Shen, with American ginsenosides	Academic review	Falsify active component to pass tests	Difficult to detect	Analytical surveillance / regulation
Case 14	Adulteration (analytical potency)	Bo He (Chinese mint)	Menthol added to pass tests for Bo He (Chinese mint)	Academic review	Falsify active component to pass tests	Difficult to detect	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Alpiniae Katsumadai Semen	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Adulteration (bulking)	Amomi Fructus	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Atractylodis Macrocellalae Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Atractylodis Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Aucklandiae Radix	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Belamcandae Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Carthami Flos	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Cimicifugae Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Adulteration (bulking)	Clematidis Radix	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Coptidis Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Dictamni Radicis Cortex	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Hong Hua	Adulteration (bulking) with Barium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Lonicerae Flos	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Polyporus	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Salviae Miltiorrhizae Radix et Rhizoma	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Adulteration (bulking)	Saposhnikoviae Radix	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Scutellariae radix	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Stemonae Radix	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 9	Adulteration (bulking)	Tetrapanacis Medulla	Adulteration (bulking) with Magnesium sulphate	Analytical surveillance	Value	Value / profit motivated substitution	Analytical surveillance / regulation
Case 6	Aristolochic acid poisonings	Mu tong aristolochic acid	Mu tong aristolochic acid	Adverse events	Lack of awareness of risk. Regulation not in place	Traditional Chinese medicine preparation methods not known and / or used	Regulation and increased practitioner surveillance
Case 7	Aristolochic acid toxic content	Long Dan Xie Gan Tang	Toxic Aristolochic acid toxic in Long Dan Xie Gan Tang	Analytical surveillance	Not specified	Traditional Chinese medicine preparation	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
						methods not known and / or used	
Case 7	Heavy metal toxic content	CMP contain heavy metals	Heavy metal toxic present generally in CMP	Analytical surveillance	Contamination - industrial and natural	Difficult to detect heavy metals, further industrialisation, and long life of heavy metals in soil	None recommended
Case 18	High variation in phytochemical quality of Mai Men Dong	Mai men dong	Substitution due of similarly named but differently grown species of Mai Men Dong. Zhe men dong, 3 years growth, Chuan Men Dong grows in 1 year.	Quality variation	Profit motivation and accepted practice	Profit motivation and error	Analytical / practitioner surveillance
Case 6	Kava kava scarcity / supply pressure due to demand	Kava Kava	Kava kava scarcity due to demand	Market surveillance	Scarcity lead to supply pressures	Rapid commercialisation of Kava Kava	Reducing vulnerability in the supply chain

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 18	Quality variation	mai men dong	Substitution of wild with tissue cultured or genetically modified Mai men dong	Commonly known / Accepted practice	Profit motivation and accepted practice	Profit motivation and difficult to detect	Analytical / practitioner surveillance
Case 17	Quality variation	Chrysanthemums	High variation in phytochemical quality of Chrysanthemums	Commonly known / Accepted practice	Variation in regional growing conditions and addition of chemical fertilisers	Acceptable practice as per GxP and Pharmacopeia regulations	Not specifed
Case 15	Rejected Material resold	Raw hooks (gou teng)	Low quality Gou teng failed Korean pharmacopeia acceptance criteria sold to UK customers	Market surveillance	Regulation standards differences in different country	Acceptable practice as per Pharmacopeia	Harmonisation of legislation
Case 7	Scarcity /Demand	Bei Mu, Fritillaria cirrhosa	Bei Mu becoming scarce in the wild	Market surveillance	Wider commercialisation / demand for Bei Mu	Supply Demand	Conservation of Bei Mu
Case 18	Scarcity /Demand	Fang Feng	Fang Feng scarcity due to demand	Scarcity	Scarcity lead to supply pressures	Overharvesting due to demand	Education of regulators to better understand

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 18	Species substitution	Sha Ren	Substitution(bulking) with of Hainan Sha Ren (expensive) , with the cheap Sha Ren with Zao Ren some can't meet ChP specification	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and difficult to detect	Analytical / practitioner surveillance
Case 18	Species substitution	Bai Shao	Substitution due of similarly names species e.g., Nei Meng Chi Shao and Chuan Chi Shao	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 18	Species substitution	Chai hu	Substitution due of similarly names species "nan' and "bei" varieties	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 18	Species substitution	Ge Gen	Substitution due of similarly names species "nan' and "bei" varieties	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 18	Species substitution	Ge Gen	Substitution due of similarly names but different species of Ye Ge Gen and Fen Ge Gen	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 18	Species substitution	Jin Yin Hua	Substitution due of similarly names species e.g., Shan	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 18	Species substitution	Mu Dan Pi	Substitution due of similarly names but different species of Dan Pi Fen / Mu Dan Pi	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 18	Species substitution	Wu Wei Zi	Substitution due of similarly names species "nan' and "bei" varieties	Commonly known / Accepted practice	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 14	Species substitution	Sang Ji Sheng	Substitution of Sang Ji Sheng with taxilos lidium recurdes	Market surveillance	Species replacement	Difficult to detect	Analytical / practitioner surveillance
Case 20	Species substitution (acceptable)	Ying Yang Huo (Epimedium)	Substitution of five different species	Commonly known / Accepted practice	Profit motivation and error	Acceptable practice as per ChP Pharmacopeia	Regulation from food industry examples
Case 20	Species substitution (acceptable)	Huo Xiang	Huo Xiang species, Pogostemon cablin and Agastache regusa can be used interchangeably	Commonly known / Accepted practice	Profit motivation and error	Acceptable practice as per ChP Pharmacopeia	Analytical / practitioner surveillance
Case 19	Species substitution (acceptable)	Goji berry (Guo Qi zi)	Substitution of different species	Commonly known / Accepted practice	Profit motivation and error	Acceptable practice as per ChP Pharmacopeia	Analytical / practitioner surveillance

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 20	Species substitution toxicity risk	Wu Jia Pi	Wu Jia Pi substituted with toxic Xiang Jia Pi	Academic review	Not known	Not detected / Not known	Not specifed
Case 8	Substitution	Eleutherococcus senticosus (Ci Wu Jia)	Eleutherococcus senticosus (Ci Wu Jia substitution with gracilistylus (Wu Jia Pi)	Market surveillance	Error / Value	Not detected / Not known	Education / Practitioner surveillance
Case 8	Substitution	Mu Tong	Toxic Mutong with aristolochic acid content used in place of safer alternatives	Adverse events	Error / Misidentification	Not detected / Not known	Education / Practitioner surveillance
Case 8	Substitution (seed)	Huang-Qin seeds (Scutellaria baicalensis	Huang-Qin seeds (Scutellaria baicalensis seeds substituted for Scutellaria altissima	Practitioner surveillance	Error / Misidentification	Not detected / Not known	Education / Practitioner surveillance
Case 9	Substitution	Bupleurum Chinese DC	Bupleurum “kaoi” is native to Taiwan but Chinese Pharmacopeia describes the “official” as Bupleurum chinense DC	Academic review	Error / Misidentification	Not detected / Not known	Education / Regulation
Case 14	Substitution	Tao Ren	Substitution of Tao Ren with by Xing Ren	Market surveillance	Value motivated and error	Difficult to detect / profit motiviated	Practitioner surveillance

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 20	Substitution (cultivated for wild)	He Shou Wu (Polygonum multiflorum)	Wild He Shou wu (endangered) substituted for wild	Academic review	Profit motivation and error	Profit motivation, error and difficult to detect	Analytical surveillance / regulation
Case 18	Substitution (differently processed herbs)	Zhi Mu	Substitution due of similarly named but differently processed species of Zhi mu / Yan Zhi Mu (vinegar processed)	Traditional knowledge	Profit motivation and error	Profit motivation and error	Analytical / practitioner surveillance
Case 20	Substitution (toxic)	Bai Fu Zi (Typhonium giganteum Araceae)	Bai Fu Zi was Fu Zi (toxic)	Practitioner surveillance	Not specifed	Not detected / Not known	Not specifed
Case 9	Toxicity (Carcinogenic)	Anisi Stellati Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Arecae Pericarpium	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Arecae Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Toxicity (Carcinogenic)	Armeniacae Amarum Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Astragali Radix	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Belamcandae Rhizoma	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Bombyx Batryticatus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Cassiae Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Citri Reticulatae Pericarpium	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Citri Reticulatae Pericarpium	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Toxicity (Carcinogenic)	Coicis Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Corni Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Corydalis Rhizoma	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Crataegi Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Cyperi Rhizoma	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Foeniculi Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Glycyrrhizae Radix et Rhizoma	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS							
Key Informant Case Number	**What Issue(s)**	**Herb**	**Specifics of issue**	**Discovered through**	**Why it occurred**	**Why it persisted**	**Solutions**
Case 9	Toxicity (Carcinogenic)	Hedysari Radix	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Hirudo	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Hordei Fructus Germinatus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Jujubae Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Ligustri Lucidi Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Lycii Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Nelumbinis Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Toxicity (Carcinogenic)	Persicae Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Pheretima	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Piperis Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Polygalae Radix	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Quisqualis Fructus	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Saposhnikoviae Radix	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Scolopendra	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 9	Toxicity (Carcinogenic)	Scorpio	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Scrophulariae Radix	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Sterculiae Lychnophorae Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 9	Toxicity (Carcinogenic)	Ziziphi Spinosae Semen	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Not detected / Not known	Analytical surveillance / regulation
Case 16	Toxicity (Carcinogenic)	Corydalis	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Oily nature engenders susceptibility to Aflatoxin / stoarge conditions in supply chains	Analytical surveillance / regulation
Case 16	Toxicity (Carcinogenic)	Polygala tenuifolia Willd	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Oily nature engenders susceptibility to	Analytical surveillance / regulation

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS							
Key Informant Case Number	**What Issue(s)**	**Herb**	**Specifics of issue**	**Discovered through**	**Why it occurred**	**Why it persisted**	**Solutions**
						Aflatoxin / storage conditions in supply chains	
Case 16	Toxicity (Carcinogenic)	Semen platycladi	Toxicity from aflatoxin	Analytical surveillance	Industrialisation / Storage conditions	Oily nature engenders susceptibility to Aflatoxin / storage conditions in supply chains	Analytical surveillance / regulation
Case 7	Toxicity (Cardiac)	He Shou Wu. Polygonum multiflorum.	He Shou Wu is toxic when unprepared	Adverse events	Use of unprepared He Shou Wu	Traditional Chinese medicine preparation methods not known and / or used	Use traditional Chinese medicine directed preparation
Case 7	Toxicity (Potential Cardiac)	Wu Jia Pi Eleutherococcus Nodiflorus with Xiang Jia Pi, Periploca	Wu Jia Pi substituted with cardioactive Xiang Jia Pi, Periploca,	Adverse events	Unknown	Unknown	Unknown

TABLE AKI 12 MASTER KI TABLE, ANALYSIS OF SPECIFIC EXAMPLES BY KEY INFORMANTS

Key Informant Case Number	What Issue(s)	Herb	Specifics of issue	Discovered through	Why it occurred	Why it persisted	Solutions
Case 8	Toxicity (Pyrrolizidine Alkaloids)	Senicio (Jacobaea vulgaris)	One senicio plant can contaminate a whole hectare of CMP	Analytical surveillance	Toxicity (intrinsic)	Not detected / Not known	None recommended

THE END