What's the choice for goji: *Lycium barbarum* L. or *L. chinense* Mill.?

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Abstract

Ethnopharmacological relevance:

For over one millennium, goji berries have been used traditionally as food and medicine in eastern Asia. In recent decades, it has become increasingly popular globally. However, the biocultural development of goji is poorly known. The botanical origin of goji is controversial: in many but not all modern regional or international quality standards, *L. barbarum* is accepted exclusively as the botanical origin of goji.

Aim of the study:

Focusing on historical, biogeographical, botanical, phytochemical and pharmacological data, the overarching aim is to understand the biological origin of goji's historical uses, as well as whether the two species can be used interchangeably.

Materials and methods:

The taxonomic literature on *L. barbarum* and *L. chinense* were analysed, followed by a study of botanical specimens and fieldwork. Historical herbals and gazetteers were employed to define the historical producing areas and medical properties of goji. An identification of the species used in history was carried out. In a final step the phytochemical and pharmacological literature on the species was compared.

Results and Discussion:

Due to their morphological similarity and different accessibility, fruits of both *L. barbarum* and *L. chinense* have been used interchangeably as food and medicine at least since 682 CE. While the fruit of *L. barbarum* was recognized to be superior in quality, the fruit of *L. chinense* was commonly used as an equivalent because of its easier accessibility. Cultivation of *L. barbarum* in China since 1960s improved its availability, which likely lead to its exclusive use as source of goji in China. The long-term safe use with no reported major safety concerns supports that these two species both are useful sources for medicinal *Lycium*.

Conclusions:

Medicinal plants had been used traditionally long before they were named in scientific nomenclature system. Therefore, the understanding of traditional herbal knowledge and the adequate use of those traditional medicines require a reliable identification based on archival records. This study developed an approach for the identification of species used historically, with an integrated analysis of specimens, historical herbals, and national gazetteers. Additionally, their different chemical profiles and pharmacological activities indicate that they should not be used interchangeably. Further scientific evidence is required for their safe and effective use.

Keywords: *Lycium*, goji, biological origin, historical use, gazetteer

1. Introduction

The genus *Lycium,* including roughly 100 species, is widely distributed globally in temperate zones, and over 30 *Lycium* spp. are used as food or medicine traditionally (Yao et al., 2018a). While the fruit, the leaf, the young shoot, and the root bark of *Lycium* spp. are often used locally, the fruits of *Lycium barbarum* L. and *L. chinense* Mill., which are commonly known as wolfberry, goji berry, or goji, have become a global commodity used especially as a health food. Its chemical composition endows goji with health properties, and goji has become popular in Europe and North America among other regions (The American Herbal Pharmacopoeia, 2019; Ye and Jiang, 2020). While the selection of plant species as food or medicine is influenced by a variety of

ethnopharmacological factors, e.g., pharmacological or nutritional properties, local beliefs, availability, versatility and diversification (Jennings et al., 2015; Leonti et al., 2020), the early biological origin of goji remains poorly understood.

A defined biological origin is essential for the safe and effective use of herbal medicines and their derived products and it is a key index for the quality standard. In recent decades, multi-disciplinary approaches have been developed for the quality control of goji, including chemical analysis, DNA barcoding, and value chain analysis (Wagner et al., 2011; Xin et al., 2013; Yao et al., 2018b; Yao et al., 2018c). Regional quality standards for goji have been published as herbal pharmacopoeias and monographs (Chinese Pharmacopoeia Commission, 2020; European Directorate for the Quality of Medicines & Healthcare, 2020; The American Herbal Pharmacopoeia, 2019), and even the International Organization for Standardization (2020) published a standard for goji. As is shown in **Table 1**, the current quality standards adopt different biological origins for goji: while *L. barbarum* is widely accepted, *L. chinense* is adopted as an equivalent in some standards additionally.

Table 1 The biological origin of goji in regional and international quality standards

Name of standard	**Recorded name for goji**	**Biological origin of goji**	**Authority and reference**
British Pharmacopoeia 2020	Barbary Wolfberry Fruit	*Lycium barbarum* L.	British Pharmacopoeia Commission (2020)
Chinese Pharmacopoeia (2020)	枸杞子, Gouqizi, *Lycii* fructus	*L. barbarum*	Chinese Pharmacopoeia Commission (2020)
European Pharmacopoeia (10.0)	Barbary Wolfberry Fruit, *Lycii fructus*	*L. barbarum*	European Directorate for the Quality of Medicines & Healthcare (2020)
ISO 23193: 2020	*Lycium barbarum* fruit, *Lycium chinense* fruit	*L. barbarum*, *L. chinense* Mill.	The International Organization for Standardization (2020)
Japanese Pharmacopoeia (17th)	*Lycium* Fruit, *Lycii Fructus*, クコシ	*L. barbarum*, *L. chinense*	Japanese Pharmacopoeia Editorial Committee (2016)
Korean Pharmacopoeia (11th)	구기자, 枸杞子, *Lycium* Fruit	*L. barbarum*, *L. chinense*	Korean Ministry of Food and Drug Safety (2014)
Taiwan Herbal Pharmacopoeia (III)	枸杞子, *Lycii Fructus*, Wolfberry Fruit	*L. barbarum*, *L. chinense*	Taiwan Herbal Pharmacopoeia Commission (2018)

US Herbal Medicines Compendium (Prososed)	*Lycium barbarum* Fruit	*L. barbarum*	The United States Pharmacopeial Convention (2013)
Vietnamese Pharmacopoeia (4th)	CẨU KỶ TỬ, *Fructus Lycii*	*L. barbarum*	Vietnam Ministry of Health (2010)
American Herbal Pharmacopoeia	*Lycium* (goji) Berry	*L. barbarum*, *L. chinense*	The American Herbal Pharmacopoeia (2019)
American Herbal Products Association's Botanical Safety Handbook	*Lycium* spp.	*L. barbarum*, *L. chinense*	Gardner and McGuffin (2013)
Ayurveda Pharmacopoeia of India (VI)	Kantakigulma	Aerial part of *L. barbarum* and *L. europeaum* L.	Department of AYUSH of India (2008)
Chromatographic Fingerprint Analysis of Herbal Medicines	*Fructus Lycii*, Gouqizi	*L. barbarum*	Wagner et al. (2011)

Obviously, closely related plant species may have similar chemical profiles and are possibly to be used interchangeable (Garnatje et al., 2017; Hao and Xiao, 2017). In the case of goji, recent studies have demonstrated the close phylogenetic relationship between *L. barbarum* and *L.chinense* (Miller et al., 2011). However, their chemical profiles are distinguishable depending on the analytical methods used and their pharmacological activities differ (Yao et al., 2018c). Therefore, it is still controversial whether these two species could be used interchangeably. Here we ask: 1) Which species are of the historical early sources of goji? 2) Are *L. barbarum* and *L.chinense* exchangeable source of goji?

In the present study we analyse this using an ethnobotanical perspective. Also incorporating historical and phytochemical data is used to understand the divergence in biological origin of goji.

2. Materials and methods

2.1 Fieldwork and specimen study

From 2015 to 2020, fieldworks were carried out in north-western China (including Ningxia, Qinghai, and Xinjiang) and some eastern provinces of China (including Beijing, Jilin, Hebei, Henan, Sichuan, Guizhou, Yunnan) during goji fruiting time. Wild and cultivated *Lycium* plants were inspected, and typical specimens were collected. Voucher specimens were preserved in the Herbaria of the University of Zurich and ETH Zurich (ZT) and the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College.

Specimens of *Lycium* preserved in PE were visited to study the morphological traits carefully and the distribution of specimens was search through iplant (http://www.iplant.cn/). Additionally, a search on on-line herbaria in the global wide was conducted to obtain the information on important specimens.

2.2 Literature review

Using "*Lycium*"(or "杞" in Chinese) as a keyword, relevant information was extracted from data sources including taxonomic monographs, Chinese historical herbals, national gazetteers, scientific journal articles, pharmacopoeia monographs, and herbal monographs. The taxonomic nomenclatural history of *L. barbarum* and *L.*

chinense was reviewed using original taxonomic records and online specimens. Using records on the production areas and/or illustrations recorded in historical Chinese herbals were assessed. Chinese gazetteers are encyclopaedias of different Dynasties and recorded the general information of different regions, and medicines were often included in the items of "Tu Chan" (土产, tǔ chǎn) or "Tu Gong" (土贡, tǔ gòng), which mean local products and tributes respectively, therefore, the gazetteers can provide additional information for the historical production of goji. The national gazetteers of Tang, Song, Yuan, Ming and Qing were used to understand the species used in corresponding times. The chemical constitutions, biological and pharmacological activities of fruits of *L. barbarum* and *L. chinense* were compared. These provided the bases for a comparative analysis of the two species in terms of their biocultural development within China.

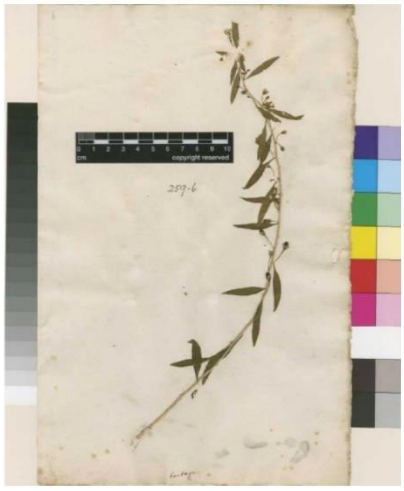
3. Results and Discussion

3.1. Taxonomy and distribution

Lycium barbarum L. was first published in *Species Plantarum* (Linnaei, 1753), where it was described as having lanceolate and thick leaves, a two-lobed calyx (which was modified into 3-lobed in later descriptions). While later studies made conflicting interpretations on this species, Pojarkova (1950) clarified C. v. Linné's *L. barbarum* and compared it with other Asian *Lycium* spp.; later on, typification confirmed the type specimen (Linnaean Herbarium 259.6) and distinguished it from other species by its dense hairy base of filaments, which is a character of the East-Asian *Lycium* (Feinbrun and Stearn, 1963; Pojarkova, 1950). Flora of China interpreted *L. barbarum* accordingly, and included a variety *L. barbarum* var. *auranticarpum* K.F.Ching, which had linear leaves, small round yellow fruits (Editorial committee of Flora of China, 1978), but the variety had not been adopted by the plant list. In 2012, *L. barbarum* var. *implicatum* T.Y. Chen & X.L. Jiang was published as a new variety (Chen et al., 2012). From an agronomic perspective, dozens of cultivars of *L. barbarum* were developed in recent years, e.g., the *Ningqi* series bred in Ningxia include cultivars with different agronomic traits (Wang, 2019; Wood, 2019). In 2020, The International Union for the Protection of New Varieties of Plants (UPOV) published a draft of guidelines for the conduct of

tests for *L. barbarum* (UPOV Code: LYCIU_BAR). Overall, there are abundant morphological and genetic variations within the species *L. barbarum.*

Lycium chinense Mill. was first published in the 8th Gardeners' Dictionary (Miller, 1768), where it was characterized by oval spear-shaped leaves, diffused branches, single spreading flowers with a longer style. Flora of China (Editorial committee of Flora of China, 1978) included a variety *L. chinense* var. *potaninii* (Pojark.) A.M.Lu, which was former *L. potaninii* Pojark.. Similar to the case of *L. barbarum*, a large number of cultivars of *L. chinense* were developed, many of which were contributed by the South Korean agronomists (Park et al., 2012). As a result, the species *L. chinense* also includes rich variations.



A. Type specimen of *Lycium barbarum* L.

B. A plant of *L. barbaurm* cultivated in Ningxia, China

C. Type specimen of *L. chinense* Mill.

D. A plant of *L. chinense* cultivated in Ningxia, China

Figure 1 The type specimens and plants of *Lycium barbarum* L. and *L. chinense* Mill. .

A: the type specimen of *L. barbarum* (Linnaean Herbarium 259.6) (The Linnean Collections, 2020); **B**: a cultivated *L. barbarum*, note the lanceolate leaves and the oblong fruits; **C**: the type specimen of *L. chinense* (NHMUK BM000906026) (Natural History Museum, 2020); **D**: a cultivated *L. chinense*, note the ovate leaves and the heart-shaped fruits.

Although these two species share similar morphologic traits, it is still possible to differentiate them by careful examination. **Figure 1** shows a comparison of type specimens and cultivated plants of *L. barbarum* and *L. chinense,* by which the difference in leaf shape and fruit shape can be recognized easily. Besides, their flower shapes are also different: Flowers of *L. barbarum* are often with 2-lobed calyx, and the corolla lobe is about half of corolla tube in length; while the calyx of *L. chinense* is often 4 to 5-lobed, and the corolla lobe is as long as the corolla tube. Additionally, the fruit shape of *L. barbarum* is oblong or globular while that of *L. chinense* is often heart-shaped; the seed size of *L. barbarum* is ca. 2 mm in length while that of *L. chinense* is ca. 2.5 to 3 mm (Editorial Committee of the Flora of China, 1994). Moreover, the taste of their fruits (dried or fresh) is also different: the fruit of *L. barbarum* is sweet with slight bitter taste while that of *L. chinense* taste bitter (fieldwork notes RY).

It is possible that the similar appearance caused the mis-identification of these two species. Long before the application of binomial nomenclature, fruits of *L. barbarum* and *L. chinense* were used interchangeably as goji in China. After the application of binomial nomenclature in the 18th century, the European scientists gave simple descriptions to these two distinct species, but it was still difficult to differentiate them. The scientific name of *Lycium* was not employed in Chinese books until the 20th century, but mis-identifications were still frequently happened. For example, the *Lycium* widely distributed in the northwest of China was identified as *L. turcomanicum* Turcz., while *L. barbarum* was not reported until 1959 (Editorial Commission of Chinese Materia Medica, 1959). In Flora of China, *L. turcomanicum* was treated as a synonym of *L. dasystemum* Pojark., although delicate differences existed between them (Editorial committee of Flora of China, 1978).

While the morphological similarity makes it difficult to differentiate these two species,

their geographic distribution provides useful clues. *L. barbarum* is mainly distributed in the northwest of China, while *L. chinense* is widely distributed in the East-Asia (Pojarkova, 1950; Yao et al., 2018c). *L. barbarum* is heliophile, xerophilous, and saline-alkali resistant, and can yield fruits of good quality when grows in the northwest of China. However, when cultivated in the temperate monsoon region, *L. barbarum* will have different appearances, which had led to mis-identification. Since 1960s, cultivars of *L. barbarum* were introduced into new producing areas from *Ningxia* (Editorial Commission of History of Goji, 2019); at that time, *Hebei* and *Tianjin* yielded a large amount of goji, which were traded by the name of *Jin Gouqi* (津枸杞, jīn gǒu qǐ), and it was identified as *L. chinense* based on the fruit appearance. *L. barbarum* cultivated in the Hebei monsoon region (including where *Jin Gouqi* is produced) had a similar appearance with *L. chinense* (Yao et al., 2018c). Due to the mis-identification, both *L. barbarum* and *L. chinense* were accepted as the source of goji in Chinese Pharmacopoeia of 1963 (Chinese Pharmacopoeia Commission, 1963). Therefore, the change of geographical origin will lead to the change of morphology, possibly resulting in misidentifications.

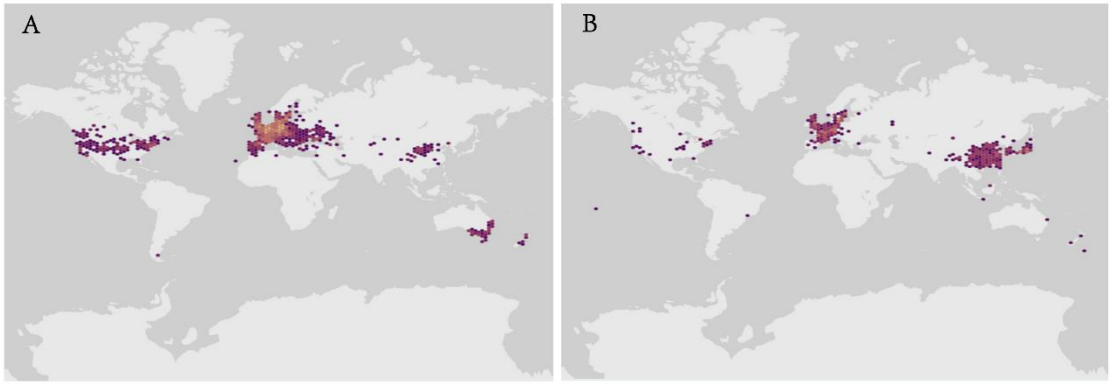


Figure 2 Distribution maps of *L. barbarum* and *L. chinense* based on data of 1600 – 2020 in Global Biodiversity Information Facility (GBIF) (GBIF Secretariat, 2020a; GBIF Secretariat, 2020b). **A**: the distribution map of *L. barbarum*; **B**: the distribution map of *L. chinense*. Note their wide distribution and the overlaps.

In recent years, *L. barbarum* has been increasingly cultivated in Europe and the North America (Dhekney and Baldwin, 2019; Kosińska-Cagnazzo et al., 2017; Kulaitienė et al., 2020; Skenderidis et al., 2018; Wojdyło et al., 2018). In the meanwhile, *L. chinense*

grows widely in the south and east of China and eastern Asia (Pojarkova, 1950; Yang et al., 2020), while in South Korea, a vast of wild resources and cultivars are distributed (Zhao et al., 2010). **Figure 2** shows distribution maps of *L. barbarum* and *L. chinense* based on data of 1600 – 2020 in Global Biodiversity Information Facility (GBIF). It can be seen that both species are widely distributed with overlaps, therefore, the geographic origin of today cannot provide reliable clues for the differentiation of these two species any more.

3.2. Historical herbals and gazetteers

Chinese herbals record a vast of ethnopharmacological information on drugs, including name, medical properties, production areas, processing approaches, texts cited from other herbals, and so on. Gazetteers are encyclopaedias of different Dynasties, in which agricultural products of specific geographic regions are recorded. The Chinese character 枸杞(gǒu qǐ) was used to name the *Lycium* plant in Chinese herbals; although herbals could not provide precise evidences for species identity, the geographical origin and taste of fruits were useful clues for the discrimination of *L. barbarum* and *L. chinense*. Practically, these two species can be differentiated based on their geographical origin (*L. barbarum* mostly grows in the northwest China) and the taste (*Lycium* with sweet fruits probably is *L. barbarum*). Illustrations of the plant could provide extra clues for the identification, such as the leaf shape, the fruit shape, and the number of calyx lobes. **Figure 3** shows an example of an historical herbal (left) and a gazetteer (right). Relying on the above historical records and the taxonomic information (including key morphological traits and distribution), the species used in the history could be deduced, or identified based on the written record.

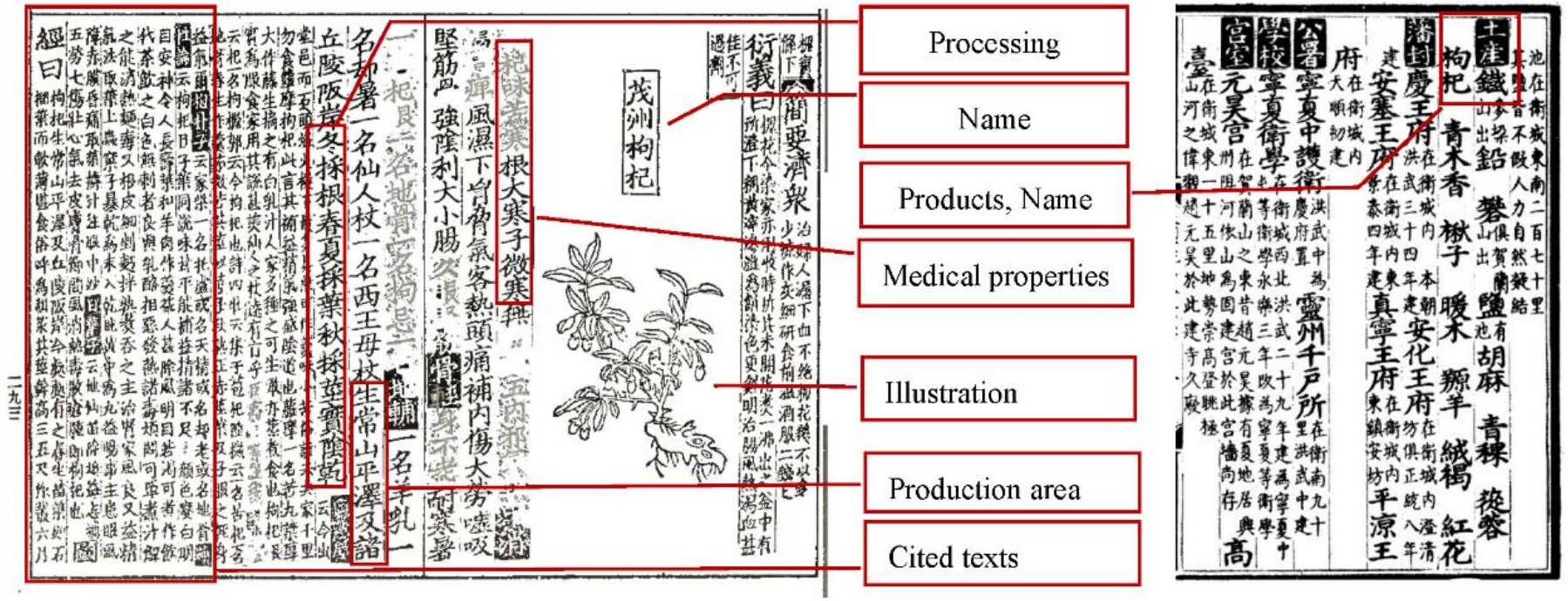


Figure 3 An example of information in historical herbals and gazetteers. Note the left is a goji monograph in *Zheng Lei Ben Cao* (Tang, 1116), and the right is a record of goji in *Da Ming Yi Tong Zhi* (Li, 1461).

The historical producing areas in herbals of different times and the identification of the used species were shown in **Figure 4A**. *Lycium* was recorded in the earliest Chinese herbal *Shennong*'s Herbal Classics (神农本草经, shén nóng běn cǎo jīng, ca. 100 CE), based on the geographical origin probably being *L. chinense* (Shang, 2008). In the *Ben Cao Jing Ji Zhu* (本草经集注, běn cǎo jīng jí zhù, ca. 500 CE), the fruit and the root of *Lycium* were described separately, with a new geographical origin t *Tangyi* (near *Liaocheng* of *Shandong* Province) was recorded, and based on the traits of fruit and the geographical origin, the species was probably *L. chinense* as well (Tao, 500). An official herbal of the Tang Dynasty recorded the similar information as above (Su, 659). *Lycium* from the northwest of China with sweet taste was first recorded in *Qian Jin Yi Fang* (千金翼方, qiān jīn yì fāng), probably be *L. barbarum* (Sun, 682). Since then fruits of both species were used as goji, and *L. barbarum* seemed to have been considered to be superior to *L. chinense*. In the Song Dynasty, *Zheng Lei Ben Cao* included an illustration of *Lycium*, identified as *L. chinense* based on the calyx and the geographical origin (Tang, 1116). *Ben Cao Meng Quan* (本草蒙荃, běn cǎo méng quán) of the Ming Dynasty recorded that goji of good quality was produced in *Gansu*, which was probably *L. barbarum* (Chen, 1565). *Ben Cao Gang Mu* (本草纲目, běn cǎo gang mù) also mentioned goji from *Ganzhou* (in the northwest of China) and, therefore, probably *L. barbarum* had the best quality (Li, 1596). In the Qing Dynasty, *Ben Cao Bei Yao* (本草备要, běn cǎo bèi yào) indicated that goji of good quality was from the north (probably *L. barbarum*), with goji of both the south and north were used (Wang, 1694). Later herbals of the Qing Dynasty included similar statements (Tu, 1863; Yang, 1842). In conclusion, *L. chinense* had a longer use history, and both *L. barbarum* and *L. chinense* were use interchangeable since no later than 682 CE, although the quality of *L. barbarum* was thought to be the better.

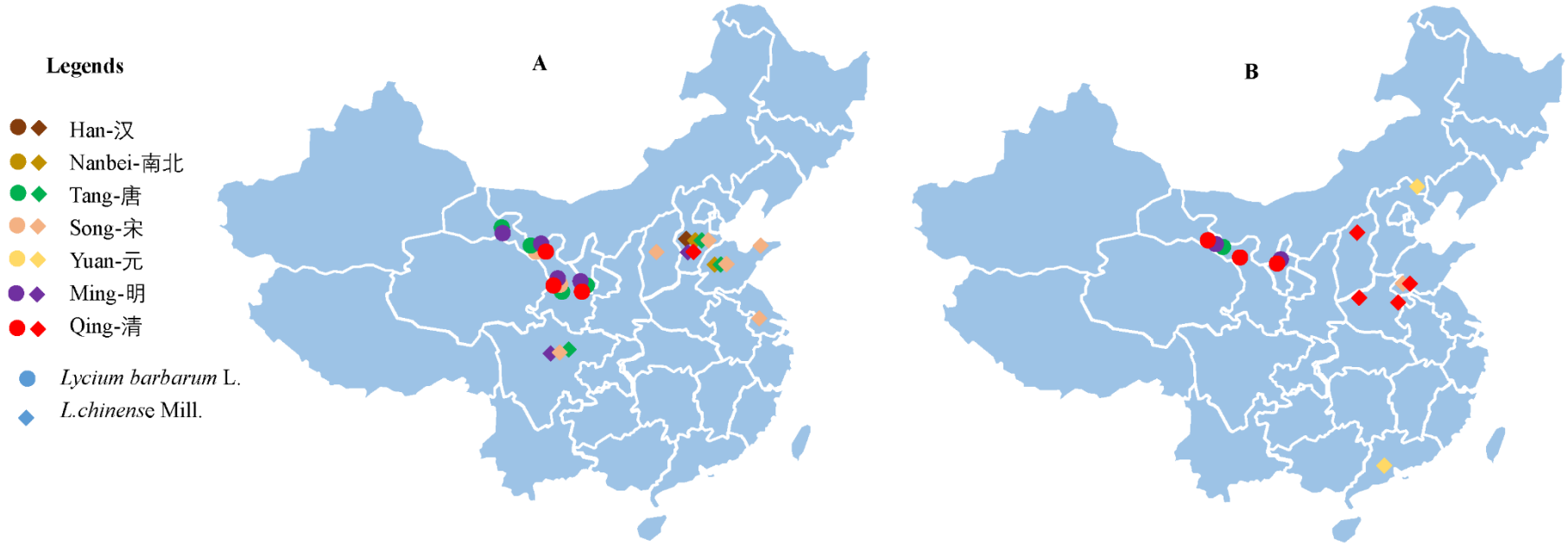


Figure 4 Historical producing areas of goji recorded in herbals (A) and gazetteers(B) in China, as well as the probable species cited. References to **A**: Shang (2008), Tao (500), Su (659), Sun (682), Su (1062), Tang (1116), Li (1230), Zhu (1406), Liu (1505), Chen (1565), Li (1596), Yang (1842), and Wang (1694); References to **B**: Li (813), Le (986), Bei (1285), Li (1461), and Mu (1842).

In the Tang Dynasty, *Yuan He Jun Xian Tu Zhi*(元和郡县图志, yuán hé jùn xiàn zhì) recorded goji as a tribute of *Ganzhou* (near *Zhangye* of Gansu Province) hinting the goji of *Ganzhou* was with best quality then (Li, 813). Later in the Song Dynasty, *Tai Ping Huan Yu Ji* (太平寰宇记, tài píng huán yǔ jì) recorded goji as a product in *Shanzhou* (near modern *Heze* of *Shandong* Province) (Le, 986). In the Yuan Dynasty, goji was recorded was products of *Da'ning Lu was recorded* (modern *Ningcheng* County of Inner Mongolia) and *Guangzhou Lu* (near Canton) in *Yuan Yi Tong Zhi* (元一统志, yuán yì tǒng zhì) (Bei, 1285). In the Ming Dynasty, *Da Ming Yi Tong Zhi* (大明一统志, dà míng yì tǒng zhì) added *Ningxia Wei* (modern *Yinchuan* of *Ningxia*) and *Shannxi Xing Du Zhi Hui Shi Si* (in the middle of *Gansu* Province) as regions of origin (Li, 1461). In the Qing Dynasty, *Shuoping Fu* (modern *Shuozhou* of *Shanxi* Province), *Caozhou Fu* (*Heze* of Shandong), *Guide Fu* (*Shangqiu* of *Hennan* Province), *Henan Fu* (*Luoyang* of *Hennan* Province), *Ningxia Fu* (*Yingchuan* of *Ningxia*), *Ganzhou Fu* (*Zhangye* of *Gansu* Province), *Liangzhou Fu* (*Wuwei* of *Gansu* Province) (Mu, 1842) (all shown in **Figure 4B)**. In conclusion, based on these archival records, while *L. barbarum* distributes in the northwest and *L. chinense* is in the south and east of China, *L. barbarum* sourced goji was thought to be of good quality since no later than the *Tang* Dynasty, in the meanwhile, *L. chinense* was also produced widely in history, and both species have been produced at least since 986 CE.

In the recent century, the used species for goji experienced several changes. After a pharmacist clarified their differences in the appearance and taste in 1901, goji from these two species were declared to be with different medicinal properties and should be used separately; additionally, the superior quality of *L. barbarum* was stated with a traditional concept (Cao, 1927). However, *L. chinense* was still widely used. In 1939, Medicinal Plants of China (中国药用植物志, zhōng guó yào yòng zhí wù zhì) adopted the scientific name, and recorded *L. chinense* is the only source for goji (Pei, 1939). Later on, both *L. barbarum* and *L. chinense* were recorded as sources of goji in 1959 by the Chinese Materia Medica (Editorial Commission of Chinese Materia Medica, 1959). The turning point came in the 1960s, when *L. barbarum* was introduced into

widespread cultivation, and the increased yield improved its accessibility (Editorial Commission of History of Goji, 2019). As a result, since 1977 the fruits of *L. barbarum* was exclusively recorded as goji in Chinese Pharmacopoeias (Chinese Pharmacopoeia Commission, 1977). Gradually, *L. chinense* was used only locally and produced less commonly (Editorial Commission of History of Goji, 2019). Interestingly, the fruits of *L. chinense* is still widely used in South Korea today, where the species is widely distributed and cultivated. Finally, as is shown in **Table 1**, the biological origins for goji vary among regional quality standards.

3.3. Relevant metabolites

While phytochemical studies have reported that fruits of both species are rich in polysaccharides, carotenoids, flavonoids, among others, their different chemical constitutes were assessed in recent systematic review articles and monographs (Amagase and Farnsworth, 2011; Qian et al., 2017; Yao et al., 2011a; Ye and Jiang, 2020). However, the comparative studies on the metabolite of these two species are limited, but still indicate the difference among them.

The polysaccharides are thought to be one of the most important active metabolites of goji berry and they vary in their contents and glycosidic composition. The contents of polysaccharides vary from 1.2 % to 23 %, which, however, is strongly affected by the analytical methods used (The American Herbal Pharmacopoeia, 2019). The contents of polysaccharides differ in genotypes and producing areas, while fruits of *L. barbarum* cultivated in *Ningxia* and nearby contained more polysaccharides than others (Yao et al., 2011b). While polysaccharides of *L. chinense* was reported to be lower than that of *L. barbarum*, a strong variation of polysaccharides within the same species is well documented (Lu et al., 2019; Skenderidis et al., 2019; Zhang et al., 2016). On the contrary, a study showed that the contents of polysaccharides from fruits of both species had not significant difference, although fruits of *L. chinense* had lower contents of total sugar (Yao et al., 2018c). Regarding to glycosidic composition, diverse compositions were found in goji of different origins, even the same species could yield different polysaccharides if different methods were used (Qian et al., 2017; The American Herbal Pharmacopoeia, 2019; Yao et al., 2011a; Ye and Jiang, 2020). However, with

metabolomics approaches, *L. barbarum* and *L. chinense* are distinguishable based on their carbohydrate constitutions (Yao et al., 2018c). As a result, the polysaccharides of goji vary in contents and glycosidic composition, and the difference of sugar profiles of these two species can be evaluated by chemometrics.

Carotenoids are another important class of constituents, with a content of 0.03% to 0.50% in dried goji. Among those carotenoids, zeaxanthin and zeaxanthin dipalmitate are predominant (The American Herbal Pharmacopoeia, 2019). Studies have reported inconsistent results on the comparison of the contents of carotenoids from *L. barbarum* and *L. chinense* (Kafkaletou et al., 2018; Peng et al., 2005; Skenderidis et al., 2019; Yossa Nzeuwa et al., 2019; Zhang et al., 2016). Therefore, since the carotenoid profiles of two species are unknown, it is uncertain which species contains more carotenoids, neither is the constitution of carotenoids in these two species.

Phenols and flavonoids contents varied greatly in different samples of *L. barbarum*, *L. chinense*, and *L. chinense* var. *potaninii* (Skenderidis et al., 2019; Yossa Nzeuwa et al., 2019; Zhang et al., 2016). A fingerprint based on High Performance Thin Layer Chromatography (HPTLC) presented the different flavonoids profiles of *L. barbarum* and *L. chinense*, e.g., the later lacked rutin (Yao et al., 2018c). Therefore, although the contents of phenols different species are not distinguishable, the phenols profiles vary among species.

However, *L. barbarum* fruit and *L. chinense* fruit are distinguishable by their chemical profiles. For example, using attenuated total reflection Fourier-transform infrared (ATR-FT-IR) spectroscopy, fruits of the two species showed different spectra (Skenderidis et al., 2019); relying on ^{1}H NMR spectra, their fruits could also be distinguished (Yao et al., 2018c). Lee et al. (2014) reported that fruits of the two species are distinctly separated by their taste pattern. Their different chemical profiles and sensory properties indicate that fruits of these two species should not be treated equally especially when used as medicines.

3.4. Chemical anti-oxidant assays and pharmacology

Only antioxidant activities were studied in a comparative way allowing a comparative study on bioactivities of goji sourced from two species, although there is no evidence

for therapeutic benefits on the basis of such chemical assays. Using DPPH (2,2-Diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis (3-ethylbenzothiazoline -6-sulfonic acid)) to evaluate the chemical antioxidant levels, the fruit of *L. chinense* showed relative lower level than that of *L. barbarum* (Skenderidis et al., 2019); contrarily, fruits of *L. chinense* showed higher level of antioxidant in another study using ABTS (Yao et al., 2018c). Since the antioxidant levels vary largely within the same species (Lu et al., 2019), the above results do not provide sufficient evidence for the comparison on antioxidant levels of goji. While most commonly chemical anti-oxidant assays like the DPPH assay were used which are of no pharmacological relevance (Heinrich et al., 2020), more relevant in vitro antioxidant tests are required to compare these two species.

The comparison of pharmacological activities using water extracts of fruits of *L. chinense* and *L. barbarum*, and solutions of polysaccharides from fruits of *L. chinense* and *L. barbarum* was conducted in Kunming mice model (Zhang et al 1999). All treatments increased the number of red blood cells of mice but to different post-intervention levels, and only the water extracts of fruits of *L. chinense* increased the hemoglobin content. Treatments had different effect on the number of sperms, the sperm viability, and the weight of epididymis and seminal vesicle gland (Zhang et al., 1999). These findings hinted that goji of different botanical sources may have different pharmacological effects, and they should be considered respectively.

4. General Discussion

The selection of plant species as foods and/or medicines has been influenced by the availability (accessibility), versatility, diversification, cultural history and pharmacology (Heinrich et al., 2006; Leonti et al., 2020; Weckerle et al., 2006). The similar morphological traits of these two species leads to uses of goji being interchangeable. According to the historical records, *L. barbarum* and *L. chinense* were not treated as different species until the recent centuries. Instead, because of their similar appearance, they were thought to be one medicinal and food resource, coming from different geographical origins, the north-western with sweet taste (*L. barbarum*) and southern and eastern with a bitter taste (*L. chinense*). They were treated as two

drugs until 1901, and the later was named as "*Tu Gouqi*"(土枸杞, tǔ gǒu qǐ), which was inferior in quality (Cao, 1927). However, both species have been widely cultivated since recent centuries, and changes of the geographic origin and the morphology has led to the mixed use of these two species. For example, when *L. barbarum* is cultivated further in the east of China, morphologically it is more similar to *L. chinense*, which has caused mis-identification in the 1960s.

The accessibility of the species is also an important factor that shapes the selection of species. Traditionally, goji fruits which are larger in size, red, and sweet are recognized to be superior in quality. Accordingly, no later than 682 CE the fruit of *L. barbarum* was thought to be better than that of *L. chinense*. However, *L. barbarum* from the northwest of China, where few people lived and with limited transportation until the 20th century, the fruit of *L. barbarum* was difficult to access. According to the local tales, in the Qing Dynasty, goji of *Ningxia* was often transported by small boats along the yellow river to the market in the north, or was carried by tramping men to the market in the south. In contrast, *L. chinense* was widely distributed in the south and east of China. Therefore, although it was thought to have inferior quality, *L. chinense* was used widely in the past, as evidenced in production status of goji in the history (**Figure 4**).

Cultivation has a great influence on the accessibility of medicinal plant species, which impacts on the use of species indirectly. It is obvious that the widespread cultivation of *L. barbarum* since the 1960s has improved its accessibility, and consequently this has led to its predominance in the markets. In recent decades, *L. chinense* still has been cultivated in *Julu* County of Hebei Province, which is a historical producing area of *L. chinense*, and goji produced there is advertised as Bitter Goji being consumed locally (Yao et al., 2018c). The cultivation of *L. chinense* in South Korea has provided sufficient materials, and the fruit of *L. chinense* is adopted in the Korean Pharmacopoeia and is the main source for goji used in South Korea (Korean Ministry of Food and Drug Safety, 2014).

The long-term use of traditional medicines provides a reasonable but preliminary evidence base for their safe and effective use (Jutte et al., 2017). Since fruits of *L. barbarum* and *L. chinense* have been used for nearly two millennia, both of them could

be used as safe source of medicinal *Lycium*. Although the pharmacological or nutritional properties may not be necessary for the traditional botanical food and medicine (Jennings et al., 2015), the effective use of the two species still relies on phytochemical and pharmacological evidences. Considering their different functional entities, these two species should not be used interchangeably.

It has been a common phenomenon that medicinal plants had been used traditionally long before they were named according to the binominal nomenclature system. Therefore, the rehabilitation of traditional herbal knowledge and the correct use of those traditional medicines require a reliable identification based on archival records of those plant species. This has been a constant challenge in historical-botanical studies (De Vos, 2010; Hibert et al., 2011). Here we combine such archival research, with a phytogeographical analysis, shedding light on the two species' uses over time.

Ethnobotanical studies serve in the conservation of traditional botanical knowledge, and a systematic study on the historical texts contributes to a unique understanding of these knowledge systems at the risk of being lost (Lardos, 2015; Leonti, 2011). While the information from historical herbals and early taxonomic monographs were limited, such an ethnobotanical approach with emphasis on the history and botany is applicable.

5. Conclusions

In this study, a transdisciplinary method was applied to explore the controversy on the biological origin of goji. The availability and similar appearance seem to be key reasons for their exchangeable uses in history. The pharmacological evidence is insufficient to allow a comparison of the benefits of the two species. With the long safe use history and the well comprehending to their chemical profiles, both species are useful as herbal medicines or health foods according to the traditional indications. However, they should not to be used interchangeably because of the obvious differences in their chemical constitutions as well as pharmacological activities, and the gaps in our understanding of potential differences between the two species. Considering their difference in chemical composition, different quality criteria should be set for these two species. However, with regard to their food and medicinal uses, a better differentiation of potential uses and benefits as medicines is warranted due to their different chemical

profiles. In order to achieve this further comparative pharmacological studies with phytochemically well-defined preparations are required.

Using a systematic ethnobotanical approach, data from taxonomy, historical herbals, gazetteers, phytochemistry, and pharmacology together achieved a differentiation of species even those in the historical records of 2000 years ago and contributed to an understanding of the development over time. Moreover, the combined use of historical herbals and gazetteers leads to more reliable evidence base for the historical uses. As a result, more generally, this study provides a strategy for the identification of traditional herbal medicines in historical texts, which will further support the conservation of traditional knowledge and the safe use of herbal products in the future.

Author contributions

RY developed the concept of the work, conducted the fieldwork, specimen study and literature study, drafted and revised the manuscript. XZ performed the search on the gazetteers and drafted the manuscript. MH provided guidance throughout the development of the MS, and edited the MS at all stages. PX supervised the work and contributed critical ideas. JW and QW contributed useful comments.

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