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Analysis on the current quality standards of Chinese materia Medica used in COVID-19 prevention and treatment



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ABSTRACT

Purpose: Traditional Chinese medicine (TCM) has fully engaged and played an essential role in the prevention and treatment of Coronavirus Disease 2019 (COVID-19). This study compares relevant standards on high-frequency Chinese Materia Medica (CMM) used in this pandemic aiming at reaching a global consensus and ensuring the use of Chinese medicines safely.

Methods: 141 representative Chinese formulas and Chinese Patent Medicines from the National Protocol and the most of Provincial Protocols for controlling COVID-19 in China have been collected to statistical analyze the composition and characteristics of CMM. Among them, the domestic and international standards of 47 varieties with the frequency usage over 10 times were selected to compare their quality requirements in the mainstream pharmacopoeias and international standards.

Results: The quality requirements of used CMM for fighting COVID-19 on the terms of overall quality control, marker compounds, and safety indicators showed different patterns in these mainstream pharmacopoeias and international standards. The uniformed and scientific quality standards of CMM were urgently needed to promote global acceptance and trade.

Conclusions: These findings will provide evidence for building unified quality and safety standards that can adapt to the characteristics of CMM and promote international trade, and also will be stated that it is of the highest priority for ISO/TC 249 to formulate high-quality standards that consolidate international consensus to ensure quality and safety of the urgently needed CMM.

1. Introduction

Since the outbreak of Coronavirus Disease 2019 (COVID-19) in China in December 2019, in the absence of a specific Western medicine and vaccine, traditional Chinese medicine (TCM) has played an essential role in COVID-19 prevention and treatment in China. From the third trial version onwards of the seventh edition of *Diagnosis and Treatment Protocol for COVID-19* (the *National Protocol*) issued by the General Office of National Health Commission of China and State

Administration of TCM, it has been clarified that COVID-19 falls under the category of "pestilences" in TCM. In accordance with the treatment principle of abidance by individuality, locality and seasons and the *National Protocol*, China's provinces (autonomous regions and municipalities directly under the Central Government) have formulated and released regional-specific TCM treatment and prevention protocols based on regional characteristics (the *Provincial Protocol*) [1,2]. With the full play of the characteristics and advantages of TCM, integrated Chinese and Western treatment has achieved satisfactory result [3–6].

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It is widely acknowledged that TCM plays an important role and is one of the merits in the epidemic prevention and control. A press conference held on the effectiveness of TCM in the treatment of COVID-19 cases in Wuhan reported that clinical observation showed that TCM has proven to be effective in the treatment of over 90 % of all confirmed COVID-19 cases on the Chinese mainland, said a TCM official on March 24, 2020. Among these confirmed cases, 74,187 were given TCM products, accounting for 91.5 % of the total [7]. It was found that TCM helped to relieve the symptoms, reduce the progression from mild to severe and critical, increase recovery rate, decrease mortality rate, and bring the convalescent to normal body functions [8–11]. Meanwhile, we noticed that China has adopted the methods of integrating traditional Chinese medicine with western medicine which led to a better outcome of this pandemic.

As Chinese Materia Medica (CMM) played a key role in this pandemic, its standards on quality and safety are attracting more attentions from the public. ISO/TC 249 has accumulated rich experience in developing international standards on CMM and relevant monographs have been recorded in national pharmacopoeias which enable CMM to be used globally. In this study, we aimed at analyzing the above-mentioned standards on CMM to recognize the current challenges in the process of their development.

2. Materials and methods

141 representative formulas and Chinese Patent Medicines from the *National Protocol (the third trial version onwards of the seventh edition)* and the *main 25 Provincial Protocol of China* [1,2] were selected and the usage frequency of each herbal medicine was counted. There are 47 varieties of CMM with the usage frequency over 10 times. Their botanical origins, morphological identification, and qualitative identification, quantification of marker compounds, heavy metals and residual pesticides in the following mainstream pharmacopoeias and international standards were summarized and compared,

Chinese Pharmacopoeia (ChP),
The Japanese Pharmacopoeia (JP),
The Korean Pharmacopoeia (KP),
European Pharmacopoeia (EP),
U.S. Pharmacopoeia (USP),
U.S. Pharmacopoeia-Herbal Medicine Compendium (USP-HMC),
WHO monographs on selected medicinal plants, and
 ISO standards.

3. Results and discussions

3.1. Statistical analysis of Chinese Materia Medica used in the Chinese formulas and Chinese Patent Medicines for COVID-19 prevention and treatment

There are 231 varieties of CMM used in the 141 representative formulas and Chinese Patent Medicines, covering botanical medicines, mineral medicines, and animal medicines. Among them, botanical medicines account for 83.55 % (193 varieties), mineral medicines for 8.66 % (20 varieties) and animal medicines for 7.79 % (18 varieties), and the number varieties types between mineral medicines and animal medicines is close to each other. The CMM used in the formulas over 10 times account for 20.35 % (47 varieties), including 45 varieties of botanical medicines, one variety of mineral medicine, and one variety of animal medicine (Table 1).

The commonly used CMM are *Glycyrrhizae Radix et Rhizoma* (*gān cǎo*), *Armeniacae Semen Amarum* (*xìng rén*), *Gypsum Fibrosum* (*shí gāo*), *Scutellariae Radix* (*huáng qín*), *Forsythiae Fructus* (*lián qiào*), *Ephedrae Herba* (*má huáng*), *Lonicerae Japonicae Flos* (*jīn yín huā*), *Atractylodis Macrocephalae Rhizoma* (*bái zhú*), etc. The formulas for COVID-19 have been put forward combined with TCM theory and clinical practice, and the commonly used pairs of CMM are *Ephedrae*

Herba-Armeniacae Semen Amarum (*má huáng-xìng rén*), *Ephedrae Herba-Gypsum Fibrosum* (*má huáng-shí gāo*), *Agastachis Herba-Magnoliae Officinalis Cortex* (*huò xiāng-hòu pò*), *Lonicerae Japonicae Flos-Forsythiae Fructus* (*jīn yín huā-lián qiào*), *Lepidii Semen-Gypsum Fibrosum* (*tíng lì zǐ-shí gāo*).

3.2. Current situations of quality standards for CMM and comparative analysis

The quality standards of CMM is a key technical link for CMM to break the barriers of international trade and gain access to international markets. Under the framework of the globalization of CMM, with the ultimate goal to gain access to international markets, it is indispensable to promote internationalization of CMM by formulating a scientific, advanced and applicable system for quality standards with international recognition to effectively ensure efficacy and safety of CMM.

The current quality standards of the above selected 47 varieties of CMM in the mainstream pharmacopoeias and international standards are shown as follows.

3.2.1. Situation of the standards

3.2.1.1. *Situation of standards collected by the mainstream pharmacopoeias* [12–17]. All varieties of used CMM have corresponding quality standards in ChP, with more than 85 % collected in JP and KP but with fewer description in EP and USP/USP-HMC for 31.91 % and 25.53 %, respectively (Table 2).

3.2.1.2. *Situation of standards collected by WHO monographs and ISO* [18,19]. There are 14 varieties included in *WHO monographs on selected medicinal plants*, and 16 varieties included in ISO international standards. For ISO standards, 2 varieties of CMM, *Lonicerae Japonicae Flos* and *Scutellariae Radix* have been officially published, and 14 varieties are under development stage (Table 3).

3.2.1.3. *Situation of standards collected by the mainstream pharmacopoeias and international standards*. The standard of *Scutellariae Radix* is the only CMM that has been recorded in ChP, JP, KP, EP, USP, ISO and WHO monograph. The standards of *Glycyrrhizae Radix et Rhizoma*, *Ginseng Radix et Rhizoma*, and *Schisandrae Chinensis Fructus* have been recorded in ChP, JP, KP, EP, USP and WHO other than ISO.

3.2.2. Comparative analysis of the standards and current challenges

Based on the characteristics of CMM, the standards of the mainstream pharmacopoeias and international standards mainly focus on the safety issues of CMM, such as botanical origins, morphological identification, and qualitative identification, quantification of marker compounds, heavy metals and residual pesticides [11–18]. However, the mainstream pharmacopoeias and international standards have different emphases on standards in terms of overall quality control of CMM, selection of marker compounds, safety issues and others. Taking *Scutellariae Radix* as an example, the comparative analysis of the standards among the mainstream pharmacopoeias, ISO and other international standards is as follows (Table 4):

- 1) Apart from the basic contents such as botanical origins, morphological features, microscopic characteristics, qualitative identification, purity test, assay, and storage, etc. of the CMM, ChP has included other factors including nature, flavor and meridian distribution, functions and indications, usage and dosage; while ISO and USP standards elaborate on packaging, transportation and labeling.
- 2) Purity test includes moisture and total ash contents, but with differences in limit values of each standard.
- 3) The regulations and requirements on safety indicators such as heavy metals and residual pesticides showed a different pattern in these mainstream pharmacopoeias and international standards.

Table 1The Chinese Materia Medica of 141 representative formulas and Chinese Patent Medicines for COVID-19 prevention and treatment (usage frequency ≥ 10 times).

Rank	Botanical/mineral/animal Name	Pharmaceutical Name	Chinese Name	English Name	Frequency of use (times)
1	<i>Glycyrrhiza uralensis</i> Root and Rhizome/ <i>Glycyrrhiza inflata</i> Root and Rhizome/ <i>Glycyrrhiza glabra</i> Root and Rhizome	Glycyrrhizae Radix et Rhizoma	甘草	Licorice Root	66
2	<i>Prunus armeniaca</i> var. <i>ansu</i> Seed/ <i>Prunus sibirica</i> Seed/ <i>Prunus mandshurica</i> Seed/ <i>Prunus armeniaca</i> Seed	Armeniaca Semen Amarum	苦杏仁	Bitter Apricot Seed	43
3	Gypsum	Gypsum Fibrosum	石膏	Plaster	36
4	<i>Scutellaria baicalensis</i> Root	Scutellariae Radix	黄芩	Baical Skullcap Root	35
5	<i>Forsythia suspensa</i> Fruit	Forsythiae Fructus	连翘	Weeping Forsythia Capsule	34
6	<i>Poria cocos</i> Sclerotium	Poria	茯苓	Indian Bread	33
7	<i>Ephedra sinica</i> Stem/ <i>Ephedra intermedia</i> Stem/ <i>Ephedra equisetina</i> Stem	Ephedrae Herba	麻黄	Ephedra	33
8	<i>Citrus reticulata</i> Pericarp	Citri Reticulatae Pericarpium	陈皮	Dried Tangerine Peel	31
9	<i>Pogostemon cablin</i> Herb	Pogostemonis Herba	广藿香	Cablin Patchouli Herb	31
10	<i>Lonicera japonica</i> Flower	Lonicerae Japonicae Flos	金银花	Japanese Honeysuckle Flower	30
11	<i>Platycodon grandiflorum</i> Root	Platycodonis Radix	桔梗	Platycodon Root	28
12	<i>Pinellia ternata</i> Tuber	Pinelliae Rhizoma	半夏	Pinellia Tuber	28
13	<i>Magnolia officinalis</i> Bark/ <i>Magnolia officinalis</i> var. <i>biloba</i> Bark	Magnoliae Officinalis Cortex	厚朴	Officinal Magnolia Bark	26
14	<i>Ophiopogon japonicus</i> Root Tuber	Ophiopogonis Radix	麦冬	Dwarf Lilyturf Tuber	23
15	<i>Atractylodes macrocephala</i> Rhizome	Atractylodis Macrocephalae Rhizoma	白朮	Largehead atractylodes Rhizome	23
16	<i>Atractylodes chinense</i> Rhizome/ <i>Atractylodes lancea</i> Rhizome	Atractylodis Rhizoma	苍朮	Atractylodes Rhizome	22
17	<i>Rheum palmatum</i> Root and Rhizome/ <i>Rheum tanguticum</i> Root and Rhizome/ <i>Rheum officinale</i> Root and Rhizome	Rhei Radix et Rhizoma	大黄	Rhurbarb	21
18	<i>Astragalus membranaceus</i> var. <i>mongholicus</i> Root/ <i>Astragalus membranaceus</i> Root	Astragali Radix	黄芪	Milkvetch Root	20
19	<i>Phragmites communis</i> Trin. Rhizome	Phragmitis Rhizoma	芦根	Reed Rhizome/ Rhizome Phragmitis	19
20	<i>Panax ginseng</i> Root	Ginseng Radix et Rhizoma	人参	Ginseng	19
21	<i>Descurainia sophia</i> Seed/ <i>Lepidium apetalum</i> Seed	Descurainiae Semen/ Lepidii Semen	葶苈子	Pepperweed Seed/ Tansymustard Seed	17
22	<i>Schisandra chinensis</i> Fruit	Schisandrae Chinensis Fructus	五味子	Chinese Magnoliavine Fruit	17
23	<i>Anemarrhena asphodeloides</i> Rhizome	Anemarrhenae Rhizoma	知母	Common Anemarrhena Rhizome	15
24	<i>Paeonia lactiflora</i> Root/ <i>Paeonia veitchii</i> Root	Paeoniae Radix Rubra	赤芍	Red Peony Root	15
25	<i>Trichosanthes kirilowii</i> Seed/ <i>Trichosanthes rosthornii</i> Seed	Trichosanthis Semen	瓜蒌子	Snakegourd Seed	15
26	<i>Bupleurum chinense</i> Root/ <i>Bupleurum scorzonerifolium</i> Root	Bupleuri Radix	柴胡	Chinese Thorowrax Root	14
27	<i>Prunus persica</i> Seed/ <i>Prunus davidiana</i> Seed	Persicae Semen	桃仁	Peach Seed	14
28	<i>Rehmannia glutinosa</i> Root	Rehmanniae Radix	地黄	Rehmannia Root	14
29	<i>Pseudostellaria heterophylla</i> Root	Pseudostellariae Radix	太子参	Heterophylly Falsestarwort Root	13
30	<i>Morus alba</i> Bark	Mori Cortex	桑白皮	Mulberry Root Bark	13
31	<i>Amomum tsao-ko</i> Fruit	Tsaoko Fructus	草果	Caoguo	13
32	<i>Areca catechu</i> Seed	Arecae Semen	槟榔	Areca Seed	13
33	<i>Coix lacrymajobi</i> var. <i>mayuen</i> Kernel	Coicis Semen	薏苡仁	Coix Seed	13
34	<i>Artemisia Annua</i> Herb	Artemisiae Annuae Herba	青蒿	Sweet Wormwood Herb	12
35	<i>Cornus officinalis</i> Sarcocarp	Corni Fructus	山茱萸	Asiatic Cornelian Chery Fruit	12
36	<i>Perilla frutescens</i> Leaf	Perillae Folium	紫苏叶	Perilla Leaf	11
37	Processed <i>Aconitum carmichaeli</i> Daughter Root	Aconiti Lateralis Radix Praeparata	附子	Prepared Common Monkshood Daughter Root	11
38	<i>Codonopsis pilosula</i> Root/ <i>Codonopsis pilosula</i> var. <i>modesta</i> Root/ <i>Codonopsis tangshen</i> Root	Codonopsis Radix	党参	Tangshen	10
39	<i>Lophatherum gracile</i> Stem and Leaf	Lophatheri Herba	淡竹叶	Lophatherum Herb	10
40	<i>Saposhnikovia divaricata</i> Root	Saposhnikoviae Radix	防风	Divaricate Saposhnikovia Root	10
41	<i>Zingiber officinale</i> Rhizome	Zingiberis Rhizoma	生姜	Zingiber	10
42	<i>Picrorhiza scrophulariiflora</i> Rhizome	Picrorhizae Rhizoma	胡黄连	Figwortflower Picrorhiza Rhizome	10
43	<i>Gardenia jasminoides</i> Fruit	Gardeniae Fructus	栀子	Cape Jasmine Fruit	10
44	<i>Fritillaria thunbergii</i> Bulb	Fritillariae Thunbergii Bulbus	浙贝母	Thunberg Fritillary Bulb	10
45	<i>Mentha haplocalyx</i> Herb	Menthae Haplocalycis Herba	薄荷	Peppermint	10
46	<i>Notopterygium incisum</i> Rhizome and Root/ <i>Notopterygium franchetii</i> Rhizome and Root	Notopterygii Rhizoma et Radix	羌活	Incised Notopterygium Rhizome or Root	10
47	<i>Bubalus bubalis</i> Cornu	Bubali Cornu	水牛角	Buffalo Horn	10

4) The main differences of the standards are the gaps in the selection of marker compounds and limitation regulation. The single marker compound of baicalin is used for quantitative analysis in ChP, EP, JP, ISO, and WHO standards, while apart from baicalin, multi-marker compounds are referred in KP and USP.

3.3. Necessity of formulating international standards for CMM and characteristics of ISO/TC 249 international standards for CMM

Pharmacopoeias are the important technical code for quality and safety management of medicines in different countries and are the legal

norms and evidence for the entry to the pharmaceutical markets. Through the coordination of pharmacopoeia standards, global free trade of high-quality pharmaceutical products can be promoted. Although TCM has been widely promoted globally, due to the inherent characteristics of CMM and the sparks between traditional and modern evaluation systems, CMM has been variously identified in different countries and has difficulties in international registration [20–22]. The phenomena mainly result from the barriers to connect the quality standards for CMM with the mainstream markets in Europe and US, and restrictions of medical regulations and policies in different countries/regions. Major differences were identified in the classification of CMM

Table 2

The status of the collection of standards for 47 varieties of Chinese Materia Medica (usage frequency ≥ 10 times) in the mainstream pharmacopoeias and international organizations.

Rank	Pharmaceutical Name	ChP	JP	KP	EP	USP	ISO	WHO
1	Glycyrrhizae Radix et Rhizoma	√	√	√	√	√	√ ^a	√
2	Armeniacae Semen Amarum	√	√	√	-	√	-	√
3	Gypsum Fibrosum	√	√	√	-	√	-	-
4	Scutellariae Radix	√	√	√	√	√	√	√
5	Forsythiae Fructus	√	√	√	-	√	-	-
6	Poria	√	√	√	√	-	-	-
7	Ephedrae Herba	√	√	√	√	-	-	√
8	Citri Reticulatae Pericarpium	√	√	√	-	√	-	-
9	Pogostemonis Herba	√	√	√	-	-	-	-
10	Lonicerae Japonicae Flos	√	√	√	-	√	√	-
11	Platycodonis Radix	√	√	√	-	-	√ ^a	√
12	Pinelliae Rhizoma	√	√	√	-	-	√ ^a	-
13	Magnoliae Officinalis Cortex	√	√	√	-	-	-	√
14	Ophiopogonis Radix	√	√	√	-	-	-	-
15	Atractylodis Macrocephalae Rhizoma	√	√	√	√	-	-	-
16	Atractylodis Rhizoma	√	√	√	√	-	-	-
17	Rhei Radix et Rhizoma	√	√	√	√	-	√ ^a	√
18	Astragali Radix	√	√	√	√	-	√	√
19	Phragmitis Rhizoma	√	-	-	-	-	-	-
20	Ginseng Radix et Rhizoma	√	√	√	√	√	√ ^a	√
21	Descurainiae Semen/ Lepidii Semen	√	-	-	-	-	-	-
22	Schisandrae Chinensis Fructus	√	√	√	√	√	√	√
23	Anemarrhenae Rhizoma	√	√	√	√	-	-	-
24	Paeoniae Radix Rubra	√	√	√	√	√	-	-
25	Trichosanthis Semen	√	√	√	-	-	-	-
26	Bupleuri Radix	√	√	√	-	-	√	√
27	Persicae Semen	√	√	√	-	-	-	-
28	Rehmanniae Radix	√	√	√	-	√	√ ^a	√
29	Pseudostellariae Radix	√	-	-	-	-	-	-
30	Mori Cortex	√	√	√	-	-	-	-
31	Tsaoko Fructus	√	√	√	-	-	-	-
32	Arecae Semen	√	√	√	-	-	√	-
33	Coicis Semen	√	√	√	√	√	-	-
34	Artemisiae Annuae Herba	√	-	-	-	-	-	-
35	Corni Fructus	√	√	√	-	-	-	-
36	Perillae Folium	√	√	√	-	-	√	-
37	Aconiti Lateralis Radix Praeparata	√	√	√	-	-	√	-
38	Codonopsis Radix	√	√	√	√	-	-	-
39	Lophatheri Herba	√	-	-	-	-	-	-
40	Saposhnikoviae Radix	√	√	√	-	-	√ ^a	-
41	Zingiberis Rhizoma	√	√	√	-	-	-	√
42	Picrorhizae Rhizoma	√	√	√	-	-	√ ^a	√
43	Gardeniae Fructus	√	√	√	√	-	-	-
44	Fritillariae Thunbergii Bulbus	√	√	√	-	-	-	-
45	Menthae Haplocalycis Herb	√	√	√	-	-	-	-
46	Notopteryqii Rhizoma et Radix	√	√	-	-	-	-	-
47	Bubali Cornu	√	-	-	-	-	-	-
Coverage ratio of standards for the 47 varieties (%)		100.00	87.23	85.11	31.91	25.53	30.04	29.79

^a These CMM as new work item proposal (NWIP) have been submitted into ISO/TC 249 platform, and they have not been officially approved as new projects.

Table 3

The list of 47 varieties of Chinese Materia Medica with usage frequency over 10 times included by ISO/TC 249 platform.

No.	English Name	Chinese Name	Sponsor Countries	Current Stage
1	ISO 21317:2019 Traditional Chinese medicine— <i>Lonicera japonica</i> flower	中医药—金银花	China	Published
2	ISO 22988:2020 Traditional Chinese medicine— <i>Astragalus mongholicus</i> root	中医药—蒙古黄芪	China	
3	ISO 23,962 Traditional Chinese Medicine—Processed <i>Aconitum carmichaelilateral</i> root	中医药—附子	China	Draft international Standard (DIS)
4	ISO 22,585 Traditional Chinese Medicine— <i>Codonopsis pilosula</i> root	中医药—党参	China	Working Draft
5	ISO 23,965 Traditional Chinese Medicine— <i>Bupleurum chinense</i> and <i>Bupleurum scorzonrifolium</i> root	中医药—柴胡	China	(WD)
6	ISO 4564 Traditional Chinese Medicine— <i>Scutellaria baicalensis</i> Georgi root	中医药—黄芩	China	
7	Traditional Chinese Medicine— <i>Panax ginseng</i> root	中医药—人参	China	New Work Item Proposal (NWIP)
8	Traditional Chinese medicine— <i>Glycyrrhiza uralensis</i> root and rhizome	中医药—甘草	China	
9	Traditional Chinese medicine— <i>Pinelliaternata</i> tuber	中医药—半夏	China	
10	Traditional Chinese medicine— <i>Rehmanniaglutinosa</i> root	中医药—地黄	China	
11	Traditional Chinese Medicine— <i>Arecae</i> Semen	中医药—槟榔	China	
12	Traditional Chinese Medicine— <i>Saposhnikoviadivaticata</i> root and rhizome	中医药—防风	China	
13	Traditional Chinese Medicine— <i>Platycodon grandiflorum</i> root	中医药—桔梗	Republic of Korea	
14	Traditional Chinese medicine— <i>Schisandra chinensis</i> fruit	中医药—五味子	Republic of Korea	
15	Traditional Chinese Medicine— <i>Rheum</i> root and rhizome	中医药—大黄	Germany	
16	Traditional Chinese Medicine— <i>Coptis</i> rhizome	中医药—黄连	Canada	

Table 4
The comparative analysis of quality standards for *Scutellariae Radix* in the standards of the mainstream pharmacopoeias, WHO and ISO.

Items	ChP, 2015	JP, 17 th	KP, 11 th	EP, 9.0	USP-HMC	WHO monograph	ISO
Definition	√	√	√	√	√	√	√
Description	√	√	√	√	√	√	√
Identification	Microscopic TLC	√	√	√	√	√	√
	Reference crude drug; Baicalin; Baicalein; Wogonin	Reference crude drug; Baicalin	Reference crude drug	Baicalin; acteoside	Reference crude drug; Baicalin; Baicalein	Baicalin	—
Loss on drying	≤10.0 %	≤12.0 %	≤15.0 %	≤12.0 %	≤12.0 %	≤12.0 %	≤15.0 %
Total ash	≤6.0 %	≤5.0 %	≤6.0 %	≤6.0 %	≤6.0 %	≤6.0 %	≤6.0 %
Acid-insoluble Ash	—	—	≤1.0 %	≤2.0 %	≤1.0 %	≤1.0 %	—
Ethanol-soluble extractives	≥40.0 %	—	≥24.0 %	—	≥18.0 %	≥15.0 %	≥26.0 %
Water-soluble extractives	—	—	—	—	≥28.0 %	≥40.0 %	—
Assay	Baicalin: ≥9.0 %	Baicalin: ≥10.0 %	≥10.0 % (total of Baicalin, baicalein and wogonin)	Baicalin: ≥9.0 %	≥11.0 % (total of Baicalin and wogonin-7-O-glucuronide); ≥3.50 % (total of Baicalin and wogonin)	Baicalin: ≥9.0 %	Baicalin: ≥8.0 %
Heavy metals	—	√	√	√	√	√	√
Pesticide residuals	—	—	√	√	√	√	√
Sulfur dioxide	≤ 150 ppm	—	≤ 30 ppm	—	—	—	—

and its products, market entry pathways, requirements of compliance with Good Manufacturing Practices; and level of evidence to demonstrate safety and efficacy based on historical use, non-clinical and clinical studies. Variations in the evaluation standards adopted by regulatory authorities pose a number of barriers and opportunities for the internationalization of TCM products [22].

It is not easy to fully understand the properties and curative effects of CMMs under the current knowledge and methodologies we have had. On the other hand, some western countries still have stipulated strict regulations on the registration of Chinese medicines before they could be sold. Such is the dilemma we meet: trying to follow the modern evidence-based approaches for registration while retaining unique characteristics of TCM. It can be highly desirable to develop ISO standards on each herbal medicine to serve as a reference during those registration processes.

Although the pharmacopoeias of different countries have a certain global impact, due to the disparities in initial motivations and target groups of the pharmacopoeias, it is difficult to apply to the standard of a specific country as supporting evidence for arbitration in international arbitration once a trade dispute occurs. Furthermore, due to the limited varieties of CMM included in the pharmacopoeias of Europe, US and other countries, or the disputes in the selection of the marker compounds, it is difficult for the existing standards to adapt to the needs of international trade of CMM.

Based on consultative and consensus-based processes, ISO/TC249 provides a platform to develop standards which represent global expert opinion across consumers, practitioners, industry, academics from universities, and government. For standards on CMMs, there are still large disparities in the levels of requirements between a range of countries and their national pharmacopoeias. Therefore, ISO/TC249 can serve the purpose of filling the gaps and supporting the appropriate use of CMMs. With a focus on the demands for the international market, ISO/TC 249 has been dedicated to filling in the blanks of the universal standards for international trade of CMM, stipulating international standards for CMM, strengthening quality control and safety requirements of CMM, and conducting a large amount of research on the detection of residual pesticides and heavy metals, etc.. In order to complete the above tasks in an organized manner, ISO/TC 249 have formulated and released 'ISO/TR 23975: 2019 Traditional Chinese medicine—Priority list of single herbal medicines for developing standards' [23] from the needs of international trade, the status of pharmacopoeias in different countries, the degree of safety issues of CMM, the status of the Convention on International Trade in Endangered Species

of Wild Fauna and Flora (CITES) collection, and the consensus of experts in all countries. It aims at establishing unified quality standards that can adapt to the characteristics of CMM, ensure safety and effectiveness, and are applicable to international trade. With the new challenges and suggestions that COVID-19 brings us, the commonly used CMM in COVID-19 prevention and treatment need to be prioritized more appropriate, and the international standards should be published in a timely manner. With the endorsement of ISO international standards, TCM should play its role in the prevention and treatment of major infectious diseases worldwide. By comparative studies, the data has shown that among the 47 varieties of CMM with a usage frequency over 10 times for fighting COVID-19, only 22 varieties (46.81 %) are currently included in ISO/TR 23975. In other words, there is much to be engaged for ISO international standards in this field.

3.4. Further thoughts on international standards of ISO/TC 249 in responding to major emergencies of public health

The outbreak of COVID-19 reminds us that in dealing with major emergencies of global public health, it is of great importance to transcend the borders and build a global community of shared wellbeing now. The understanding and diagnosis and treatments of TCM for diseases and health care, over hundreds of years' application supports the efficiency and safety of Chinese medicines, and its contribution to the wellbeing should be shared by the mankind. It is an important mission of ISO/TC 249 to promote TCM contribution to the wellbeing of the mankind by stipulating international standards of high quality.

CMM have the characteristics of diversity and complexity of ingredients, which is difficult to comprehensively evaluate by the quality control and assessment mode of single ingredient of modern chemical medicines. For the key scientific problems urgently needed to be solved in the internationalization and standardization of CMM, with the focus on the methodology for comprehensive characterization of the overall composition of CMM and the establishment of quality evaluation system, the demarcation of toxic CMM between effectiveness and safety, and the formulation of the limitation range of effect-toxic ingredients [24–26], we need to integrate the concepts of stipulating standards of the mainstream pharmacopoeias and ISO standards, etc., and to establish a scientific quality standard system that can adapt to the characteristics of CMM and can be generally recognized by the international community. Based on the experience of fighting COVID-19, it is urgent for ISO/TC 249 to formulate high-quality standards that consolidate international consensus to ensure the quality and safety of

the urgently needed CMM.

4. Conclusions

In this study, the characteristics of used CMM for prevention and treatment of COVID-19, and the quality requirements of 47 main varieties of CMM in mainstream pharmacopoeias and international standards were comprehensively analyzed and compared. These findings provide evidence for developing harmonized standards which can be relied on to guarantee the safety and quality of CMM. This study also stated that it is of the highest priority for ISO/TC 249 to formulate high-quality standards that can consolidate global consensus and contain the characteristics of CMM at most.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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References

- [1] General Office of the National Health and Health Commission, Office of the State Administration of Traditional Chinese Medicine. Notice on Issuing a New Coronary Virus Pneumonia Diagnosis and Treatment guidelines (Trial Version 7) [EB/OL]. <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>, (accessed Mar 4, 2020, in Chinese).
- [2] Jiangsu Research Center for Chinese Medicine Development, Trend Book of Diagnosis and Treatment Protocol of Traditional Chinese Medicine for COVID-19, (2020) [EB/OL]. <http://www.jstcm.com/uploadfile/20200228215356601.pdf> (accessed Feb 19, 2020, in Chinese).
- [3] K.W. Chan, V.T. Wong, S.C.W. Tang, COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease, *Am. J. Chin. Med.* 43 (2020) 737–762.
- [4] L. Ni, L. Zhou, M. Zhou, J. Zhao, D.W. Wang, Combination of western medicine and chinese traditional patent medicine in treating a family case of COVID-19 in Wuhan, *Front. Med.* 14 (2020) 210–214.
- [5] M. Liu, Y. Gao, Y. Yuan, K. Yang, S. Shi, J. Zhang, J. Tian, Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Corona Virus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis, *Pharmacol. Res.* 158 (2020) 104896.
- [6] J.L. Ren, A.H. Zhang, X.J. Wang, Traditional Chinese medicine for COVID-19 treatment, *Pharmacol. Res.* 155 (2020) 104743.
- [7] The State Council Information Office, The People's Republic of China, TCM treatment effective on over 90% of COVID-19 patients on China's mainland: Official [EB/OL], http://english.scio.gov.cn/pressroom/2020-03/24/content_75852369.htm (accessed March 24, 2020, in English).
- [8] K. Hu, W.J. Guan, Y. Bi, W. Zhang, L. Li, B. Zhang, Q. Liu, Y. Song, X. Li, Z. Duan, Q. Zheng, Z. Yang, J. Liang, M. Han, L. Ruan, C. Wu, Y. Zhang, Z.H. Jia, N.S. Zhong, Efficacy and safety of Lianhuaqingwen Capsules, a repurposed chinese Herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial, *Phytomedicine* (2020) 153242, <https://doi.org/10.1016/j.phymed.2020.153242>.
- [9] D. Zhang, B. Zhang, Lv J.T., R.N. Sa, X.M. Zhang, Z.J. Lin, The clinical benefits of chinese patent medicines against COVID-19 based on current evidence, *Pharmacol. Res.* 157 (2020) 104882.
- [10] E. Luo, D. Zhang, H. Luo, B. Liu, K. Zhao, Y. Zhao, Y. Bian, Y. Wang, Treatment efficacy analysis of traditional chinese medicine for novel coronavirus pneumonia (COVID-19): an empirical study from Wuhan, Hubei Province, China, *Chin. Med.* 15 (2020) 34.
- [11] Y. Yang, M.S. Islam, J. Wang, Y. Li, X. Chen, Traditional chinese medicine in the treatment of patients infected with 2019-New coronavirus (SARS-CoV-2): a review and perspective, *Int. J. Biol. Sci.* 16 (2020) 1708–1717.
- [12] National Pharmacopoeia Committee, Chinese Pharmacopoeia, Part 1, Chemical Industry Press, Beijing, 2015.
- [13] Japanese Pharmacopoeia Convention, Japanese Pharmacopoeia, 17th ed., Society of Japanese Pharmacopoeia, Tokyo, 2016.
- [14] Korea food and drug administration, The Korean Herbal Pharmacopoeia, 10th ed., Yakup Daily, Seoul, 2002.
- [15] The European pharmacopoeia directorate for the quality of medicines & HealthCare of the council of Europe (EDQM), European Pharmacopoeia, 9th ed., (2016).
- [16] The United States Pharmacopoeial Convention, The United States Pharmacopoeia (USP40-NF35), New York, (2016).
- [17] The United States Pharmacopoeial Convention, United States Pharmacopoeia-Herbal Medicines Compendium 1.0, (2015).
- [18] World Health Organization (WHO): Essential medicines and health products - WHO monographs on Selected Medicinal Plants (Vol.1-Vol.3), https://www.who.int/medicines/technical_briefing/tbs/2009_traditionalmedicines_rdg_prs/en/.
- [19] The International Organization for Standardization/ Technical Committee of Traditional Chinese medicine (ISO/TC 249): <https://www.iso.org/committee/598435.html>.
- [20] A.X. Lin, G. Chan, Y. Hu, D. Ouyang, C.O.L. Ung, L. Shi, H. Hu, Internationalization of traditional Chinese medicine: current international market, internationalization challenges and prospective suggestions, *Chin. Med.* 13 (9) (2018) 1–6.
- [21] W. Knoess, J. Wiesner, The globalization of Traditional Medicine: perspectives related to the European Union regulatory environment, *Engineering* 5 (2019) 22–31.
- [22] J. Li, J. Zhu, H. Hu, J.E. Harnett, C.I. Lei, K.Y. Chau, G. Chan, C.O.L. Ung, Internationalization of Traditional/Complementary Medicine products: market entry as medicine, *Chin. Med.* 13 (50) (2018) 1–15.
- [23] ISO/TR 23975, Traditional Chinese Medicine–Priority List of Single Herbal Medicines for Developing Standards, (2019).
- [24] W.Y. Wu, W.Z. Yang, J.J. Hou, D.A. Guo, Current status and future perspective in the globalization of traditional Chinese medicines, *World J. Tradit. Chin. Med.* 1 (1) (2015) 1–4.
- [25] Y. Gao, A. Liang, X. Fan, L. Hu, F. Hao, Y. Li, Safety research in traditional Chinese medicine: methods, applications, and outlook, *Engineering* 5 (2019) 76–82.
- [26] T. Zhang, G. Bai, Y. Han, J. Xu, S. Gong, Y. Li, H. Zhang, C. Liu, The method of quality marker research and quality evaluation of traditional Chinese medicine based on drug properties and effect characteristics, *Phytomedicine* 15 (2018) 204–211.