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How Current Clinical Practice Guidelines for Low Back Pain Reflect Traditional Medicine in East Asian Countries: A Systematic Review of Clinical Practice Guidelines and Systematic Reviews

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Abstract

Objectives: The aims of this study were to investigate whether there is a gap between evidence of traditional medicine (TM) interventions in East-Asian countries from the current Clinical Practice Guidelines (CPGs) and evidence from current systematic reviews and meta-analyses (SR-MAs) and to analyze the impact of this gap on present CPGs.

Methods: We examined 5 representative TM interventions in the health care systems of East-Asian countries. We searched seven relevant databases for CPGs to identify whether core CPGs included evidence of TM interventions, and we searched 11 databases for SR-MAs to re-evaluate current evidence on TM interventions. We then compared the gap between the evidence from CPGs and SR-MAs.

Results: Thirteen CPGs and 22 SR-MAs met our inclusion criteria. Of the 13 CPGs, 7 CPGs (54%) mentioned TM interventions, and all were for acupuncture (only one was for both acupuncture and acupressure). However, the CPGs did not recommend acupuncture (or acupressure). Of 22 SR-MAs, 16 were for acupuncture, 5 for manual therapy, 1 for cupping, and none for moxibustion and herbal medicine. Comparing the evidence from CPGs and SR-MAs, an underestimation or omission of evidence for acupuncture, cupping, and manual therapy in current CPGs was detected. Thus, applying the results from the SR-MAs, we moderately recommend acupuncture for chronic LBP, but we inconclusively recommend acupuncture for (sub)acute LBP due to the limited current evidence. Furthermore, we weakly recommend cupping and manual therapy for both (sub)acute and chronic LBP. We cannot provide recommendations for moxibustion and herbal medicine due to a lack of evidence.

Conclusions: The current CPGs did not fully reflect the evidence for TM interventions. As relevant studies such as SR-MAs are conducted and evidence increases, the current evidence on acupuncture, cupping, and manual therapy should be rigorously considered in the process of developing or updating the CPG system.

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Introduction

Low back pain (LBP) is a common condition that affects a significant proportion of the population, with an estimated prevalence of 70%–85% [1]. Current Clinical Practice Guidelines (CPGs) recommend various LBP treatments, such as pharmacotherapy, physical therapy, manual therapy, educational therapy, psychological therapy, and invasive therapy [2,3].

Traditional medicine (TM) is defined as indigenous medicine used to maintain health and to prevent, diagnose, and treat physical and mental illnesses and is distinct from allopathic medicine based on theories, beliefs, and experiences [4]. In East-Asian countries, especially China, Korea, and Japan, the main therapeutic methods of TM consist of acupuncture, moxibustion, cupping therapy, herbal medicines, and manual therapies (called Tuina in China, Chuna in Korea, and Shiatsu in Japan) [5]. In East-Asian countries, 80% of the population depends on TM for primary health care, and 70% to 80% of the population in many developed countries has used some form of alternative or complementary medicine (e.g., acupuncture) [4]. Although studies

on the use of TM are increasing [6,7], differences in medical circumstances, culture, or poor evidence in support of TM seem to complicate the inclusion of TM in CPGs.

CPGs are systematically developed to assist practitioners and patients in making decisions about appropriate healthcare in specific clinical circumstances [8]. In contrast with previous approaches that were often based on tradition or authority, modern CPGs are based on an examination of current evidence within the paradigm of evidence-based medicine [9]. SR-MAs are literature reviews focused on a research question that attempts to identify, appraise, select, and synthesize all high-quality research evidence relevant to that question. SR-MAs of high-quality randomized controlled trials (RCTs) are crucial for evidence-based medicine [10]. Although it seems easy to write an SR-MA, good SR-MAs take time, and they frequently encounter delays but do not update the literature review. The additional typical delays for peer review and publishing add extra time, and SR-MAs may be printed two to four years after the end of the information retrieval. Finally, most SR-MAs are published worldwide without an accompanying CPG [11].

The purpose of this review was to investigate whether there is a gap between evidence of traditional medicine (TM) interventions in East-Asian countries from the current Clinical Practice guideline (CPGs) and evidence from current systematic reviews and meta-analyses (SR-MAs) and to analyze the impact of this gap on present CPGs.

Methods

Data Sources and Searches

Two types of databases were searched according to their database content. The first database was a CPG-related database for LBP that was used to understand the current status of LBP management. The other database included systematic reviews or meta- analyses (SR-MAs) and was used to compare the current evidence to current CPGs. Following the core, standard, ideal search (CoSI) model [12], we searched the following electronic databases from database inception to December 2012.

Our CPG database searches were the core searches because representative databases were more highly recommended than ideal searches. The CPG databases included the National Guideline Clearinghouse (NGC), Guidelines International Network (G-I-N), National Institute for Health and Clinical Excellence (NICE), and Scottish Intercollegiate Guidelines Network (SIGN). Additionally, we searched 3 representative East-Asian countries' databases: the Chinese National Knowledge Infrastructure (CNKI) for China, the Korean Medical Guideline Information (KoMGI) for Korea, and the Medical Information Network Distribution Service (MINDS) for Japan.

For SR-MAs, we conducted an ideal search because all relevant SR-MAs of LBP were needed for the TM area. We found TM in the following databases: The Cochrane Database of Systematic Review (CDSR), PubMed, MEDLINE, EMBASE, DH-DATA, AMED, Chinese databases (China Knowledge Resource Integrated Database, Wanfang database, and Chinese VIP information), a Korean database (Oriental Medicine Advanced Searching Integrated System), and a Japanese database (Japan Medical Abstracts Society).

Each East-Asian country's CPG and SR-MA databases were searched by authors from their own county.

The search keywords for CPG were (back pain OR low back pain OR lumbago) in each CPG database mentioned above. The search keywords for SR-MAs were (acupuncture OR acup*) for acupuncture, (moxa OR moxibustion) for moxibustion, (cupping) for cupping therapy, (herbal medicine OR traditional Chinese medicine OR Chinese herbal medicine) for herbal medicine, (manual therapy OR manipulation OR massage OR Chinese massage OR Tuina OR Chuna OR Shiatsu) for manual therapy, (low back pain OR back pain OR lumbago) for LBP, and (systematic review OR meta analysis OR meta analyze) for SR-MAs in each language. These search terms were combined in the form of [(LBP) AND (TM interventions) AND (SR-MA)]. This search strategy was adjusted for each database.

In addition, the bibliographies of relevant CPGs and SR-MAs were manually searched. Gray literature, consisting of theses, dissertations, letters, government documents, research reports, conference proceedings, and abstracts, was searched to avoid publication bias. The reference section for each study was searched. Personal contacts were made with the original authors of the searched studies to identify any data that were potentially missing from the publications.

The title and abstract of searched articles were read by a single primary researcher (H-WC), who conducted the screening process. Articles that were not written in English were translated into Korean or English prior to screening. The articles for potential inclusion in our review were checked by 2 independent reviewers (H-WC, E-HH). After screening the titles and abstracts retrieved in our search, we excluded all articles that did not meet our pre-defined inclusion/exclusion criteria. Then, the full text of the articles for inclusion was carefully read. The final inclusion was determined by two independent reviewers (H-WC, E-HH), who used the matching method.

Study Selection

Types of CPG and SR-MA. Current CPGs regarding the treatment of non-specific LBP, which were used universally and considered the standard, were evaluated. When we conducted the preliminary search, there were few CPGs not written in English, and they were from the Netherlands, Spain, Germany, France, Finland, and Brazil. The CPGs' development dates were relatively older than the English versions, and the relevance of their content was low. Thus, we concluded that they would have no effect on the analysis. Because we wanted to show the current state of TM through the representative CPGs, the authors reached a consensus to limit the language of the CPGs to English.

Non-specific LBP was searched and evaluated to understand the current evidence from SR-MAs research studies on the effectiveness of 5 major TM interventions (acupuncture, moxibustion, cupping therapy, manual therapy, and herbal medicine). Language was not restricted during the selection of SR and MA.

Types of participants in CPG and SR-MA. LBP was defined as pain localized to the area between the costal margin or the 12th rib to the inferior gluteal fold. Non-specific LBP indicated the lack of a detectable specific cause, such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, fracture, or inflammatory process [13].

The CPGs and SR-MAs in our review included all stages of non-specific LBP with or without radiating pain, such as acute (lasting up to six weeks), sub-acute (lasting six to 12 weeks), or chronic (lasting longer than 12 weeks) non-specific LBP [14].

Types of interventions in SR and MA. We analyze the TM of the primary therapeutic interventions, including acupuncture, moxibustion, cupping therapy, herbal medicines, and manual therapies, found in East-Asian countries. We selected these 5 types of interventions because they were medical insurance reimbursement items in East-Asian countries [15].

Table 1. Comparison of Clinical Practice Guidelines for Low Back Pain.

Database	Guideline & Year	Target population	Interventions and practices considered	Presence of Traditional Medicine Interventions	Recommendation	AGREE II Overall Assessment
NGC (USA)	NGC-8959/2012 [21]	(Sub)acute/Non-specific LBP with or without radiculopathy/ including pregnant women	1, 2, 3, 5	None	NA	6/Y
	NGC-8744/2011 [24]	(Sub)acute/Non-specific LBP with or without back-related leg symptoms	1, 2, 3	None	NA	5/YWM
	NGC-8517/2011 [28]	(Sub)acute & chronic/ Non- specific LBP	1, 2, 3, 5, 6	Yes (acupuncture/ Acupressure)	Acupuncture/Acupressure considered, but are not recommended	6/Y
	NGC-8193/2010 [22]	(Sub)acute & chronic/ Non- specific LBP with or without radiculopathy	1,2,3,4	None	NA	3/YWM
	NGC-8009/2010 [26]	(Sub)acute/Non-specific LBP	1,2,3,6	None	NA	3/YWM
	NGC-7704/2009 [25]	(Sub)acute & chronic/ Non-specific LBP	(sub)acute LBP : 1, 2, 3, 5, 6/ Chronic LBP : 1, 2, 5, 6	Yes (acupuncture)	1. (Sub)acute: acupuncture - Do Not Know/2. Chronic: acupuncture - Do	3/YWM
	NGC-7510/2009 [27]	Work-related injuries or illnesses related to the low back, elbow, shoulder, forearm, wrist, or hand	2, 3, 4	None	NA	3/YWM
	NGC-7428/2009 [2]	Chronic/Non-specific LBP	6	None	NA	4/YWM
	NGC-6456/2007 [23]	Work-related low back disorders with radiculopath	1, 2, 3, 5, 6	Yes (acupuncture)	1.(Sub)acute LBP:acupuncture - Not recommended (Insufficient)/ 2.Chronic LBP: acupuncture for select use during a limited course with a clear objective and functional goals –Recommended (C-weak)/acupuncture - Notrecommended (Insufficient)	4/YWM
	NGC-5968/2007 [20]	(Sub)acute & chronic/ Non- specific LBP	1, 2, 3, 4, 5, 6	Yes (acupuncture)	Moderate quality evidence, Weak recommendation	3/YWM
NICE (UK)	CG-88/2009* [29]	(Sub)acute & chronic/ Non-specific LBP	1, 2, 3, 4, 5, 6	Yes (acupuncture)	Consider offering a course of acupuncture needling comprising up to a maximum of 10 sessions over a period of up to 12 weeks.	5/YWM
G-I-N (International)	Prodigy(UK) Back pain - low (without radiculopathy) /2009 [3]	(Sub)acute & chronic/ Non-specific LBP without radiculopathy(sciatica) (including sprains and strains)	1, 2, 3, 4, 5, 6	Yes (acupuncture)	The course should have up to 10 sessions given over a period of up to 12 weeks	3/YWM
MINDS (Japan)	Clinical Practice guideline for the management of LBP/2012 [30]	(Sub)acute & chronic/ Non-specific LBP	1, 2, 3, 4, 5, 6	Yes (acupuncture)	(Sub)acute – Do not know/ Chronic- It is hard to say acupuncture is better than other conservative therapies.	4/YWM

Abbreviations: LBP, low back pain; AT, acupuncture; NA, Not applicable YMA, yes with modification; Y, yes.
Items of Interventions and practices: 1 = pharmacological therapy, 2 = physical therapy, 3 = education, 4 = psychological therapy, 5 = manual therapy, 6 = invasive therapy; Items of outcomes considered: 1 = pain, 2 = Global measure, 3 = functional status, 4 = Quality of Life, 5 = Safety, 6 = Cost effectiveness, 7 = Other outcomes.; All AGREE II items are rated with the following 7-point scale: Score of 1 (Strongly Disagree) = There is no information relevant to the AGREE II item or very poor reporting of the concept.; Score of 7 (Strongly Agree) = quality of reporting is exceptional and the full criteria and considerations articulated in the User's Manual have been met.; Scores between 2 and 6 = The reporting of the AGREE II item does not meet the full criteria or considerations. A score is assigned depending on the completeness and quality of reporting. Scores increase as more criteria are met and considerations are addressed. We classified scores of 1 or 2 as low quality, scores of 3, 4 or 5 were moderate quality and 6 or 7 were high quality.; Domain scores are calculated by summing all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The scaled domain score will be: (Obtained score – Minimum possible) score/(Maximum possible score – Minimum possible score)*100.
*: NGC-7269 was originated from CG88 and it was summary of CG-88; thus, it was excluded.
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Table 2. Systematic Reviews of Low Back Pain.

Type of Traditional Medicine	Stage of LBP	First Author & Year	Intervention	Outcome measurement	Direction of Outcome (Number of RCTs)	Level of Evidence/ Recommendation (SIGN)	Total AMSTA R score
Acupuncture							
	(Sub)acute						
		McIntosh 2008 [45]	Acupuncture	1, 2, 3, 7	P+(3)	1−/A	5
	Chronic						
		Hutchinson 2012 [44]	Acupuncture	1, 3, 4, 6, 7	P+ (7)	1+/A	4
		Trigkilidas 2010 [40]	Acupuncture	1, 3, 4, 6	I (4)	Not applicable	2
		Rubinstein 2010 [42]	Acupuncture	1, 3	P+ (18)	1+/A	10
		Yuan 2009 [39]	Acupuncture	1, 3, 4	Chronic LBP: P+ (23)	1+/A	7
		Ammendolia 2008 [37]	Acupuncture	1, 3, 4, 5, 7	I (19)	1+/A	4
		McIntosh 2008 [38]	Acupuncture	1, 2, 3, 7	P+ (32)	1−/A	4
		Henderson 2002 [34]	Acupuncture	Not reported	I (5)	2+/C	2
	Mixed						
		Furlan 2012 [41]	Acupuncture	1, 3, 5, 6	(Sub)acute LBP : I/chronic LBP : P+ (33)	1−/B	9
		Lu 2011 [43]	Acupuncture	1, 3, 4, 6, 7	P+ (5)	1+/A	8
		Furlan 2005 [35]	Acupuncture	1, 2, 3, 4, 5, 7	(Sub)acute LBP : I (3)/chronic LBP : P+ (32)	1+/A	3
		Maurits 2005 [46]	Acupuncture	1, 3, 7	acute LBP : I (2)/chronic LBP : P+ (13)	1+/A	9
		Manheimer 2005 [36]	Acupuncture	1, 2, 3, 7	P+ (33)	1+/B	8
		Ernst 2002 [33]	Acupuncture	1, 3	I (12)	1−/A	10
		Smith 2000 [32]	Acupuncture	1, 2, 7	(sub)acute LBP : N+ (2)/chronic LBP : N+ (8)	1+/A	7
		Tulder 1999 [31]	Acupuncture	1, 3, 7	I (11)	1−/A	8
Cupping Therapy							
	Mixed						
		Kim 2011 [52]	Dry/Wet cupping	1, 5	(sub)acute & chronic LBP : P+ (2)	1−/B	8
Manual Therapy							
	Chronic						
		Kim 2012 [50]	Acupressure	1, 3, 7	P++ (3)	1−/B	10
		Imamura 2008 [47]	Acupuncture massage, Acupressure	1, 2, 3, 4, 5, 6, 7	P+ (4)	1+/A	5
	Mixed						
		Moon 2012 [51]	Chuna	1	P+ (2)	1−/B	6
		Robinson 2011 [49]	Shiatsu, Acupressure	1, 3	Shiatsu: I (1)/Acupressure : P+ (3)	1−/B	6
		Furlan 2009 [48]	Acupuncture massage, Acupressure	1, 2, 3, 4, 5, 6, 7	P++ (5)	1+/A	10

Abbreviations: LBP, low back pain; I, insufficient; P, positive; N, negative;
+ = weak; ++ = moderate; +++ = strong.
Items of outcomes measurement: 1 = pain; 2 = Global measure; 3 = functional status; 4 = Quality of Life; 5 = Safety; 6 = Cost effectiveness; 7 = Other outcomes.
The total AMSTAR score was calculated by adding the average scores for all 11 items. We averaged item scores across guidelines. Item scores were classified such that 0–3 indicated low quality, 4–7 indicated moderate quality and 8–11 indicated high quality.
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1. Acupuncture: only included needle acupuncture with or without electrical stimulation. Acupuncture without needling, such as laser or TENS on acupoints, was excluded.
2. Moxibustion: included when acupoints were heated with moxibustion.
3. Cupping therapy: included both dry and wet cupping.
4. Manual therapy: included Tuina in China or Chuna in Korea. Massage techniques were included, such as Chinese massage, acupressure, acupuncture massage, or Shiatsu when applied to acupoints or meridians.
5. Herbal medicine: included herbal medicine according to the TM diagnosis.

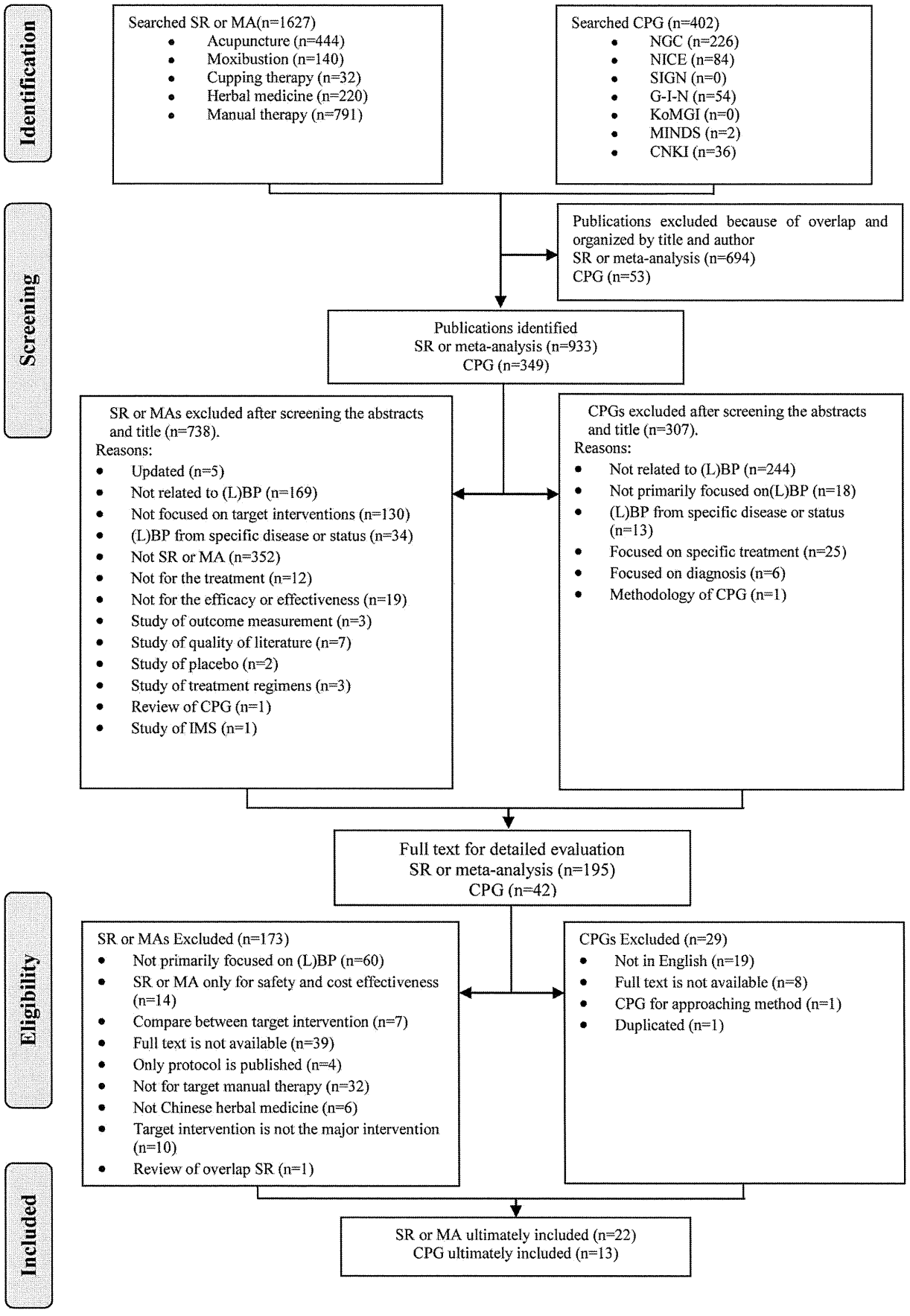
Identification
Searched SR or MA(n=1627)
Acupuncture (n=444)
Moxibustion (n=140)
Cupping therapy (n=32)
Herbal medicine (n=220)
Manual therapy (n=791)
Searched CPG (n=402)
NGC (n=226)
NICE (n=84)
SIGN (n=0)
G-I-N (n=54)
KoMGI (n=0)
MINDS (n=2)
CNKI (n=36)
Screening
Publications excluded because of overlap and organized by title and author
SR or meta-analysis (n=694)
CPG (n=53)
Publications identified
SR or meta-analysis (n=933)
CPG (n=349)
SR or MAs excluded after screening the abstracts and title (n=738).
Reasons:
Updated (n=5)
Not related to (L)BP (n=169)
Not focused on target interventions (n=130)
(L)BP from specific disease or status (n=34)
Not SR or MA (n=352)
Not for the treatment (n=12)
Not for the efficacy or effectiveness (n=19)
Study of outcome measurement (n=3)
Study of quality of literature (n=7)
Study of placebo (n=2)
Study of treatment regimens (n=3)
Review of CPG (n=1)
Study of IMS (n=1)
CPGs excluded after screening the abstracts and title (n=307).
Reasons:
Not related to (L)BP (n=244)
Not primarily focused on(L)BP (n=18)
(L)BP from specific disease or status (n=13)
Focused on specific treatment (n=25)
Focused on diagnosis (n=6)
Methodology of CPG (n=1)
Eligibility
Full text for detailed evaluation
SR or meta-analysis (n=195)
CPG (n=42)
SR or MAs Excluded (n=173)
Not primarily focused on (L)BP (n=60)
SR or MA only for safety and cost effectiveness (n=14)
Compare between target intervention (n=7)
Full text is not available (n=39)
Only protocol is published (n=4)
Not for target manual therapy (n=32)
Not Chinese herbal medicine (n=6)
Target intervention is not the major intervention (n=10)
Review of overlap SR (n=1)
CPGs Excluded (n=29)
Not in English (n=19)
Full text is not available (n=8)
CPG for approaching method (n=1)
Duplicated (n=1)
Included
SR or MA ultimately included (n=22)
CPG ultimately included (n=13)

Figure 1. Flow chart of the study selection process. SR = systematic review; MA = meta-analysis; CPG = clinical practice guideline; (L)BP = (low) back pain; IMS = Intra Muscular Stimulation.
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When studies addressed various symptoms or interventions in one acupuncture SR, we limited the inclusion criteria if the majority (>50%) of the participants and the intervention were acceptable for predefined criteria because there were numerous acupuncture SR-MAs. However, there were few available SR-MAs of moxibustion, cupping, manual therapy, and herbal medicine. Therefore, we included the SR-MAs when the RCTs of those interventions were greater than 10% of all RCTs when the data could be separately extracted.

When it was difficult to evaluate the independent effectiveness of TM intervention, such as comparing the same interventions or mixed treatments, the SR-MAs were excluded.

Data Extraction and Quality Assessment

Two reviewers (H-WC, E-HH) independently extracted the data based on predefined characteristics to describe each study (refer to Tables 1, 2). In CPG, we extracted the type of interventions, the presence of TM, and the recommendation. In SR-MAs, we extracted outcome measures and their directions of outcome for each intervention and condition of LBP.

Outcome measures. The outcome measures that we considered are described below. SR-MAs that used at least one outcome measure related to pain were included. The other outcome measures were considered, and their inclusion may be important for the study of LBP.

1. Primary outcome: Pain intensity
2. Secondary outcome: Global measure of improvement or recovery/Back-specific functional status/Quality of life/Safety/Cost-effectiveness/Other outcomes

Level of Evidence and Recommendation

We reassessed the evidence level and recommendations of the SR-MAs using the SIGN grading system [16]. All disagreements were resolved through discussion and consensus or by the first author (H-WC).

Quality Assessment of CPGs and SR-MAs

The SR-MAs of 24 different appraisal tools and some studies have shown that the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument is an acceptable standard for guideline evaluation. Therefore, the AGREE Instrument for reporting the quality of CPGs was used [17,18], and the Assessment of Multiple Systematic Reviews (AMSTAR) checklist for reporting the quality of SR-MAs was used to evaluate the methodological quality of the included publications. The AMSTAR instrument has recently been used in another study [19].

Four reviewers (H-WC, E-HH, K-HH, and B-CS) were fully trained in the quality assessment and data extraction methodology.

Data Synthesis and Analysis

We identified the directions for future CPG of LBP through deep discussion and expert consensus among authors. All authors were CPG-related experts from East-Asian countries (China, Korea, and Japan). The authors discussed and reached consensus through e-mail contact. In cases of disagreement, the final recommendation was made by consensus. Per the authors' recommendations, we recommend studies based on the results in Table 1 and Table 2.

Results

Study Description

A total of 402 CPGs and 1627 SR-MAs were identified. After manually removing the duplicates and screening the titles and abstracts, 42 CPGs and 195 SR-MAs were identified as potentially relevant. After a detailed evaluation of the full text, 29 CPGs and 173 SR-MAs were excluded. Finally, 13 CPGs and 22 SR-MAs met our inclusion criteria. The literature search process is summarized in Figure 1, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram. The key data are summarized in Table 1.

Current Clinical Practice Guidelines

Of the 13 CPGs, 10 originated in the USA [2,20–28], 2 were from the UK [3,29], and 1 was from Japan [30]. There were no CPGs from any East-Asian country. There were 7 CPGs for both (sub)acute and chronic LBP [3,20,22,25,28–30], 1 for chronic LBP [2], 3 for (sub)acute LBP [21,24,26], and 2 for work-related LBP [23,27]. The CPGs addressed various interventions, such as pharmacological therapy, physical therapy, education, psychological therapy, manual therapy, and invasive therapy. However, TM interventions were only included in 7 CPGs [3,20,23,25,28–30]. All TM interventions were for acupuncture, and only 1 CPG [28] mentioned both acupuncture and acupressure.

Of 7 CPGs, 6 recommended acupuncture, but all of these CPGs had weak recommendation strength or made the recommendation with session limitations [3,20,23,25,29,30]. However, 3 CPGs did not recommend acupuncture for (sub)acute LBP [23,25,28]. Only 1 CPG [28], which analyzed acupressure, did not recommend the treatment (Table 1).

Quality Assessment of Clinical Practice Guidelines

The overall assessment mean of the included CPGs was 4±1 (range: 3–6), indicating that CPGs have moderate quality. There were 2 high-quality CPGs [21,28], 11 moderate-quality CPGs [2,3,20,22–27,29,30], and no low-quality CPGs. We assessed 2 CPGs [21,28] as "recommend without modification" due to high quality and 11 other CPGs as "recommend with modifications" (Table 1). In each domain, the CPGs showed comparatively more than moderate quality (Table S1).

Evidence of Systematic Review and Meta-analysis

Of 22 SR-MAs, 16 were for acupuncture [31–46], 5 were for manual therapy (Chuna, acupressure, acupuncture massage, shiatsu) [47–51], and 1 was for cupping therapy [52]. For chronic LBP, 1 SR reported a moderately negative conclusion [32], 5 SR-MAs reported an insufficient conclusion [31,33,34,37,40], and 9 SR-MAs reported weakly positive effects of acupuncture [35,36,38,39,41–44,46]. For (sub)acute LBP, 1 SR reported a moderate negative conclusion [32], 5 SR-MAs reported insufficient conclusions [31,33,35,41,46], and 3 SR-MAs reported weakly positive effects of acupuncture [36,38,43]. The evidence level and recommendation strength were reassessed using the SIGN grading system. For the level of evidence, 5 SR-MAs were assessed 1− [31,33,38,41,45], 9 SR-MAs were 1+ [32,35–37,39,42–44,46], 1 SR was 2+ [34], and 1 SR was not applicable [40]. For recommendation strength, 12 SR-MAs were assessed as grade A [31–33,35,37–39,42–46], 2 SR-MAs were grade B [36,41], 1 was grade C [34],and 1 was not applicable [40].

Table 3. Directions for future Clinical Practice Guideline of Low Back Pain.

	Database	Guideline & Year	Acupuncture		Moxibustion		Cupping Therapy		Manual Therapy		Herbal Medicine	
Current												
	NGC (USA)	NGC-8959 2012	–		–		–		–		–	
		NGC-8744 2011	–		–		–		–		–	
		NGC-8517 2011	U		–		–		U		–	
		NGC-8193 2010	–		–		–		–		–	
		NGC-8009 2010	–		–		–		–		–	
		NGC-7704.2009	E		–		–		–		–	
		NGC-7510 2009	–		–		–		–		–	
		NGC-7428 2009	–		–		–		–		–	
		NGC-6456 2007	U		–		–		–		–	
		NGC-5968 2007	U		–		–		–		–	
	NICE (UK)	CG-88 2009	U		–		–		–		–	
	G-I-N (International)	Prodigy (UK) 2009	U		–		–		–		–	
	MINDS (Japan)	CPG for the management of LBP 2012	E		–		–		–		–	
Future												
	Authors Recommendation	Condition of LBP	Level of Evidence	Grade of Recommendation	Level of Evidence	Grade of Recommendation	Level of Evidence	Grade of Recommendation	Level of Evidence	Grade of Recommendation	Level of Evidence	Grade of
	Recommendation											
		(Sub)acute	1−	B	–	–	1−	B	1−	B	–	–
		Chronic	1+	A	–	–	1−	B	1−	B	–	–
			Moderate recommendation for chronic LBP/Inconclusive for (Sub)acute LBP		Do not know		Weak recommendation for both (Sub)acute and chronic LBP		Weak recommendation for both (Sub)acute and chronic LBP		Do not know	

Abbreviations: U, underestimated; E, enough.

–:There were no available data, and assessments were not applicable.

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Only 1 SR-MA on cupping for pain, including 2 RCTs for both (sub)acute and chronic LBP, reported weakly positive conclusions. The study partially considered pain and safety (adverse effect). The evidence level was assessed to be 1−, and the recommendation strength received a grade of B [52].

Of 5 SR-MAs of manual therapy, 1 considered Chuna [51], and 4 considered acupressure (including acupuncture massage and Shiatsu) [47–50]. All of these SR-MAs were compared with other interventions and reported positive conclusions, except for an inconclusive conclusion reported in 1 study of Shiatsu [49]. The study evidence level was assessed to be 1−, and the recommendation strength received a grade of B [51]. In 4 studies of acupressure, 2 were on chronic LBP alone [47,50], and the other 2 included both (sub)acute LBP and chronic LBP [48,49]. The evidence level was assessed to be 1− in 2 studies [49,50] and 1+ in the other 2 studies [47,48]. The recommendation strength received a grade of A in 2 studies [47,48] and B in the other 2 studies [49,50] (Table 2).

Quality Assessment of Systematic Reviews

The mean (± standard deviation) score of total quality assessment of the SR-MAs was 6.59±2.65 (range: 2–10) (Table S2). A total of 10 SR-MAs (47.6%) were assessed to be high quality [31,33,36,41–43,46,48,50,52], 9 SR-MAs (38.1%) were moderate quality [32,37–39,44,45,47,49,51], and 3 SR-MAs (14.3%) were low quality [34,35,40](Table 2).

Directions for Future CPG of LBP

Of the 7 CPGs that included acupuncture, 2 showed a similar recommendation compared with current research on SR-MAs [25,30], but 5 CPGs were underestimated [3,20,23,28,29]. Only 1 CPG included manual therapy and showed effectiveness underestimation [28]. Similar to moxibustion, cupping therapy and herbal medicine were not discussed in current CPGs and thus could not be compared.

We moderately recommended acupuncture for chronic LBP with a 1+/A evidence level and recommendation grade. However, we inconclusively recommended acupuncture for (sub)acute LBP due to the current SR-MA evidence. We weakly recommended cupping therapy for both (sub)acute and chronic LBP with a 1−/B evidence level and recommendation grade. We weakly recommend manual therapy for both (sub)acute and chronic LBP with a 1−/B evidence level and recommendation grade. Moxibustion and herbal medicine were not applicable due to the lack of data available at this time (Table 3).

Discussion

The main aim of our review was to analyze TMs in East-Asian countries (China, Korea, and Japan) in the current CPGs for LBP. The results showed that TMs in East-Asian countries were not sufficiently included in current CPGs.

Notably, moxibustion, cupping therapy, and herbal medicine are not mentioned in current CPGs. The lack of eligible RCTs and the aggregation of SR of moxibustion for LBP might be the primary causes of this lack of inclusion. This omission leads to a lack of evidence for the CPG. The use of moxibustion has become more common; 67% of Korean Oriental medical doctors have used moxibustion [53]. Additionally, 40% of health care in China is currently based on traditional Chinese medicinal approaches that include moxibustion [54]. The adverse effects and difficulties of placebo moxibustion that are reported in the literature [55] may have emerged due to the limited moxibustion studies.

The relevant studies on cupping therapy were of poor quality [56], which might lead to a lack of inclusion in current CPGs. However, the only SR showed a positive effect for both sub(acute) and chronic LBP.

The heterogeneity of herbal medicine products may be a considerable problem. The various types of preparation and the amount of chemical constituents per dose influence the pharmacokinetics and relative efficacy of the herbal medicine [57]. These differences may make it difficult to conduct a high-quality study.

Some acupuncture recommendations had both favorable and unfavorable conclusions. Of all of the studies, 7 CPGs (54%) mentioned acupuncture, but only 1 study recommended acupuncture for chronic LBP without use limitations. The other studies recommended acupuncture for limited treatment sessions or did not recommend acupuncture. These results demonstrate a gap with the results of current SR-MAs. Negative or insufficient effects in SR-MAs were dominant for (sub)acute LBP [31–33,35,41]. However, the positive effects were dominant for chronic LBP [35,36,38,39,41–44]. Similar results were reported for the evidence-based medicine approach to LBP [58]. Therefore, we conclude that the recommendations for (sub)acute LBP seem appropriate, and the recommendations for chronic LBP are underestimated.

Regarding manual therapy, 1 CPG mentioned acupressure but did not recommend acupressure for both (sub)acute and chronic LBP. However, we found some gaps in SR-MAs. There were 5 SR-MAs with a positive result [47–51] (1 on Chuna [51] and 4 on acupressure or acupuncture massage [47–50]) and 1 insufficient SR on Shiatsu [49]. Additionally, 1 related SR-MA that was not included in this study supported the possibility of Tuina-integrated treatment t for LBP [59]. Thus, we find that the current CPGs underestimate the effectiveness of TM manual therapy for LBP.

The overall evidence available was usually published in the US and European countries, Thus, a lack of familiarity with East-Asian TM may influence the lack of interventions. These problems may explain the underpowered evidence for TM.

One important thing to consider is the need for more objective methods in TM practice. In contradistinction to classical approaches in Eastern medicine, where the methodology is much more concrete, TM is mainly considered an "art". This understanding complicates an objective study of the results.

We also conducted a quality assessment that included CPGs and SR-MAs. The AGREE assessment showed that the quality of included CPGs was acceptable. The average scores of 5 domains (with the exception of 1 domain) were greater than 60%, and the mean score in the overall assessment was 4±1 [range: 3–6], indicating a moderate quality of CPG (Table 1). The domains of applicability obtained the lowest score, suggesting that more attention should be paid to quality enhancement during CPG development (Table S1).

The SR-MAs were assessed using the AMSTAR instrument [19]. Although the item "Was a priori design provided?" received the lowest score, the overall scores were quite high. The total mean score showed moderate quality of 6.59 [range: 2–10] for included SR-MAs (Table S2). Therefore, future authors should conduct an a priori design to ensure better study quality.

The strength of our study is its successful completion of the first review of TM in current CPGs for LBP. Previous CPGs of Traditional Chinese Medicine [60] did not focus on specific diseases or make further suggestions to address the lack of evidence. To prevent this bias, we attempted to determine whether current TM interventions were adequately included in current, rigorous CPGs of LBP. Thus, we searched current available CPGs and SR-MAs with systematic search methods and assessed CPG

and SR-MA quality. In this study, we reanalyzed the evidence level and grade of recommendation of SR-MAs and aimed to identify directions for future research via a CPG-related expert consensus.

Several study limitations should be considered. Despite our best efforts to retrieve all CPGs and SR-MAs on this subject, we are not convinced that our search was inclusive. Notably, the definition of manual therapy categories in Oriental medicine is a considerable problem. Because we selected the subjects for TM in East-Asian countries, there is a potential question regarding whether the 5 types of intervention represent all TM interventions. To address this problem, we selected the interventions that consider the use of traditional Chinese medicine [61]. Although we suggested recommendation reassessments, we did not follow the entire procedure involved in crafting CPGs [62]. Instead, we made decisions via the expert consensus method. Therefore, biased conclusions are possible.

To address these weaknesses, we suggest important recommendations for future research in this area. First, high-quality RCTs were not conducted despite the use of TM, and there is a remarkable lack of studies on moxibustion, cupping therapy, Tuina (or Chuna), and herbal medicine, which deserve increased interest and further study. Second, a broader scope of TM interventions should be searched in further studies, and accurate recommendations for TM interventions should be drawn via proper procedures by larger organizations or teams. The increasing TM evidence should be included in the process of updating CPGs, and TM interventions based on LBP CPGs should be developed in collaboration with TM experts.

Conclusion

Although interest in and use of TM is increasing, the CPGs identified did not fully reflect the TM interventions in East-Asian countries. In particular, acupuncture, cupping therapy, and manual therapy were underestimated or not mentioned despite their current evidence. The current evidence on acupuncture for chronic LBP and evidence on cupping and manual therapy for both (sub)acute and chronic LBP should be rigorously considered in the process of developing or updating the CPG system. However, a lack of evidence on moxibustion and herbal medicine prevented us from providing recommendations in these areas.

Supporting Information

Table S1 Assessment of Clinical Practice Guidelines (CPG) by AGREEII.
(DOCX)

Table S2 Assessment of Systematic Reviews by AMSTAR.
(DOCX)

Checklist S1 PRISMA checklist.
(DOCX)

Author Contributions

Conceived and designed the experiments: H-WC E-HH K-HH B-CS. Performed the experiments: H-WC E-HH. Analyzed the data: H-WC BML B-CS. Wrote the paper: H-WC. Contributed to assess the level of evidence, grade of recommendation and methodological quality of the CPGs and SR-MAs: H-WC J-PL KT. Contributed to search the CPGs and SRs from each countries: H-WC E-HH K-HH B-CS. Contributed to the consensus of recommendation of future CPGs: H-WC E-HH B-CS BML K-HH J-PL KT MS-L.

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特集
国際標準化と漢方：ISO/TC249 を中心に

漢方・生薬製剤に関わる国際標準化

新井 一郎

Key words　*ISO TC249, Standardization, Kampo Products, Traditional Chinese Medicine*

はじめに

現在，ISO/TC249（International Organization for Standardization，Technical Committee 249，国際標準化機構 専門委員会 249）において“manufactured TCM（Traditional Chinese Medicine）Products”（以下，「TCM 製品」）の品質と安全性に関する国際標準化が進められている。原案作成を担当しているのは TC249 の Working Group 2（WG2）であり，そのタイトルおよびスコープ（業務範囲）は，2012 年 5 月に韓国・テジョンで開催された第 3 回 Plenary meeting（全体会議）において下記のように定められている。

Title: Quality and safety of manufactured TCM* products

Scope: To create international standards for testing, processing (other than traditional processing) and manufacturing of TCM* products, from starting materials to finished products, in a framework of quality and safety.

“TCM*products” に “*” がついているのは，この “TCM”という言葉の意味は TC249 のタイトル，スコープに連動するということを示している。現在の ISO/TC249 のタイトルは “TCM（provisional)” と，暫定的なものであり，そのスコープも決められていない。したがって，この “TCM* products” がどこまでのものを含むかは現時点では明確になっていない。

本総論においては，「TCM 製品」に関する世界の現状と標準化について概説するが，ここでは「TCM 製品」という言葉は，ISO/TC249 で標準化の対象となる “可能性のあるもの” という広い意味で使用しており，今後 ISO/TC249 のタイトル，スコープが決定された場合，本総説における「TCM 製品」とは意味が異なってくる可能性があることをお断りしておく。

TC249 における標準化については，タイトルやスコープの問題も含め，日々刻々，進展・変化しており，本総説が出版されたときには，すでに状況が変化している可能性もある。この総説における記載は，2013 年 1 月末の状況である。

2013 年 2 月 1 日受理
ARAI Ichiro: International Standardization of TCM products (provisional)
東邦大学薬学部生薬部：〒 274-8510 千葉県船橋市三山 2-2-1

1. 世界における「TCM製品」の現状

“Traditional Chinese Medicine”という言葉は中国語の「中医薬学」の英語表記であるが，TC249においては，中国の伝統医学という狭い意味で使用される場合と，漢方や韓医学など，古代中国医学に源流を持つ医学をも含めた広い意味で使用される場合とがあり，混乱の原因になっている。また，“Traditional Chinese Medicine”という言葉は，“Traditional”，“Chinese”，“Medicine”という3つの言葉から成るが，TC249においては，鍼電極低周波治療機のように中国以外の国で新規に開発されたものに関する標準化の提案も出されている。また，医薬品か医薬品でないかは，各国のレギュレーションに依存し，同じモノでも，ある国では医薬品として，ある国では食品として扱われるなど，複雑である。これらのことが，さらに混乱に拍車をかけており，タイトルとスコープが決まらない一因にもなっている。

1）日本における「TCM製品」

日本の漢方製剤を「TCM製品」と呼ぶことに違和感を覚えられる方は多いであろう。しかし，中国，韓国以外の外国の方と話をした場合，“TCM”という言葉は知っていても，“Kampo”という言葉はほとんど知られておらず，知っていても，KampoはTCMのひとつの流派くらいに理解されている方が大多数である。日本の漢方・生薬製剤はほとんど外国には輸出されていないのに対し，中国のTCM製品は，実際，多くの国で目にする。

わが国においては，漢方製剤は，処方自体は“Traditional”なものであるが，エキス剤が大部分を占めており，これを“Traditional”と呼んでよいかについては議論があろう。また，伝統医学の医師制度がある中国や韓国とは異なり，日本においては，漢方製剤は西洋医学のシステムの中で用いられていることから，この面でも，必ずしも“Traditional”とは言えない。漢方製剤は，日本では，当然，医薬品であるわけであるが，「TCM製品」の中には，日本では食品として流通しているものもあり，「TCM製品」の標準化は，我が国の漢方製剤以外の製品にも影響を与える可能性がある。以上のことから，「TCM製品」と漢方製剤とは別物であるとの主張もありうるが，漢方製剤の原料である生薬は，大部分中国産の生薬から製造されており，また，多くのISO参加国は両者を区別できないことから，実際の標準化の現場では，漢方製剤とTCM製品とを完全に切り離すことは，現時点では非常に困難である。

2）中国における「TCM製品」

そもそも，「TCM製品」とは中国由来のものを指しているわけであるから，TC249における「TCM製品」とは何かを定義するのは中国であるとも言える。しかし，「TCM製品」は既に世界中に広まっており，各国の思惑もあり，未だに「TCM製品」とは何かが明確になっていない。

しかし，中国がISO/TC249に提出した提案書の1つには，今後，Chinese Patent Medicines（中成薬）の標準化も行うことが書かれている。これは明らかに“Traditional”なものではない。また，ISO/TC249では，今後，アメリカ人参やイチョウに関する標準化の提案が出される可能性があるが，これらは，純粋な“Chinese”とは言いがたい面もある。また，2012年12月20日付けの中国中医薬報（国家中医薬管理局主管の中国中医薬報社が発行）に，国家中医薬管理局による中医薬標準化中長期発展計画綱要（2011-2020）[1]が掲載されたが，この中には，薬膳の調理方法の標準化を中国国内で今後行うことが書かれている。中国にとっては薬膳も「TCM製品」であるということになり，今後，ISOの場に提案されてくる可能性も考えられる。

		2010年	2011年	2012年 (1-10月)
中薬類総計		19.44	23.32	20.03
	ヘルスケア製品	1.61	2.06	1.75
	抽出物	8.15	11.29	9.48
	中成薬	1.93	2.30	2.19
	生薬，刻み生薬	7.76	7.67	6.61

単位：1億米ドル
中国医薬保健品輸出入商工会議所のホームページ[2]のデータより作成

図1　中国からの中薬輸出額の年次推移

日本においては，漢方の国内標準化というものはなされていないが，中国では，多くのTCMに関係するものが国内標準として既に多数存在する。例えば，国家標準（GB）には，“The licorice”（GB-079），“Determination of ginsenosides in ginseng - LC-UV method”（GB-138），“Chinese medicinal spray dryer system”（GB-184，現在は廃止）などある。また，業界標準（GH）には，“American ginseng products”（GH-020），“Ginseng products”（GH-021），Method for determination of BHC and DDT residues in Chinese medicinal material for export（GH-062），“Method for the determination of copper, lead, mercury and arsenic in traditional-prepared Chinese medicine for export–atomic absorption spectrophotometer”（GH-069），“extracting tank”（GH-074），“To-and-fro type herbal medicine cutting machine”（GH-077），“Herbal medicine washing machine”（GH-078），“Rotary herbal medicine slicing machine”（GH-079），“Herbal medicine roaster”（GH-081），“Medicinal material cutting machine”（GH-086）などある。今後，これらの中国国内標準がISOの場で国際標準として提案されてくる可能性が考えられる。これらの中国国内標準タイトルを見ると，TCMか，漢方か，と分類できないものが多くあることがおわかりになると思う。

中国医薬品保健品輸出入商工会議所では，ホームページ[2]にて中薬の輸出統計を発表している。製品カテゴリー別輸出金額（図1）では，抽出物（エキス，日本のメーカーが中国で生産した日本向けのエキス原末も含まれると思われる）が，約半分を占めており，次いで，生薬・刻み生薬，中成薬，ヘルスケア製品となっている。2010年の地域別輸出額（図2）ではアジア地域が圧倒的に多く（全体の66%，ただし，香港向けの輸出を含む），次いで欧州（16%），北米で（11%）ある。国別では，日本が第一の輸出先となっている。中国は，「TCM製品」の標準化による輸出増をTC249の目標のひとつとしているが，まだ，輸出金額の少ないアジア以外の地域もターゲットにしているものと思われる。EUと中国は2012年にGood Practice in Traditional Chinese Medicine Research in the Post-genomic Era（中医薬規範研究学会）[3]をたちあげ，10のWGで中薬に関する規範研究を開始しているが，この中には品質管理に関するWGも含まれている。アフリカに目を向けると，TC249の参加国の1つであるガーナに中国の援助により病院が建設され，TCMセクションが設けられている[4]。TC249のリエゾン（協力団体）になっているWorld Federation of Chinese Medicine Societies（WFCMS，世界中医薬学会連合会）も，世界中の国々のTCM関係者と種々の活動を行っており，そのホームページ[5]では，いくつかの国のISO代表者の写真が見受けられる。

輸出地域

	2010年
1 アジア	12.8
2 ヨーロッパ*	3.1
3 北アメリカ	2.2
4 ラテンアメリカ	0.9
5 アフリカ	0.3
6 オセアニア	0.2
総額	19.4
*うちEU	2.9

輸出国

	2010年	2012年
1 日本	3.3	3.9
2 香港	2.7	3.0
3 米国	2.0	2.8
4 韓国	1.4	1.3
5 マレーシア	1.0	0.5
6 ベトナム	1.0	0.8
7 インド	0.8	0.6
8 台湾	0.8	no data
9 シンガポール	0.7	0.5
10 ドイツ	0.7	0.8
11 メキシコ	0.7	no data
12 スペイン	0.7	no data
13 フランス	0.4	0.5
14 オランダ	0.4	no data
15 インドネシア	0.3	no data
16 英国	0.3	no data
17 タイ	0.3	no data
18 オーストラリア	0.2	no data
19 カナダ	0.2	no data
20 イタリア	0.1	no data

単位：1億米ドル
中国医薬保健品輸出入商工会議所のホームページ[2]のデータより作成

図2　中薬の地域別輸出額（2010年）

WFCMSでは2012年9月にはメキシコで，第1回アメリカ大陸中医薬国際協力開発フォーラムを開催しており[6]，中米へのTCMの普及を行っている。このように，「TCM製品」の標準化の布石が着々と進みつつあるのが現状である。

3）韓国における「TCM製品」

韓国は，従来，自国の伝統医学をTraditional Korean Medicineと呼んでいたが，大韓韓医学会では2012年からは“traditional”を取り，単にKorean Medicineと表現するようになった。これは，もう，“traditional”ではないとの自負の表れであると思われる。

韓国の「TCM製品」も，大部分は外国には輸出されていないが，唯一，コウジンだけは大量に世界中に輸出され，主要メーカーであるKorea Ginseng Corporation（韓国人参公社）の売り上げは年間0.5-1億米ドルに達している[7]。このことから，TC249における「TCM製品」に関する韓国の提案は，コウジンを中心に行われている。

4）米国における「TCM製品」

米国では2004年のFDAによる植物薬ガイダンス（Guidance for Industry -Botanical Drug Products-）[8]の発出以来，医薬品としての植物製剤の開発が盛んに行われるようになった。いままでに，2006年に緑茶カテキン画分外用剤のVeregen（商品名）[9]が陰部疣贅（ゆうぜい），肛門周囲疣贅に対して，2012年末に南米原産植物であるCroton lechleriの樹脂タンニン系化合物である

Fulyzaq（商品名は Crofelmer）[10]が抗ウイルス治療を受けているHIV/AIDS患者の非感染性下痢に対して承認されている。しかし,「TCM製品」の医薬品としての承認はまだなされていない。「TCM製品」としては，2010年8月に天津天士力集団の複方丹参滴丸（心臓・脳血管疾患薬）[11]が，2013年1月に血脂康（高脂血症薬）[12]がFDAのPhase2を終了したと報道されている。

米国における「TCM製品」には，DSHEA法（Dietary Supplement Health and Education Act of 1994）[13]に従い，Dietary Supplementとして，申請・登録がなされて販売されているものがある。DSHEA法では，パッケージ表示のやり方を定めているが，それに従っていない製品もあり，Dietary Supplementとして登録されずに販売されているものもあるようである。

米国のISO代表団の代表は American Herbal Products Association（AHPA）の会長であり，会員会社からも数社がISO会議に参加している。AHPAの中にはChinese Herbal Products Committeeが設けられており，その活動内容は“Promotes responsible commerce of those herbs and herbal products that are included in and/or based on traditional use of Chinese herbs”となっている。AHPの会員の中で「TCM製品」に関係する会社は20社あり，内訳は，Botanical Supplier3社，Distributor 5社，Finished Product Marketer: Consumers 3社，Finished Product Marketer: Professionals 1社，Manufacturer 6社，Educational Institution 2社となっている[14]。このManufactureには「TCM製品」以外を取り扱っている会社もあり，6社全てが「TCM製品」を製造しているかどうかはわからないが，少なくとも数社は「TCM製品」の製造を行っている事が確認できている。したがって，米国は，「TCM製品」の消費国であるとともに，製造国という側面も有している。

5）ヨーロッパにおける「TCM製品」

ヨーロッパでは，植物薬の伝統があり，古くより，植物性医薬品が用いられてきている。欧州薬局方（EP）にも多数の生薬が収載されており，人参など，日本や中国で使用されている生薬もある。

2004年4月に，EUでは植物薬に関する承認制度 Traditional Herbal Medicine Registration Scheme（THMRS）が開始された。この制度以前に欧州で販売されていた植物薬は2011年4月末まではOTC薬として販売できるが，それ以後は，有効性のエビデンス（EUの中での15年間の使用経験，世界的な30年の使用経験）がないと，市場から撤退させられることになった。この条件をクリアした西洋系の植物薬は多数あったが，中成薬でこの条件をクリアしたものはわずか1製品（地奥心血康カプセル[15]）であり，その他の全ての中成薬は欧州市場から締め出されることとなった[16]。このことにより，2012年1-7月期，中国の対EUの中薬輸出額は，前年同期比で36.5%も下落した[17]。なお，EUで通常の医薬品（market authorization）として承認された「TCM製品」はない。現在，EU諸国で，合法的に流通している「TCM製品」は，地奥心血康カプセルを除いては効能のない刻み生薬や，調剤用の単味生薬エキスだけである。

2. TC249 WG2設立の経緯

2010年6月中国・北京で開催されたISO/TC249第1回 Plenary meetingにおいては医療機器（鍼を含む）と天然物の品質と安全性分野の新規提案（New Work Item Proposal）を作成するタスクフォースを組織し，ドイツが責任国となることが決定された。

2011年5月にオランダ・ハーグで開催された第2回 Plenary meetingにおいては，この医療機器と天然物の品質と安全性分野の標準を同一の専門

家（Expert）で作成していくことは難しいことから，まず，医療機器領域と天然物領域とに分けて議論することになった。次いで，天然物領域に関して，今後，どのように標準を作成していくかについて議論がなされた。この議論の参加国は，日本，中国，韓国，ドイツ，米国，カナダ，オーストラリア，オランダ，南アフリカ，タイの10ヵ国であった。最終的には生薬を担当するWG1（議長国：中国）と，工業製品（加工調整を含む）を担当するWG2（議長国：ドイツ）とに分けて議論していくこととなった。

ハーグ会議で，WG1，2が設立され，その分担領域が決定されたものの，両者の担当領域は一連のものであり，その境界線は明確にはなっていなかった。この2つのWGのうち，まず，WG1が2011年12月に中国・北京で開催され，WG1の担当領域に関する議論がなされた。当初は，議長は，農産物を採取，収穫するところまでがWG1の担当領域であるとしていたが，議論の中で，生薬の加工調整や，刻み生薬の品質（指標成分や汚染物質，毒性物質）までWG1が担当するということが，WG1として決定された。

2012年4月にドイツ・ベルリンで開催されたWG2会議においては，このWG1の決定を受けて議論がなされたが，ハーグでの議決通り，WG2では生薬の加工調整も取り扱い，刻み生薬も工業製品の1つであることから，WG2で担当することがWG2として再確認された。

2012年5月の韓国・テジョンでの第3回Plenary meetingでは，WG1とWG2との主張が矛盾することから調整が行われ，最終的には，WG1のタイトルとスコープは下記のようになった（WG2のタイトルとスコープは上述参照）。

Title: Quality and safety of raw materials and traditional processing

Scope: To create standards related to raw materials at any stage up to and including harvest of a plant ingredient and collection of an animal or mineral ingredient, and the traditional processing of raw materials.

3. WG2における標準提案の状況

WG2においては，現在3件の予備作業項目（PWI: Preliminary Work Item）が提案されている。

1）Quality and Safety of natural materials and manufacturing products made with natural materials used in and as traditional Chinese medicine (TCM)*（提案国：ドイツ）

本提案は，工業製品の品質と安全性を，原料（Starting materials）と最終製品（Finished products）との2つの段階で保証しようというものである。ドイツの主張では，この2つの段階で保証すれば十分であるとのことである。これは，ヨーロッパは「TCM製品」の製造国ではなく輸入国であることから，輸入された製品の保証をターゲットとした考え方である。

2）Quality and Safety of natural materials and manufacturing products made with natural materials used in and as traditional Chinese medicine (provisional)（提案国：日本）

日本の漢方・生薬製剤の品質保証も，当然，原料（生薬）と最終製品とで行われているが，これに加えて中間製品（エキス）での品質保証，製造工程における品質管理を加えることで，より完璧な品質保証となっている。日本としては，他国にもこのような品質保証の方法を推奨するため，ドイツの提案を補完するものとして，このPWIを提案している。

日本には，製造工程における品質管理として，業界の自主基準である漢方GMP[18]があり，最新版は2012年3月に改訂されたものである。この改訂は，日本がPIC/S（The Pharmaceutical

Inspection Convention and Pharmaceutical Inspection Co- operation Scheme）[19]に加盟申請するにあたり，PIC/SのAnnex 7 "Manufacture of herbal medicinal products"（最新版は2013年1月1日改訂版[20]）に対応するためである。また，中国でも医薬品GMPの付録として，中薬のGMPが存在する[21]。この他の国にも植物薬GMPのようなものがあり，これらを参考に，ISOとしての「TCM製品」の工程管理の保証を行おうとする提案である。

3）General requirements of manufacturing process for Red Ginseng（提案国：韓国）

韓国の主要輸出品の「TCM製品」であるコウジンの製造工程の標準化の提案である。

これら，3つの提案は2012年3月のWG2 web会議を経て，2012年5月の南アフリカ・ダーバンでの第4回Plenary meetingにおいて，新作業項目（NWIP: New Working Item Proposal）としての投票の承認を得る計画である。

WG2内では，各国のレギュレーションが異なることから，これらの標準には特定の方法，特定の規格値を盛り込まないことで，現時点では一致している。

また，第4回Plenary meetingには，韓国から"Therapeutic equivalence of single herb products for herbal decoction/preparation"，"Guidelines for manufacturing safe and regular herb preparations in individual clinics"の2件の提案がなされ，議論がなされる予定である。

さいごに

今まで，中国は5つのWGの中で，唯一WG2だけは標準化の新規提案を行っておらず，感心が低いように見える。ただ，2013年1月7日の中国中医薬報に掲載された記事[22]では，今後，中成薬の標準化を積極的に行うとともに，国際標準と，生薬や中成薬の各国の局方や法規との関係を処理していくことが述べられてしる。したがって，今後，中国からWG2に対し中成薬の標準化の提案が出される可能性がある。この中成薬の定義は現在のところ不明であるが，漢方製剤との関係で注意が必要である。今後も，日本国民の健康に悪影響が出ないよう，注意して活動していきたい。

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シリーズ和漢　第3回

品質の「よい」漢方エキス製剤とは

株式会社ツムラ 医薬営業本部 ツムラ図書館
新井　一郎

医療用漢方エキス製剤が、1976 年に大量に保険収載されてから 30 年以上がたちます。皆さんの中には、病院薬剤師になられたときには、既に、医療用漢方エキス製剤が薬局にあったため、特別なものとは思っておられない方も多いと思います。

漢方エキスの品質規格が日本薬局方に収載されはじめたのは、実は、ごく最近の 2006 年の 15 局からです。従いまして、生薬の品質に関する教育は受けたことはあっても、漢方エキスの品質については教育を受けたことはないという方が多いのではないでしょうか。そこで、今回は、漢方エキス製剤の品質について、医療用漢方エキス製剤を中心に説明します。

漢方エキス製剤に求められる品質は、新薬とは同じではない

医薬品は有効で安全なものがよいということは、言うまでもないことです。医薬品では、その有効性と安全性が、どのロットでも均一であることが、当然、求められます。

単一化合物を有効成分（成分本質）とする、いわゆる新薬では、有効成分の純度を高め、不純物の割合を極力減らすとともに、GMP により安全で安定した製造を行うことで、均一性を保証しているわけです。

漢方エキス製剤も医薬品ですので、基本的な考え方は同じです。しかし、新薬との大きな違いは、全ての含有成分が解明されていないことです。また、天産物を原料としているため、各含有成分量が全てのロットで完全に同じにはならないということです。したがって、漢方エキス製剤の品質は、新薬とは、別の観点からも考える必要があります。

甘草の有効成分はグリチルリチン？

「甘草の主成分はグリチルリチンである」と、よく、言われます。皆さんもそのように習われたと思います。しかし、甘草の煎液中のグリチルリチンを定量しても数%にすぎません。「甘草の主成分はグリチルリチンである」とは、「甘草の知られている成分の中で、甘草に特異的でかつ定量可能な（低分子）物質のうちで量が多いものはグリチルリチンである」というのが本当の意味です。甘草からのグリチルリチンの単離は古くから行われており、グリチルリチンを用いた薬効研究も多く行われてきたため、その多様な作用が動物において数多く報告されています。そのため、「甘草の有効成分はグリチルリチンである」と言われる場合が多いのですが、正しくは「甘草の有効成分の“ひとつ”はグリチルリチンである」と言うべきでしょう。もし、甘草の有効成分がグリチルリチンだけであるのなら、甘草を含有する漢方エキス製剤では、原料として甘草を用いる必要はなく、グリチルリチンを配合すればよいことになります。甘草の大部

分を占めるグリチルリチン以外の成分（低分子物質だけでなく、多糖類やタンパクなども含む）は、全ては同定されておらず、それらが、甘草が含有される漢方エキス製剤の薬効に全く無関係であるとは言えませんので、現在も、漢方製剤の原料としては、グリチルリチンではなく甘草が用いられているわけです。「よい」品質の漢方エキス製剤とは、グリチルリチンのような特定のひとつの物質の量だけが多ければよいということではありません。

品質をコントロールする

皆さんがスイカを食べられる時、毎回、同じ甘さであったということはないでしょう。今回はアタリ、今回はハズレと、一喜一憂されている方もおられると思います。同じ農家が同じ年に作ったスイカでも、常に 100%同じ味であるということはありえません。収穫してから熟すまでの時間も、味に影響があるでしょう。このようなことは、天産物を原料としている漢方エキス製剤にも当てはまります。スイカでしたら、「今回はハズレか」ですみますが、医薬品である漢方エキス製剤では、「今回は効きが悪かった」、「今回は効きすぎた」、「今回は副作用が多かった」ではすみません。

漢方製剤の品質を、全ロットで 100%同じにすることはスイカ同様、不可能です。ただ、ある一定の範囲の中におさめることはできます。欧米も含め、植物製剤においては “Quality Control” という言葉をよく使いますが、これは、完全に同一なものを求めるのではなく、一定の範囲の中で、ばらつきのない製品を作ろうという考え方です。

従って、「よい」品質の漢方エキス製剤とは、いつ、どのロットの製品を用いても、大きな差のない有効性、安全性が担保されているもの、ということになります。

現在の漢方エキス製剤の品質規格

1976 年に医療用漢方エキス製剤が大量に保険収載された直後は、その品質や 1 日製剤量中のエキス量は各社の判断で決められていました。しかし、1981 年頃から、富山医薬大の薬剤部などから、1 日製剤量中の特定物質の量がメーカーによって大きくばらつくことが学会で報告されるようになりました。これらの報告を受け、国の方でも漢方エキス製剤の品質が問題になり、1982 年-1984 年に厚生科学研究「漢方エキス製剤の規格基準作成に関する研究」が行われました。そして、この研究結果をもとに、1985 年 5 月に厚生省薬務局審査課長通知 薬審 2 第 120 号「医療用漢方エキス製剤の取り扱いについて」が出され、各社は、原則 1 年以内に、医療用漢方エキス製剤の規格を、この通知にあわせて申請しなおすように求められました。この代替申請に当たっては、申請書の右肩に丸で囲った「漢」という文字を朱色で入れるように求められましたので、このことは、通称 “マル漢”と呼ばれています。この時の“マル漢”規格が、今日まで続く医療用漢方エキス製剤の品質であり、日本薬局方への漢方エキス収載のもとになった考え方です。したがって、“マル漢”以前の、医療用漢方エキス製剤を用いた臨床論文や学会報告は、同じ名前の処方の報告でも、現在の医療用漢方エキス製剤を用いたものではないということになります。なお、医療用漢方製剤の中には、一部、生薬末を混合しただけのもありますが、これらは、エキス剤ではないため、“マル漢”の対象にはなりませんでした。