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Chrysanthemum species used as food and medicine: Understanding quality differences on the global market

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ABSTRACT

Background: Chrysanthemum flowers [*Ch.* x *morifolium* (Ramat.) Hemsl. and *Ch. indicum* L.] are a globally used and pharmacologically interesting botanical drug, however, with variable product quality.
Objective: We aim at understanding the chemical variability of primary material available commercially based on different origins and associated quality problems like contamination with heavy metals. This needs to be assessed in the context of the current regulations for this botanical drug and associated problems.
Material and Methods: 15 *C. indicum* L. and 50 C. x *morifolium* (Ramat.) Hemsl., including a range of geographical cultivars recognized in China, samples from the USA, Europe and China were analyzed using High Performance Thin Layer Chromatography (HPTLC) to compare their general chemical profile. Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) was used to quantify heavy metal contamination.
Results: The: HPTLC fingerprints of *C. indicum* samples are clearly distinguishable from *C.* x *morifolium*. Fingerprints of samples from the same cultivars collected from markets in different countries (USA and China) show different patterns. Large variance of fingerprints within each cultivar group was observed. The heavy metal analysis showed excessive amounts of some harmful heavy metal in some commercial products with excessive cadmium being the most frequent problem.
Conclusions: The Chinese medicinal cultivars vary. Differences between samples sourced from the USA and China might be ascribable to geographical factors (e.g. soil composition), degradation during transport/storage or adulteration, but geographical differences should also be taken into account. Importantly, a much more detailed definition of the drug are needed for better quality control. In addition, with continuous contamination problem observed, a more widespread regulation is an essential requirement for better quality.

1. Introduction

As one of the largest plant families, the taxonomy and systematics of the *Asteraceae* Bercht. & J.Presl is still under intensive discussion (Beentje et al., 1994; Heywood, 2007; Giberti, 2018). *Chrysanthemum* L., as one of its genera, also has a very complicated taxonomy. Many studies showed different pharmacological activities of the four most commonly used species, *Ch.* × *morifolium* (Ramat.) Hemsl., *Ch. indicum* L., *Ch. lavandulifolium* Makino and *Ch. zawadskii* Herbich (Table 1), consulting two interconnected botanical databases, POWO (Plants of the World Online) (Royal Botanic Gardens, 2021) and the MPNS (Medicinal Plant Name Service) (Royal Botanic Gardens, 2020), information on uses, pharmacological activities and geographical. *Ch. morifolium* (Ramat.) Hemsl. (*C.* x *morifolium*) and *C. indicum* L. (*C. indicum*) are two of the most widely used species important as a food (tea) and medicine included in some pharmacopoeias (Youssef et al., 2020; Shahrajabian, 2019). However, differences among pharmacopoeias concerning the herbal ingredient 'Chrysanthemum flower' (ChF) result in ambiguities. Most Asian pharmacopoeias, such as The Chinese Pharmacopoeia (2020c, 2020d), The Japanese Pharmacopoeia (2016a), The Korean Herbal Pharmacopoeia (2012) and The Ayurvedic Pharmacopoeia of India (Government of India, 2008), report this herbal ingredient, but the species accepted under this definition differ, some only accept *C.* x *morifolium*, while others accept both *C.* x *morifolium* and *C. indicum* (Table 2). In addition to the two species recorded as 'Chrysanthemum flower' in some pharmacopoeias, in the

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Table 1
Four commonly used *Chrysanthemum* species - a summary of their use, distribution (data from POWO), and number of recorded sources covered in MPNS on medicinal plant resources.

Scientific name	Parts used	Use	Distribution	Number of recorded sources (MPNS)	References
Chrysanthemum indicum L.	Capitulum / flower	Food / medicine Anti-inflammatory, antibacterial, anti-oxidation, immune regulation, anti-tumor, regulation of cardiovascular function, etc.	Native to: East Asia	24	Shao et al., 2020
Ch. lavandulifolium Makino	Flower, leaf, stem	Food / medicine Antioxidant, anti-melanosis, promote keratinocyte proliferation and promote skin regeneration	Native to: East Asia (China to Japan)	7	Jang et al., 1998; Kim et al., 2003; Kim et al., 2015a & 2015b; Kim et al., 2018
Ch. × *morifolium* (Ramat.) Hemsl.	Capitulum / flower / inflorescence, leaf	Food / medicine Antioxidant, antibacterial, anti-inflammatory, hepatoprotective, immune regulatory, anti-tumor, anti-melanosis, anti-virus, anti-aging, fatigue resistance, anti-genotoxicity, anti-ulcer, anti-plasmodium and promotion of cholesterol metabolism	Native to: Southeast China	32	Youssef et al., 2020; Yuan et al., 2020
Ch. zawadskii Herbich	Whole dried plants, dried aerial parts, leaf	Food / medicine Anti-inflammatory, antibacterial, anti-oxidative stress, hepatoprotective, anti-osteoarthritic, hypoglycemic, anti-adipogenic, hair growth promoting	Native to: Central, East, North Europe and East Asia	1	Begum et al., 2015; Byun et al., 2020; Kim and Kim, 2014; Kim et al., 2017; Kim et al., 2018; Kim et al., 2019; Kim et al., 2020; Li et al., 2014; Park et al., 2016; Wu et al., 2011

Chinese Pharmacopoeia they are separated as 'Chrysanthemum flower' and 'Wild Chrysanthemum flower', respectively. The Chinese Pharmacopoeia (2020c) also divides 'Chrysanthemum flower' into five groups based on the regions of origin, i.e. 'Bo' (亳), 'Chu' (滁), 'Gong' (贡), 'Hang' (杭) and 'Huai' (怀). These are based on the main production zones and differentiate the geographical cultivars on the basis of their macromorphology, as well as processing methods. Importantly, The European Pharmacopoeia (The Council of Europe, 2016a), British Pharmacopoeia (2018) and The United States pharmacopeia 35-The National formulary 30 (2011a) do not have a monograph on this botanical drug (Table 2), but proposals for its introduction are in progress.

Though ChF crude drug can be easily found on the market, especially in Asian countries, quality problems, such as adulteration with other species and severe heavy metal contamination have been reported multiple times (Lal et al., 2008; Liu et al., 2003; Nie et al., 2013; Zhang et al., 2019; Zuo et al., 2020). The situation relating to different geographical cultivars adds to this problem since their chemical profile and medical benefits remain poorly understood (Abid et al., 2020; Chen et al., 2019).

In general, ChF was widely used as herbal drug but in taxonomic terms, the reported definition remains highly ambiguous a variety of quality problems were reported. In order to understand and improve quality of commercial ChF product, an understanding of the variability of ChF herbal products on the global market is required (Booker and Heinrich, 2016). This project aims to disentangle the complexity in definition of ChF, and find out deficiency in current quality regulation on ChF.

2. Ethnobotanical background

For over 2000 years, species from the genus *Chrysanthemum* have been used in China. The first known record on ChF could be found in the *Shen Nong Ben Cao Jing* (Shang et al., 1993; Shao and Guo, 2009;

Table 2
'Chrysanthemum flower' records in some major pharmacopoeias.

Pharmacopoeias	Records of *Chrysanthemum* spp.
The Chinese Pharmacopoeia (2020c, 2020d)	*1. Chrysanthemum morifolium* (Ramat.) Hemsl. - as 'Chrysanthemum flower' - [divided into 5 medicinal cultivars: 'Bo', 'Chu', 'Gong', 'Hang' and 'Huai'] 2. *Ch. indicum* L. - as 'Wild chrysanthemum flower' (recorded separately)
The Japanese Pharmacopoeia (2016a)	*1. Ch. morifolium* Ramat. 2. *Ch. indicum* L. (both recorded under 'Chrysanthemum flower')
The Korean Herbal Pharmacopoeia (2012)	*1. Ch. morifolium* Ramat. 2. *Ch. indicum* L. (both recorded under '*Chrysanthemum flos*')
The Ayurvedic Pharmacopoeia of India (2008) (Government of India 2008)	*1. Ch. indicum* L.
The European Pharmacopoeia (2016a) (The Council of Europe 2016a)	-
British Pharmacopoeia (2018)	-
The United States pharmacopeia 35 -The National formulary 30 (2011a)	-

Wang et al., 2009), which is believed to be a compilation of oral traditions on medicinal plants, written around 200-250 C.E. Unfortunately, its original text has been lost. Herbals published later continuously showed written records of ChFs, but before the Song dynasty (960 - 1279 AD) little graphical representation was available. Most herbals only describe ChF as '季秋之月, 鞠有黄华', which means chrysanthemum flower are yellow flowers bloom in autumn, which is ambiguous. After the Song dynasty, morphology records of ChF began to show up, and display the record of ChF as herbal medicine in a clearer way. Shao and Guo, 2009 and Shang et al., 1993 pointed out that at first *Chrysanthemum* species used were mainly wild species, such as *C. indicum, C. lavandulifolium* and *C. zawadskii*, rather than the cultivated *C.* x *morifolium*. While it seems not possible to define the exact time of the first introduction or recording on *C.* x *morifolium*'s medicinal use, according to Wang et al., 2009, the appearance of *C.* x *morifolium*'s medicinal uses during the Song dynasty might be linked to the rise of *Chrysanthemum* cultivation in that period. People hybridized different species to cultivate chrysanthemum flowers with different characters meeting different needs, such as decoration, food or medicine. In addition, since hybrids are less stable, this artificial hybridization gave rise to the variety within *C.* x *morifolium*. The first depiction of ChF can be dated to 1116 CE (Fig. 1) including Tang, 2013; Zhu, 2008; Liu, 2005; Li, 2005; Chen and Zhang, 2009; Li, 2007; Ni, 2005; Chen, 2015; Wu, 2018 and Zhang, 1958, arranged chronologically, based on their original publishing date (and using recent re-editions of these works). With the development of Chrysanthemum cultivation, more and more graphical depictions could be found, generally showing a variety in the appearance of ChFs. The morphology depicted in the herbals changes over time. The most noticeable difference is a change in the size of ChFs' flower heads in the drawings throughout history. This assessment is similar to the ones by Shang et al., 1993, Shao and Guo, 2009 and Wang et al., 2009: At first mainly wild species *Chrysanthemum* species were used and then cultivars were developed,. According to the information collected from ancient Chinese herbals and other historical reviews from Shang et al., 1993, Shao and Guo, 2009 and Wang et al., 2009, it is likely that 'ChF' has in fact changed its identity over time, depending on the development, popularity and availability of different *Chrysanthemum* species. In the beginning, *C.* x *morifolium*'s potential uses esp. as medicines have not been recorded widely. Around the publication in 1612 of the 'Ben cao shi yuan', *C.* x *morifolium* began its 'career' as a medicinal species. In conclusion, with the development of cultivation, *C.* x *morifolium*, as a hybrid species, had the opportunity to thrive and differentiate.

It would also be interesting to look at the ethnobotany of ChF in other Asian countries, e.g. Japan and KoreaHowever, because of language limitation, the authors only look at Chinese herbals.

3. Material and methods

3.1. Botanical materials

Sixty-three commercial crude drug samples were purchased from different suppliers including Chinese online stores, such as Tmall and Taobao, two online herbal retailers (Phoenix Medical Ltd. based in the UK and Shen Zhou based in the Netherlands), local herbal markets in the U.S.A. and a local herbal retailer in London (UK). Additionally, some companies, such as Sun Ten Pharmaceutical Co., Ltd. and American Herbal Pharmacopoeia (AHP), kindly contributed to the sample collection. Overall, the collection includes 6 Taiwanese, 21 Chinese, 23 US-American, and 13 European samples. Two botanical standards, crude drug powders of authenticated *C.* x *morifolium* (Ramat.) Hemsl. and *C. indicum* L., were purchased from Beijing Laiyao Biotech Company (http://www.gjbzwz.com). All samples are deposited in the UCL School of Pharmacy Herbarium. Sample information, such as collection site, drying method and supplier, were collected when available (for detailed sample information list see the supplementary material - Table A.1).

3.2. Solvents, reagents and chemicals

3.2.1. Chemicals

Glacial acetic acid, *p*-anisaldehyde, *n*-butyl acetate, ethyl formate, formic acid, sulfuric acid, tetramethylsilane (TMS, NMR grade) and

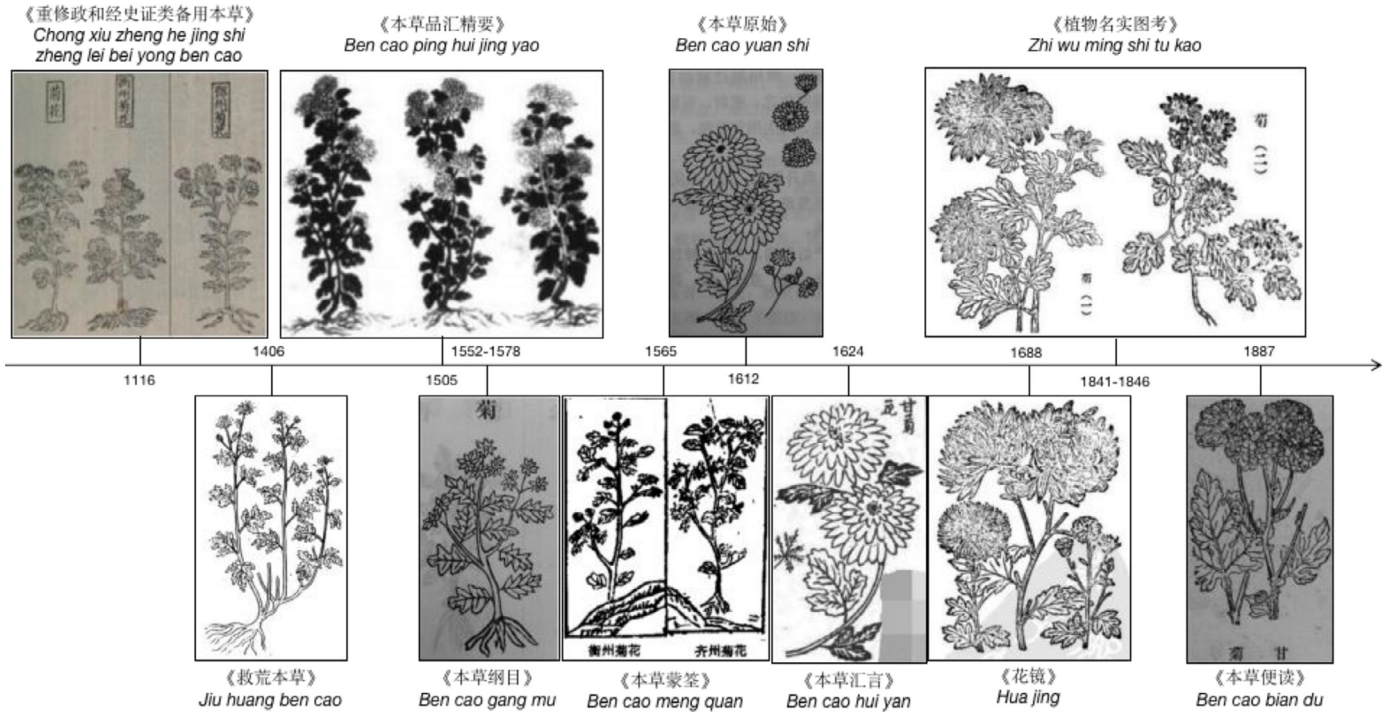


Fig. 1. Paintings of 'chrysanthemum flowers' in ancient Chinese herbals through Chinese history (Paintings gathered by Jingyi Gu).

Table 3
Heavy metal quality limitations of different pharmacopoeias for 'chrysanthemum flower' or herbal drugs in general.

		ChP2020	THP3rd	KP10th	Ph. Eur9th	JP17th	USP 39	FDA
Heavy metal limit (mg/kg)	Pb	5	5	5	5	Not Found	Not Found	Not Found
	Cd	1	1	/	1			
	As	2	3	3	/			
	Cu	20	/	/	/			

toluene were purchased from Acros, Belgium. 2-Aminoethyl diphenylborinate was purchased from Sigma-Aldrich, and methanol was purchased from Rotisolv HPLC Solvents, C. Roth, Karlsruhe, Germany.

HNO_3 supra quality (69%), HCl supra quality (35%) and 30% H_2O_2 were bought from C. Roth, Karlsruhe, Germany.

Deuterated methanol (MeOD) was purchased from Cambridge Isotope Laboratories.

3.2.2. Standards

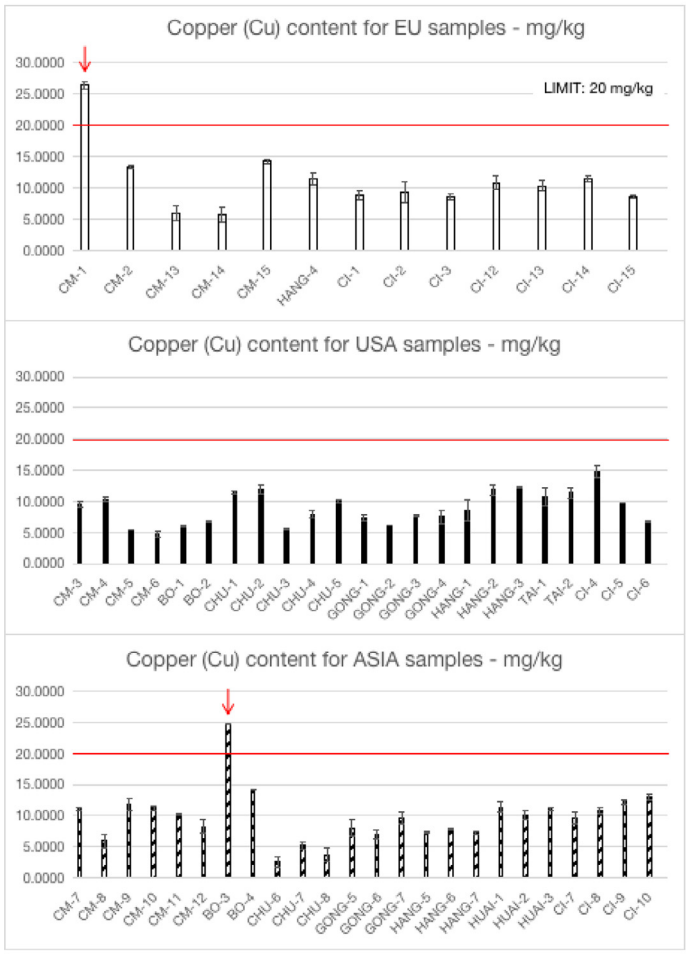
Chlorogenic acid (F0C420), luteolin-7-*O*-glucoside (Lot #B140471) and apigenin-7-*O*-glucoside (lot F) were obtained from the United States Pharmacopoeia (USP). 3.5-di-*O*-caffeoylquinic acid and linarin were obtained from Extrasynthese, while Universal HPTLC mix (UHM), a pre-defined mixture of eight reference substances: guanosine, sulisobenzone, thymidine, paracetamol, phthalimide, 9-hydroxyfluorene, thioxanthen-9-one, and 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol, was obtained as a 'ready to use' solution from Sigma-Aldrich.

3.3. Methodology

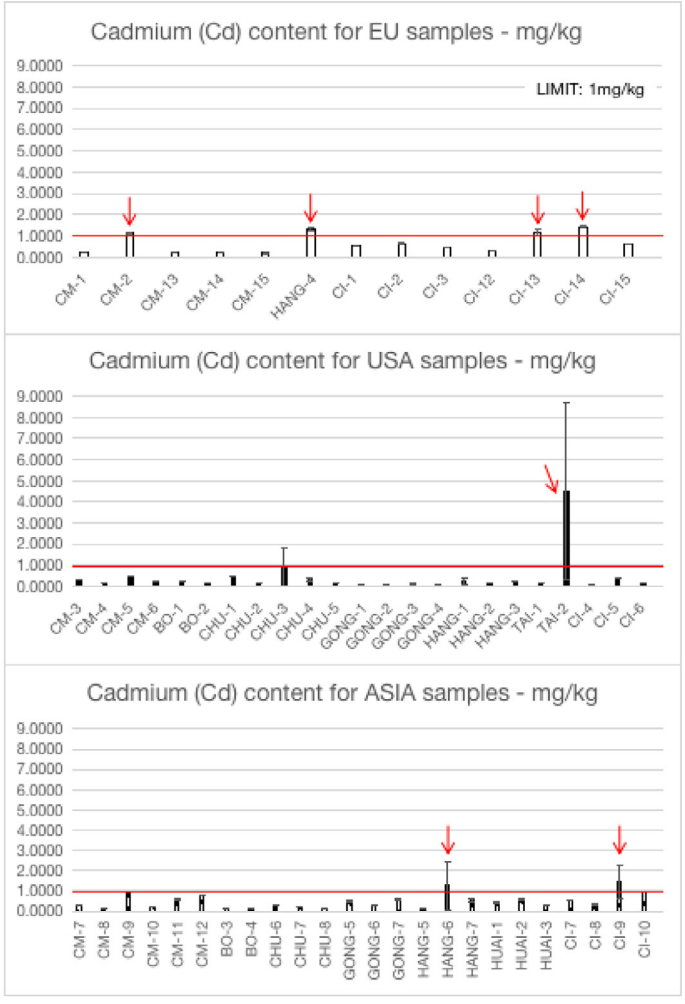
3.3.1. High performance thin layer chromatography (HPTLC)

Standards were prepared in methanol at a concentration of 1 mg/ml (apigenin-7-*O*-glucoside, luteolin-7-*O*-glucoside and linarin) or 2.5 mg/ml (chlorogenic acid and 3.5-di-*O*-caffeoylquinic acid). Samples were prepared as described below according to the unpublished proposal of the European Directorate for the Quality of Medicines & Health Care (EDQM).

Each plant sample were grinded with an IKA tube mill, and the milled material were sieved through a 355 standard sieve. 0.5 g of powdered samples were extracted in 5 ml of 70% methanol (100.0 mg/ml), sonicated for 10 min, centrifuged or filtered and



(A) Content of copper in mg/kg



(B) Content of cadmium in mg/kg

Fig. 2. Individual heavy metal content in each sample (A) copper in mg/kg (B) cadmium in mg/kg.

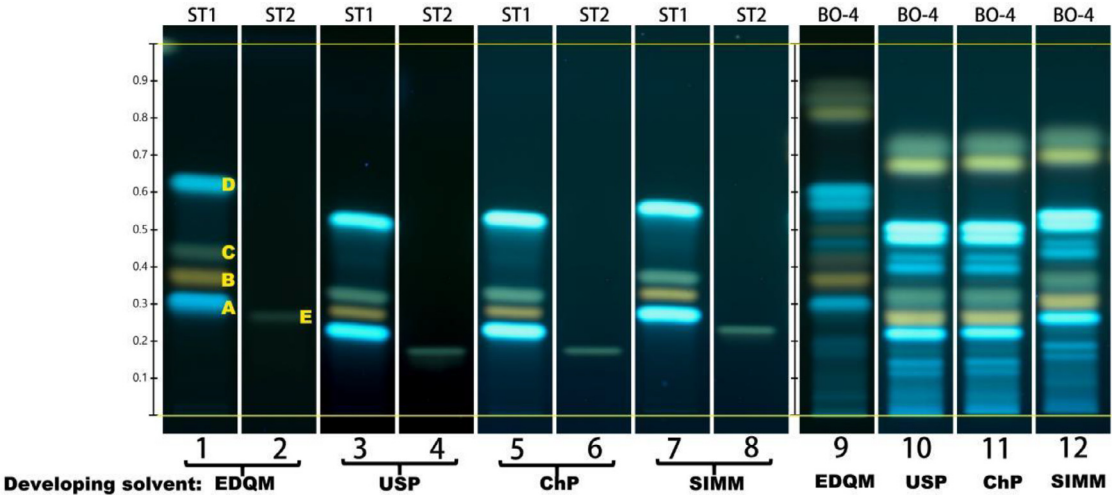


Fig. 3. A comparison of different mobile phases from different protocols, where A: chlorogenic acid; B: luteolin-7-O-glucoside; C: apigenin-7-O-glucoside; D: 3,5-dicaffeoylquinic acid; E: linarin.

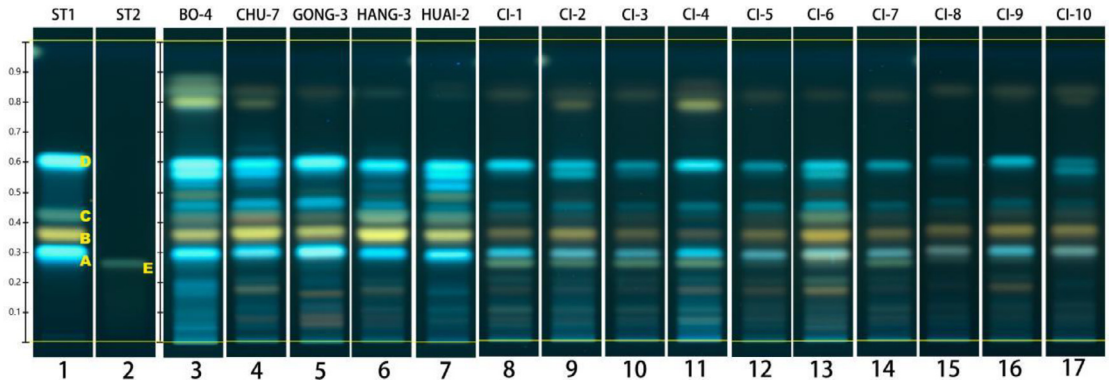


Fig. 4. A comparison of tracks based on intensity. Track 3-7 are exemplary samples of the four different *C.* x *morifolium* geographical cultivars; track 8-17 are samples of *C. indicum*.

used the supernatant or filtrate. 2.0 μl of UHM and 1.0 μl of standards or samples were applied to the plate (20 × 10 cm HPTLC glass plates Si60 F_{254}, Merck, Germany) using a CAMAG Automatic TLC Sampler 4. HPTLC followed The European Pharmacopoeia (2016a) general chapter 2.8.25 for plate layout and development. Development with ethyl formate, toluene, formic acid, water (30:1.5:4:3 v/v) and subsequent dried was performed in a CAMAG Automatic Developing Chamber 2. Fingerprints were documented under white light, UV 254 nm, and UV 366 nm using CAMAG Visualizer 2.

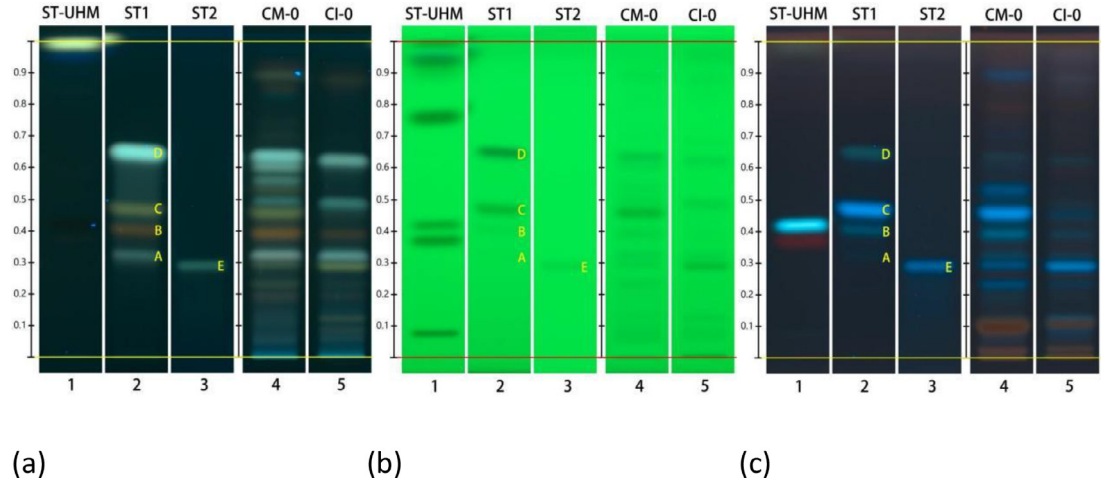


Fig. 5. Comparison of two botanical standards. (a) detection mode: 366 nm derivatized with NP reagent; (b) detection mode: 254 nm; (c) detection mode 366 nm derivatized with NP reagent and AS reagent. Tracks: 1) UHM 2) (ST1): chlorogenic acid, luteolin-7-O-glucoside, apigenin-7-O-glucoside and 3,5-dicaffeoylquinic acid (from bottom to top); 3) (ST2): Linarin; 4) botanical standard for C. x morifolium; 5) botanical standard for C. indicum.

Derivatization with the NP reagent was achieved by heating the plate at 100 °C for 3 min, then spraying 3.0 ml of reagent, using a CAMAG Derivatizer at level 3 with the green nozzle. The results were documented under white light and UV 366 nm. Anisaldehyde reagent preparation: 85 mL of ice-cooled methanol carefully mixed with 10 ml of acetic acid and 5 mL of sulfuric acid. After cooling to room temperature 0.5 ml of anisaldehyde are added. Anisaldehyde derivatization was carried out by spraying 3.0 ml of anisaldehyde reagent at level 3, with the blue nozzle. Then the plate was heated to 100°C for 3 min and visualized under white light, and UV 366 nm.

VisionCATS software version 3.1 was employed for chromatography and data acquisition and elaboration.

The UHM was applied to each plate as a System Suitability Test, ensuring that the chromatography was performed correctly and data can be compared across plates.

3.3.2. Heavy metal detection using ICP-OES

Preparations of standard solutions and samples: Sample preparation for ICP-OES followed the method reported by Kum et al, 2021. Flower head samples were ground into fine powder using a miller (Retsch Ltd.; ultracentrifugal mill ZM200, sieve 0.25 mm). 400.0 ± 1.0 mg of milled samples were placed in a 50 mL Teflon vessel and combined with 1 mL H_2O_2 (30%), 4 mL of HNO_3 (69%) and 9 mL of HCL (35%). The reaction mixture was digested according to ISO 16968 with a microwave (Anton Paar Ltd.; Multiwave GO 3000; digested at 190 °C for 20 min with a heat ramping by 12.6 °C min^{-1}). After cooling the digestion vessels, the samples were aliquoted to 50 mL with double distilled water and measured using the ICP-OES system (Ametek Ltd. Spectro; Spectroblue TI with a Cetac Ltd. autosampler ASX-260).

Statistical analysis: Four replications for each ChF sample were conducted. The average amount of each detected heavy metal in each ChF samples were compared, and the standard deviation was calculated.

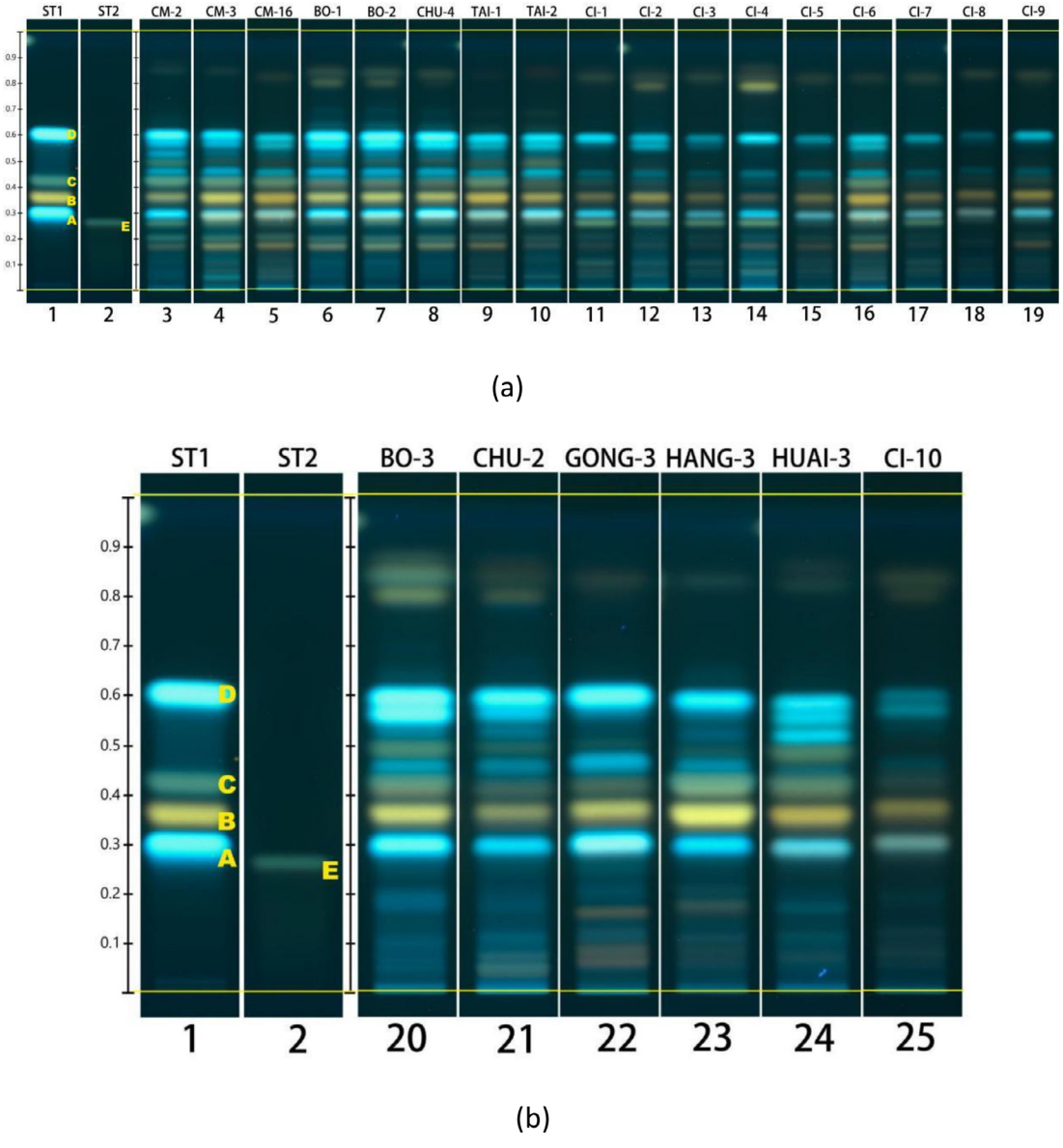


Fig. 6. (a) Tracks contain reference standard E (linarin). Tracks 3-10 are *C.* x *morifolium* samples while tracks 11-19 are *C. indicum*'s. (b) Representative tracks do not contain reference standard E (linarin). Track 20-24 are *C.* x *morifolium* samples while tracks 25 is *C. indicum*'s.

Fig. 7. Morphology of ChF samples labeled with the same geographical cultivar name under *C.* x *morifolium* (images: Jingyi Gu).

4. Results and discussion

4.1. Heavy metal detection using ICP-OES

Different pharmacopoeias stipulate different limits for heavy metals in ChF or herbal drugs in general (Table 3). Among 31 trace elements detected, Pb, Cd, As and Cu are the four heavy metals that have limits reported in some pharmacopoeias, such as The Chinese Pharmacopoeia, 2020f. Some pharmacopoeias, including The Taiwan Herbal Pharmacopoeia (Ministry of Health and Welfare 2018); The Korean Pharmacopoeia, 2012 and The European Pharmacopoeia (The Council of Europe, 2016b) report limits for only two or three of these four elements. In other pharmacopoeias, e.g. The Japanese Pharmacopoeia, 2016b and USP35-NF30, 2011b no well-defined limits are reported. The Keller and Heckman LLP.'s resource (accessed 7th June 2021) (Keller and Heckman, 2021) shows that even though USA Food and Drug Administration (FDA) reports As and Pb limits on drinking water and apple juice, its limitation for ChF products or any other herbal materials are not defined. Other studies (Abid et al., 2020; Chen et al., 2019; Lal et al., 2008; Nie et al., 2013; Zhang et al., 2019) on the heavy metal contamination in ChF mainly focused on Cd, As, Pb, Hg and Cu (in this project, detection of Hg was not possible due to a machine fault).

Results obtained for Pb, Cd, As and Cu content in 60 samples were assessed in detail. Fig. 2 (A-B) shows the content of copper and cadmium, while Table A.2 (in appendix) lists the amount of arsenic and lead in each sample.

All samples studied are under the limit for arsenic and lead contamination, and most samples contain undetectable to very low levels of arsenic or lead. On the other hand, samples with excessive amounts of heavy metal could be observed for both copper and cadmium (Fig. 2). Based on the ChP's threshold of 20 mg/kg, 2 out of 60 samples exceed the limit. Both samples belong to *C.* x *morifolium*, one purchased from the Chinese market and one from the European market.

The most serious problem detected relates to the cadmium content. With the limit for cadmium being 1 mg/kg based on several pharmacopoeias, 7 out of 60 samples show an excessive amount of cadmium, resulting in the highest rate of non-compliance among the four selected trace elements. Four of the samples came from the European market, two from China and one from the USA. Most samples contained 1–2 mg/kg cadmium, except sample TAI-2 which has a significantly higher amount of cadmium (4.5 mg/kg). TAI-2 is a special ChF product, which contains the dried flower buds, rather than the fully blossoming flowers of *C.* x *morifolium*, and this specific sample came from the USA.

As reported (Abid et al., 2020; Chen et al., 2019; Lal et al., 2008; Nie et al., 2013), ChF shows a particular preference for the accumulation of cadmium over other heavy metals and geographic differences was observed in the ability of cadmium absorption. Our study showed a higher number of samples above the accepted limits for cadmium in *C. indicum* (20%), than in *C. x morifolium* (9%). Samples from the USA show the lowest incidence (4%), compared to samples collected from the Chinese (8%) and European (31%) markets. However, the sample pool is not large enough to come to any definitive conclusion. Further studies with a larger number of samples are needed to endorse these findings.

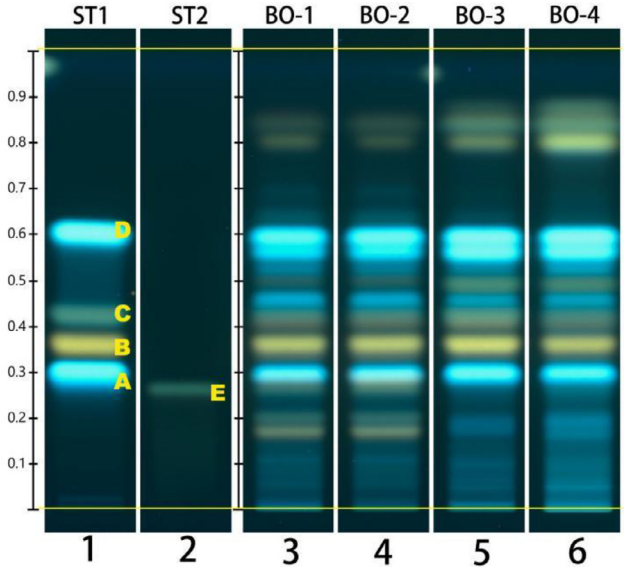


Fig. 8. HPTLC results of geographical cultivar 'Bo'. Track 3 and 4 are samples collected from the American market, track 5 and 6 are samples collected from the Chinese market.

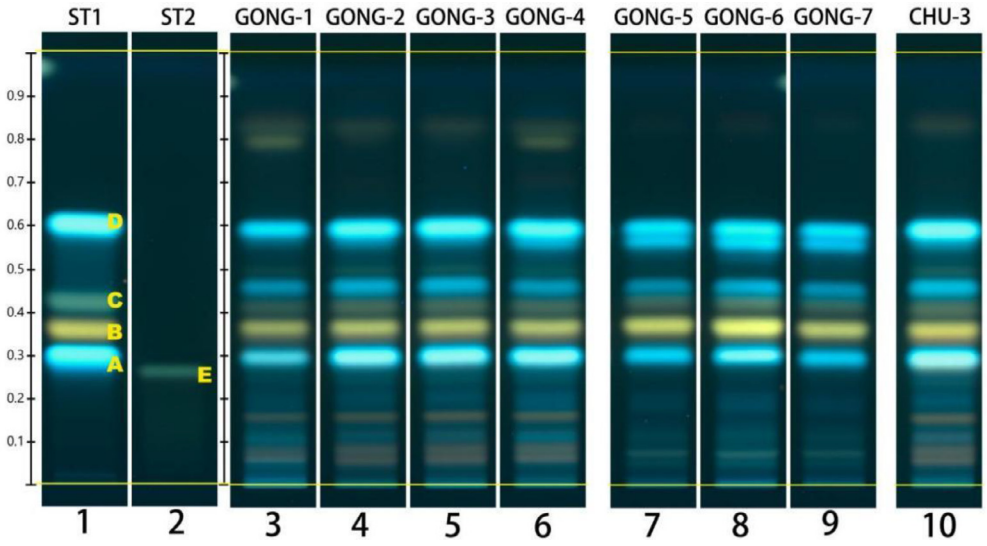


Fig. 9. HPTLC results of geographical cultivar 'Gong'. Track 3-6 are 'Gong' samples collected from the USA market, track 7-9 are 'Gong' samples collected from the Chinese market. Track 10 is the geographical cultivar 'Chu'.

4.2. Comparison of chemical fingerprints using HPTLC

For the HPTLC analysis of the 65 samples, including the two botanical standards, four different mobile phases were tested. This is based on different recommended protocols: ethyl formate, toluene, formic acid and water (30:1.5:4:3 v/v) according to the European Directorate for the Quality of Medicines and HealthCare (EDQM); *n*-butyl acetate, formic acid and water (15:8:8 v/v) upper phase, according to the USP; *n*-butyl acetate, formic acid and water (2:1:1 v/v) upper phase according to the Chinese Pharmacopoeia; *n*-butyl acetate, formic acid and water (7:5:5 v/v) upper phase, according to the Shanghai Institute of Materia Medica (SIMM).

The results obtained with the EDQM mobile phase show lower intensity (see Fig. 3), but best separation, compared to those obtained with the USP, ChP and the SIMM mobile phases. Therefore, the EDQM method was chosen for the conduction of this study.

As shown in (Fig. 4), overall, C. indicum samples have a relatively lower intensity compared to C. x morifolium samples especially sample CI-3, CI-5, CI-8 and CI-10. After purchase, contamination with live insects was observed for sample CI-8 and CI-10 (sealed packages). Therefore, the contamination took place before or during packaging. With unknown health risk and obviously being revolting to consumers, these products are simply defective and unacceptable. Comparing the samples with the botanical standards of C. x morifolium and C. indicum (Fig. 5), lower intensity for C. indicum can also be observed Therefore, in general, the quality of C. indicum seems to be poorer than C. x morifolium.

All samples contain chlorogenic acid, luteolin-7-O-glucoside, apigenin-7-O-glucoside and 3,5-dicaffeoylquinic acid (references A-D), but only C. indicum samples generally contains, linarin (E; Fig. 6). Of note, linarin is recorded in The Chinese Pharmacopoeia, 2020d as a standard for C. indicum, but some C. x morifolium samples (Fig. 6)

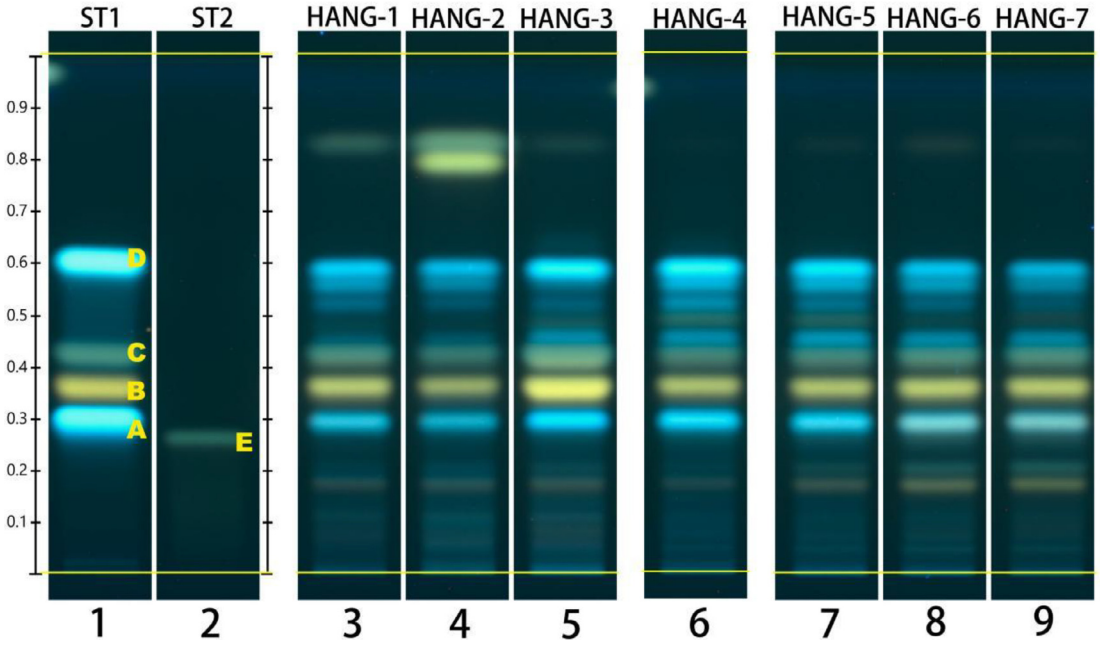


Fig. 10. HPTLC results of geographical cultivar 'Hang'. Track 3-5 are samples collected from the U.S.A. market, track 6 is the sample purchased from a retailer in UK, track 7-9 are samples collected from the Chinese market.

and the botanical standard of C. x morifolium (Fig. 5) also contain linarin. Therefore, based on this analysis, linarin cannot be used as a characteristic compound for the unequivocal identification of C. indicum. However, the fingerprints of the two species are distinctly different and a few positive markers are detectable in many samples of C. x morifolium (apigenin-7-O-glucoside, green zone at Rf 0.5, Fig. 5).

The morphology of collected ChF samples, labeled with the same geographical cultivar name under *C.* x *morifolium,* differ from each other (Fig. 7). Therefore, it is hard to distinguish different geographical cultivars, no unique band could be identified for any particular geographical cultivar, and more samples of each kind are required. However, by comparing the similarities and differences among the same geographical cultivar, some geographical differences could be observed for *C.* x *morifolium* geographical cultivar 'Bo', 'Gong' and 'Hang'.

'Bo' samples from the USA (Fig. 8), have only two bands with lower intensity at Rf≅0.8, while the Chinese samples show three bands with stronger intensity. Chinese samples also have a stronger intensity for bands at Rf ≅ 0.5. Finally, it could be noticed that USA samples have two bands at Rf ≅ 0.2 which are either not present in the Chinese ones or have lower intensity.

Looking at geographical cultivar 'Gong' (Fig. 9), samples from the USA show one or two bands at the top (Rf≅0.8), while Chinese samples do not have these bands or have too low intensity to be visible. Additionally, the USA samples do not have a band below the one of 3,5-dicaffeoylquinic acid (ref. D), or with low intensity, while the Chinese samples clearly show such a band. Finally, three to four orange/brown bands are visible in the bottom fourth of the tracks of USA samples. However, these bands are missing in the tracks belonging to samples from China. These orange/brown bands are not characteristic of geographical cultivar 'Gong' only, as they can be found in a sample of geographical cultivar 'Chu'.

Regarding geographical cultivar 'Hang' (Fig. 10), one sample from the European market does not show much difference from the Chinese samples. However, the difference between the USA and Chinese samples can be observed clearly. USA samples show stronger intensity of the bands at the top (Rf≅0.8), and slightly lower intensity for the bands at bottom.

Importantly, the overall number of samples collected and analyzed for each geographical cultivar provides some new insights into their chemical characteristics, but it is too low for the results to be representative and thus preliminary.

5. Conclusion

Variability is, of course, a general feature of biological diversity. In the context of medicinal plants, the situation is exacerbated by the complex use patterns (in this case as food and medicine) and the creation of a wide range of cultivars (Booker et al., 2016; Lei et al., 2021; Chinese Pharmacopoeia, 2020e). The botanical drugs used today is an outcome of centuries of hybridization and cultivation, e.g. genus *Nerine* (Cahlíková et al., 2019), genus *Dendrobium* (Chinese Pharmacopoeia, 2020a), *Citrus* reticulata (Chinese Pharmacopoeia, 2020b), etc. Interestingly, the species are both ornamentals and used as a food/medicine. Their historical development as ornamentals has also impacted on the species use as food/medicine. C. x *morifolium*, as a cultivated hybrid, has become popular, compared to the three wild species used originally. The variety and chemical complexity within *C.* x *morifolium* has also increased with the development of numerous cultivars, resulting in problems with their characterization and differentiation. In the future and with the development of artificial hybridization, this chemical complexity is likely to increase.

With severe cadmium contamination detected in a small but relavant number of samples, it is evident that more stringent regulations, more frequent testing of heavy metal content, and better supply chain management are needed to ensure product safety.

The HPTLC results showed the likely existence of geographical differences for the collection sites of *C.* x *morifolium* samples possibly related to the complexity and variety of *C.* x *morifolium* and highlighting its challenges in quality control. A regulatory framework defining the different medicinal geographical cultivars of *C.* x *morifolium* is needed. The current study showed well-defined chemical differences between *C.* x *morifolium* and *C. indicum*, with a presence of linarin in most but not all samples of *C. indicum.* Clearly, these two species need to be separate in the international trade and any research. Based on our work this is feasible. Monographs on chrysanthemum flowers are needed in pharmacopoeias, focusing on distinction of the two main species and general quality control.

Despite the numerous studies showing strong pharmacological activities (Table 1), not many comprehensive or reliable reviews on the genus *Chrysanthemum* can be found. While there are reviews looking at single species, either *C.* x *morifolium* (Yuan et al., 2020) or *C. indicum* (Shao et al., 2020), they only focus on the Chinese market, but neglect the popularity of chrysanthemum products on the global market. This study gives the first detailed overview of chrysanthemum products from the global market, highlighting some of the quality issues and the complexity of the genus *Chrysanthemum.*

However, our sample pool is too small to be statistically significant. Quality differences examined might also be caused by different processing methods, conditions during transport or adulteration and not so much by geographical origin. Any specific or unique HPTLC fingerprint could not be found for medicinal cultivars of *C.* x *morifolium*. Therefore, further studies with a larger sample size should be conducted in order to better define the starting material. Also, the present study has examined only two species: *C.* x *morifolium* (including five recognized but poorly defined geographical cultivars) and *C. indicum*. Similar studies including other species are needed to better understand the common characteristics and the differences among commercially used species and geographical cultivars of *Chrysanthemum*. Last but not least, the samples collected in this study are all for medicine / tea purpose. However, based on our ethnobotanical review, ChF are also widely used as ornamental plants, especially for *C.* x *morifolium*. It is essential to explore characters for ChF used for different purpose to help sharpen regulation.

More generally, this comparative analysis of geographical cultivars and species sheds light on the biological and chemical complexity of cultivated plants with a diverse usage, in this case as an ornamental and a medicine / tea plant, highlighting the need for characterizing the material used in these different commercial sectors more precisely.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices

Table A.1
Detailed sample information on collection site / production zone, processing method and supplier.

Sample No.	Scientific name	Labelled Name	Collection Site	Drying Method	Supplier
CI-0	*Chrysanthemum indicum L.*	Ye Ju Hua	/	/	CN - http://www.gjbzwz.com
CI-1	*Ch. indicum L.*	Ye Ju Hua	Hebei Hauadu	Bake drying	UK - Pheonix
CI-2	*Ch. indicum L.*	Ye Ju Hua	/	/	UK - TRT
CI-3	*Ch. indicum L.*	Ye Ju Hua	Anhui	/	Holland - Shenzhou
CI-4	*Ch. indicum L.*	Ye Ju Hua	/	/	USA - AHP
CI-5	*Ch. indicum L.*	Ye Ju Hua	/	/	USA - AHP
CI-6	*Ch. indicum L.*	Ye Ju Hua	An hui	Bake drying	CN - Kang Mei (Tmall)
CI-7	*Ch. indicum L.*	Ye Ju Hua	An hui - Bo zhou	Bake drying	CN - Hui Yang Tang (Tao bao)
CI-8	*Ch. indicum L.*	Ye Ju Hua	An hui - Liu an - Da bie mountain	Sun-drying	CN - Song Cao Tang (Tao bao)
CI-9	*Ch. indicum L.*	Ye Ju Hua	Xin jiang	Bake drying	CN - Jia Yan (Tao bao)
CI-10	*Ch. indicum L.*	Ye Ju Hua	An hui - Liu an - Da bie mountain	Sun-drying	CN - He Yun Tang (Tao bao)
CI-11	*Ch. indicum L.*	Ye Ju Hua	/	/	EU - Erich Stoeger
CI-12	*Ch. indicum L.*	Ye Ju Hua	/	/	EU - Erich Stoeger
CI-13	*Ch. indicum L.*	Ye Ju Hua	/	/	EU - Erich Stoeger
CI-14	*Ch. indicum L.*	Ye Ju Hua	/	/	EU - Erich Stoeger
CI-0	*Ch. indicum L.*	Ju Hua	/	/	CN - http://www.gjbzwz.com
CM-1	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	Hebei Hauadu	Bake drying	UK - Pheonix
CM-2	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	Anhui	/	Holland-Shenzhou
CM-3	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	USA-AHP
CM-4	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	USA-AHP
CM-5	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	USA-AHP
CM-6	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	processed with sulphur dioxide	USA-AHP
CM-7	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-8	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-9	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-10	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-11	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-12	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	CN - Sunten
CM-13	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	EU - Erich Stoeger
CM-14	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	EU - Erich Stoeger
CM-15	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	EU - Erich Stoeger
CM-16	*Ch. × morifolium (Ramat.) Hemsl.*	Ju Hua	/	/	USA - AHP
BO-1	*Ch. × morifolium (Ramat.) Hemsl.*	Bo Zhou Hua	Brentwood, CA	/	USA-AHP
BO-2	*Ch. × morifolium (Ramat.) Hemsl.*	Bo Zhou Hua	Petaluma, CA	/	USA-AHP
BO-3	*Ch. × morifolium (Ramat.) Hemsl.*	Bo Ju	An hui - Bo zhou	Sun-drying	CN - Ying Hui Tang (Tao bao)
BO-4	*Ch. × morifolium (Ramat.) Hemsl.*	Bo Ju	An hui - Bo zhou	Bake drying	CN - An Hui Guang He (Tao bao)
BO-5	*Ch. × morifolium (Ramat.) Hemsl.*	Bo Ju	An hui - Bo zhou	Bake drying	CN - Ye Xiao Fei (Tao bao)
CHU-1	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	/	/	USA-AHP
CHU-2	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	Petaluma, CA	/	USA-AHP
CHU-3	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	/	/	USA-AHP
CHU-4	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	Santa Cruz, CA	/	USA-AHP
CHU-5	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	Petaluma, CA	/	USA-AHP
CHU-6	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	An hui - Chu zhou	Bake drying	CN - Huan Chu Quan Jiao (Tao bao)
CHU-7	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua (Sa)	An hui - Chu zhou	Bake drying	CN - Huan Chu Quan Jiao (Tao bao)
CHU-8	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	An hui - Chu zhou	Sun-drying	CN - Hong Fu (Tao bao)
CHU-9	*Ch. × morifolium (Ramat.) Hemsl.*	Chu Ju Hua	An hui - Chu zhou	Bake drying	CN - An Hui Ju Tai (Tao bao)
GONG-1	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	Petaluma, CA	/	USA-AHP
GONG-2	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	Santa Cruz, CA	/	USA-AHP
GONG-3	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	Santa Cruz, CA	/	USA-AHP
GONG-4	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	Petaluma, CA	/	USA-AHP
GONG-5	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	An hui	Bake drying	CN - Kang Mei (Tmall)
GONG-6	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	An hui - Huang shan - She xian	Bake drying	CN - TRT (Tmall)
GONG-7	*Ch. × morifolium (Ramat.) Hemsl.*	Gong Ju Hua	An hui - Huang shan	Bake drying	CN - Chen Yi Fan (Tao bao)
HANG-1	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Ju Hua	Santa Cruz, CA	/	USA-AHP
HANG-2	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Ju Hua	Santa Cruz, CA	/	USA-AHP
HANG-3	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Ju Hua	/	peocessed with solfites	USA-AHP
HANG-4	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Bai Ju	/	/	UK-TRT
HANG-5	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Bai Ju	Zhe Jiang	Bake drying	CN - Kang Mei (Tmall)
HANG-6	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Ju Hua	Zhe Jiang	Sun-drying	CN - TRT (Tmall)
HANG-7	*Ch. × morifolium (Ramat.) Hemsl.*	Hang Ju Hua	Zhe Jiang	Bake drying	CN - TRT (Tmall)
HUAI-1	*Ch. × morifolium (Ramat.) Hemsl.*	Huai Ju (white)	He nan	Sun-drying / Bake drying	CN - Xin Cheng (Tao bao)
HUAI-2	*Ch. × morifolium (Ramat.) Hemsl.*	Huai Ju (yellow)	He nan	Sun-drying / Bake drying	CN - Xin Cheng (Tao bao)
HUAI-3	*Ch. × morifolium (Ramat.) Hemsl.*	Huai ju	He nan	Bake drying	CN - Huai Huo Zhuang (Tao bao)
TAI-1	*Ch. × morifolium (Ramat.) Hemsl.*	Tai Ju Hua	/	/	USA-AHP
TAI-2	*Ch. × morifolium (Ramat.) Hemsl.*	Tai Ju Hua	/	/	USA-AHP

Table A.2
Arsenic and Lead content in each sample.

Species & Cultivar	Sample label	Arsenic (As) content mg/kg	Lead (Pb) content mg/kg
C. x morifolium cultivar 'Bo'	BO-1	0.0599	0.0000
	BO-2	0.0482	0.0000
	BO-3	0.3390	0.0000
	BO-4	0.5125	0.0000
C. x morifolium cultivar 'Chu'	CHU-1	0.3572	1.0629
	CHU-2	0.0739	0.0000
	CHU-3	0.1074	1.1443
	CHU-4	0.0153	1.3928
	CHU-5	0.0528	0.0000
	CHU-6	0.0663	0.0000
	CHU-7	0.0551	0.0000
	CHU-8	0.0513	0.0000
C. x morifolium cultivar 'Gong'	GONG-1	0.0475	0.0000
	GONG-2	0.0619	0.0000
	GONG-3	0.0550	0.0000
	GONG-4	0.0468	0.0000
	GONG-5	0.0000	0.4334
	GONG-6	0.0000	0.1628
	GONG-7	0.0000	0.0000
C. x morifolium cultivar 'Hang'	HANG-1	0.0000	0.0000
	HANG-2	0.0000	0.0000
	HANG-3	0.1087	0.0000
	HANG-4	0.0617	0.0000
	HANG-5	0.0390	0.0000
	HANG-6	0.1998	1.9355
	HANG-7	0.0119	0.2923
C. x morifolium cultivar 'Huai'	HUAI-1	0.1739	0.0000
	HUAI-2	0.1099	0.0000
	HUAI-3	0.2195	0.6925
C. x morifolium Flower bud	TAI-1	0.0423	0.0000
	TAI-2	0.4846	1.4026
Chrysanthemum indicum L.	CI-1	0.1819	0.4493
	CI-2	0.2650	1.1540
	CI-3	0.1482	0.0000
	CI-4	0.0941	0.0000
	CI-5	0.2397	0.0000
	CI-6	0.1900	0.2439
	CI-7	0.0178	0.0000
	CI-8	0.0532	0.0000
	CI-9	0.1297	0.0976
	CI-10	0.1536	0.0000
Chrysanthemum morifolium (Ramat.) Hemsl. - unlabelled	CM-1	0.1955	0.2373
	CM-2	0.1294	0.0000
	CM-3	0.3815	0.6001
	CM-4	0.1539	0.0000
	CM-5	0.0355	0.0000
	CM-6	0.1213	0.0000
	CM-7	0.2475	0.0000
	CM-8	0.0835	0.0000
	CM-9	0.0000	0.6437
	CM-10	0.0645	0.1327
	CM-11	0.4600	1.8094
	CM-12	0.0044	0.0000
	CM-13	0.1696	0.0000
	CM-14	0.1477	0.0000
	CM-15	0.2764	0.0000

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