



Regulation and status of herbal medicine clinical trials in Korea: a narrative review



Boram Lee , Yujin Choi , Pyung-Wha Kim , Changsop Yang , Myeong Soo Lee *

Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

ARTICLE INFO

Article history:

Received 23 July 2020

Received in revised form

28 September 2020

Accepted 22 October 2020

Available online 4 November 2020

Keywords:

Herbal medicine

Clinical trial

Investigational new drug application

IND

ABSTRACT

Background: Herbal medicine has been used frequently in Korean medicine. We aimed to summarize the relevant regulations for herbal medicine clinical trials and to analyze their current status in the Republic of Korea.

Methods: We searched for legislation to find regulations on herbal medicine clinical trials. Additionally, the websites of the Korean Ministry of Food and Drug Safety (KMFDS) and Clinical Research Information Service (CRIS) were searched to investigate the current status of them.

Results: To conduct herbal medicine clinical trials for new drugs or previously approved drugs outside of indications, investigational new drug (IND) approval should be obtained from the KMFDS. For clinical trials of herbal medicines that have been used for more than 3 years with 200 cases at the clinical trial institution, nonclinical data can be exempted from IND approval. Total 95 and 108 herbal medicine clinical trials from the KMFDS and CRIS websites were analyzed. The number of clinical trials showed an increasing trend each year, as did KMFDS-regulated clinical trials. Recently, three clinical trials targeting new herbal formulations frequently used in Korean medicine institutions have been approved based on relevant regulations.

Conclusion: We confirmed that herbal medicine clinical trials are managed through strict regulations, which can ensure the safe and effective use of herbal medicine. Despite strict regulations, attempts to accumulate evidence through clinical trials for herbal medicine are increasing. High-quality clinical trials should be conducted to develop new drugs that reflect the clinical setting using relevant regulations, evaluate the efficacy and safety of the drugs, and strengthen insurance coverage.

© 2020 Korea Institute of Oriental Medicine. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Herbal medicine has been used for the treatment of various diseases and symptoms for a long time in the Republic of Korea. It has been developed based on long-term clinical experience and the unique theoretical system of Korean medicine (KM). However, since the 1990s, the importance of evidence-based medicine (EBM), which includes providing the best care to patients by selecting appropriate treatment methods based on scientific evidence and integrating them with clinical experiences in clinical decision-making, has expanded.¹ Therefore, to clarify efficacy and safety according to EBM, the verification of treatment effects through well-designed clinical trials is required. Such evidence is also increasingly required for herbal medicine.

The Investigational New Drug (IND) application is the process of applying for approval from the Korean Ministry of Food and Drug Safety (KMFDS) for those who want to conduct clinical trials using a drug for the purpose of collecting safety and efficacy data from humans.² In the Republic of Korea, IND was introduced in December 2002 with the aim of protecting participants' rights, establishing a new drug development track by facilitating entry into clinical trials, and promoting global multinational clinical trials through improving the level of domestic clinical trials by harmonizing with the level of advanced countries.³ IND is classified into commercial IND (for marketing approval) and non-commercial IND (for research and treatment) according to the purpose. Non-commercial IND corresponds to clinical trials conducted independently by investigators for new efficacy, effectiveness, or dosages that are not approved for previously approved drugs or new drugs without external referral (investigator IND)² or corresponds to use other than clinical trials for the treatment of patients with serious life-threatening diseases or patients without alternative treatment (treatment IND).⁴

* Corresponding author at: Clinical Medicine Division, Korea Institute of Oriental Medicine, 1672 Yuseongdae-ro, Yuseong-gu, Daejeon 34054, Republic of Korea.
E-mail address: drmslee@gmail.com (M.S. Lee).

Especially in the case of the herbal medicines listed in a few well-known traditional KM references, safety and effectiveness examinations for product licensing are exempted in the Republic of Korea.⁵ However, in the clinical setting of KM, various individualized herbal medicine not listed in traditional KM references is frequently used based on the theory of traditional KM. Therefore, even though these herbal medicines have long been used based on clinical experience, it is necessary to conduct clinical trials step by step like new conventional drugs to accumulate scientific evidence. The purpose of this study is to provide a narrative analysis of the regulations applied to herbal medicine clinical trials in the Republic of Korea and their current status, identify current situations, and suggest future directions for herbal medicine clinical trials.

2. Methods

2.1. Searched sources and searched terms

2.1.1. Regulation of herbal medicine clinical trials in the Republic of Korea

We searched for legislation related to clinical trials to find regulations on herbal medicine clinical trials in the Korea Ministry of Government Legislation website (<https://www.law.go.kr/>). We summarized the laws and regulations related to target for IND application, approval procedure, and data requirements of herbal medicine clinical trials, updated until April 20, 2020.

2.1.2. Current status of herbal medicine clinical trials in the Republic of Korea

Information on clinical trials conducted in the Republic of Korea can be found on three representative sites: the KMFDS website, the Clinical Research Information Service (CRIS), and the Korea Clinical Trials Information Center (K-CLIC). On the KMFDS website, information on clinical trials approved by the KMFDS, including the title, investigational product, and institution, can be found. In the case of clinical trials that are approved by the KMFDS after October 26, 2019, more detailed information, including inclusion and exclusion criteria of participants and outcome measurements, is presented (<https://nedrug.mfds.go.kr/searchClinic>). CRIS is one of the World Health Organization International Clinical Trials Registry Platforms managed by the Korean Centers for Disease Control (KCDC), where researchers register information about clinical trials (<https://cris.nih.go.kr/>). The K-CLIC website provides clinical trial information for participants and investigators and regularly summarizes the status of clinical trials (<https://www.koreaclinicaltrials.org/>). In the case of KM clinical trials, some information can be found on the National Clearinghouse for Korean Medicine (NCKM) website (<http://www.nckm.or.kr/>).

In terms of regulation, clinical trials can be classified into KMFDS-regulated studies and KMFDS-non-regulated studies. Information on KMFDS-regulated clinical trials can be obtained from the KMFDS website, and information on clinical trials that are not subject to regulation by KMFDS can be found on the CRIS website only if the researcher has registered the information. To investigate the current status of herbal medicine clinical trials, searches were conducted on two representative sites of the KMFDS and CRIS. In general, the titles of herbal medicine clinical trials refer to the preparation form including decoctions, tang, and granules (ex. Hwangryunhaedok-tang), and there are few cases where the titles include the phrase “herbal medicine” or “herb”. In addition, there are cases in which the name of the herbal medicine is not specified in the clinical trial title due to the development of new drugs. Most herbal medicine clinical trials are conducted at KM hospitals in the Republic of Korea; therefore, we searched for herbal medicine clinical

trials that included the phrase “Korean Medicine (한방)” in the name of the institution.

The search and selection of clinical trials were conducted by one researcher (YC), and the search dates were April 26, 2020 (KMFDS) and April 23, 2020 (CRIS), respectively. Other researchers reviewed the search and selection results, and if there were disagreements between researchers, a decision was made by agreement between the researchers. For the inclusion and exclusion criteria, we only included clinical trials for herbal medicine and excluded observational studies as well as non-herbal medicine clinical studies. For interventions, we included both single and multi-herbal formulas. In addition, herbal medicines administered according to the East Asian traditional theory were included, and dietary supplements were excluded. There were no other restrictions such as preparation form and administration period.

2.2. Data analysis

We qualitatively described the related regulation of herbal medicine clinical trials. With regard to the clinical status of herbal medicine clinical trials, the information provided by the KMFDS and CRIS websites is slightly different and the types of information that can be extracted from the KMFDS website differ depending on the time period. Therefore, we extracted the following information from each site. We extracted information on the date (IND-approved), phase, clinical trial application holder, and characteristics of the study drug from the KMFDS website. From the CRIS website, the date (CRIS registered), principal organization, sources of research funds, category of diseases, herbal medicine used, characteristics of study drug, and study design were extracted. For clinical trials registered with CRIS, information was extracted by separating KMFDS-regulated and non-regulated trials. Categorical data were presented by frequencies (percentages, %). The results were analyzed using Microsoft Excel 2016 (Microsoft Office 2016, Microsoft, Redmond, WA, United States).

3. Results

3.1. Regulation of herbal medicine clinical trials in the Republic of Korea

3.1.1. Target for IND application

All clinical trials using a drug for the purpose of collecting safety and efficacy data on the human body are subject to IND application.² However, a clinical trial is exempted if it targets a drug approved by the KMFDS and is conducted within the scope of the indication permitted.⁴ However, institutional review board (IRB) approval should be obtained before the trial begins, and all clinical trials should be conducted according to Korean Good Clinical Practice (KGCP).

The herbal medicine formula listed in the 10 traditional Korean medicinal references (*Donguibogam*, *Bangyaghabyeon*, *Hyangyakjipseongbang*, *Gyeongagjeonseo*, *Euihakipmun*, *Jeungsinyeon*, *Dongeuiseubowon*, *Kwangjebigeup*, *Bonchogangmok*, and *Hanyakjojechimseo*) is considered to have proven clinical safety and efficacy in the traditional use experience and publishing process.⁵ Therefore, KMFDS exempts some of the clinical trial IND filings. However, in addition to the above literature evidence, based on long-term clinical experience and traditional KM theory such as Sasang constitution or pattern identification, herbal medicines are being administered to diseases or symptoms other than indications in the clinical setting. Therefore, although certain herbal medicines are already widely used for certain diseases and symptoms in the KM clinical settings, entirely packaged IND application is still required when conducting clinical trials of targeting diseases

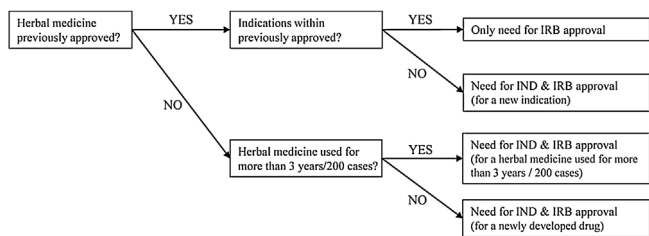


Fig. 1. Flow chart of regulation scope in herbal medicine clinical trial application.

and symptoms not included in the efficacy and effectiveness indications. In addition, various herbal medicine formulas are widely used in KM clinics and hospital; however, there are many challenges and difficulties in conducting clinical trial with herbal medicine formulas which are not previously developed by pharmaceutical company and approved for commercial use. Considering characteristics of herbal medicine that has been used for a long time, there is a special regulation of data requirements for the approval of investigator initiated clinical trial of herbal medicine which has been used for more than 3 years and 200 cases in KM hospital. In this case, nonclinical data including toxicology data are not required, and instead, data to demonstrate safety and effectiveness based on enough clinical cases and expert opinions are needed according to Paragraph 2 of Article 7 of “Guideline for Approving Clinical Study Plans on Drugs” (Fig. 1).²

3.1.2. Approval procedure and data requirements

To obtain approval for a clinical trial for a drug, an application form and required data should be submitted through the KMFDS online website (<https://nedrug.mfds.go.kr>). After submission, the Clinical Trials Management Division of KMFDS receives the application form and checks for the adequacy of the submitted documents. The application for the herbal medicine clinical trial is then returned to the Herbal Medicines Division of KMFDS for scientific and technical review. After the review process, the application is returned to the Clinical Trials Management Division, where a certificate of IND approval is issued. The period from submission to the first supplementary notice is 30 working days.⁶ To reduce the time required for IND approval, the IND review and IRB application can be conducted simultaneously. Exceptionally, in the case of a clinical trial for herbal medicine that has been used for more than 3 years/200 cases (see 3.1.2.7 for detailed information), conditional approval of the IRB is required before the approval of the IND.²

Table 1 Summary of data requirements for IND approval in Republic of Korea.

Data requirements	Commercial IND	Investigator IND		
		General case	Previously approved drugs or natural product	Herbal medicine used for more than 3 years/200 cases
Study protocol	○	○	○	○
Investigator's brochure	○	○	-	-
Manufacturing and quality data	○	○	○	○
Nonclinical data	○	○	-	-
Previous clinical experience with investigational product	○	○	-	-
Good manufacturing practice certificate	○	○	○	○
Institution, investigator, and contract research organization	○	○	○	○
Development plan	○	○	-	-
Informed consent form	○	○	○	○
The rules for compensation for victims	○	○	○	○
Academic papers proving the scientific validity of conducting clinical trials	-	-	○	-
Certificate from the director of institution	-	-	-	○
Institutional review board approval	-	-	-	○
Letter of recommendation from the Minister of Health and Welfare or related organizations	-	-	-	○

IND, investigational new drug.

The data requirements for commercial or non-commercial IND are basically the same. However, commercial clinical trials focus on objectively demonstrating safety and effectiveness when the product is licensed; therefore, commercial IND requires stricter standards and evidence to ensure objectivity and reliability in the inclusion and exclusion criteria of participants, sample size, validity of the outcome measure, and statistical analysis methods. The list of data to be submitted when applying for IND is as follows. However, if the researcher intends to obtain approval for an investigator-initiated trial of a previously approved drug or natural product, the investigator's brochure, nonclinical data, data on previous clinical experience, and development plan are exempted, and additional academic papers that can prove the scientific validity of conducting clinical trials should be submitted for approval (Table 1).²

3.1.2.1. Study protocol. The study protocol is a document that provides the background or evidence for the trial. It should contain the following: introduction (background, rationale, etc.), purpose, target participants (sample size, inclusion, exclusion and dropout criteria, etc.), trial design (trial period, treatment and control group, assignment, blinding, trial flowchart, etc.), trial termination and early termination criteria, information and management of the investigational product, trial methodology and dosing plan, trial procedure and assessment, data analysis and statistical consideration, data management, ethical consideration and administrative procedures, and information about the investigator, sponsor, and institution.⁴ When developing a clinical trial protocol for herbal medicine, guidelines including Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018 and CONSORT Extension for Chinese Herbal Medicine Formulas 2017 can be referenced.^{7, 8}

3.1.2.2. Investigator's brochure. The investigator's brochure provides information to promote the understanding of key features of study protocols related to the investigational product, such as dosage, dosing method, and safety monitoring procedures. Additionally, it has the purpose of promoting compliance with the study protocol by investigators and other clinical trial-related personnel.²

3.1.2.3. Manufacturing and quality data. Data on the active pharmaceutical ingredient and its dosage, manufacturing method, manufacturer, or standard test method for the investigational product and the result of quality control should be submitted.²

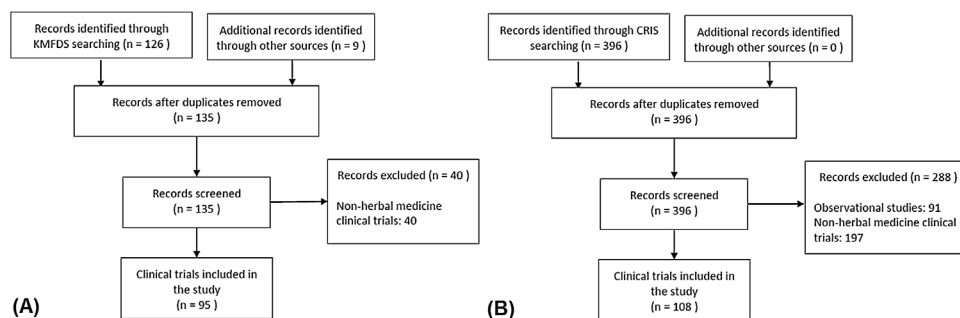


Fig. 2. Flow charts for herbal medicine clinical trial screening and selection processes on (A) KMFDS and (B) CRIS websites.

3.1.2.4. Nonclinical data. Pharmacological and toxicology data are required depending on the characteristics of individual drugs. Pharmacological data include efficacy test data, general pharmacology test data, safety pharmacology test data, and test data on absorption, distribution, metabolism, and excretion. The data can be submitted with results directly obtained from a university or research institute or from published peer-reviewed articles. Toxicology data include single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive toxicity, carcinogenicity, and other toxicological test data according to the characteristics of the investigational substance. The submission of toxicology data is not usually required for previously approved drugs. The toxicology data and safety pharmacology data (central nervous system, cardiovascular system, and respiratory system test) should be collected in Good Laboratory Practice (GLP)-certified agencies and documents proving that the tests were conducted in compliance with GLP should be submitted.⁹ For other tests, data tested by non-GLP institutions can also be submitted. For herbal medicine, the submission of nonclinical data can be partially exempted when it is considered impossible or meaningless. If researchers apply for an IND to investigate new drugs in healthy volunteers and to derive the maximum safe starting dose, human equivalent doses can be translated from the levels of no observed adverse effects in animals with reference to US Food and Drug Administration guidance.¹⁰

3.1.2.5. Previous clinical experience with investigational product. In principle, the rationale and clinical discussion of clinical trials should be included. In the case of drugs that have already been clinically tested or marketed, a description of available pharmacokinetics, pharmacodynamics, dose response, safety, and efficacy results should be submitted.²

3.1.2.6. Others. Data on the institution, investigator, and contract research organization, an informed consent form, and the rules for compensation for victims should be submitted. Clinical trials should be conducted in institutions designated by the KMFDS. Documents proving that the product is manufactured in accordance with good manufacturing practice (GMP) to ensure that the company can adequately produce and supply consistent batches of the drug should be submitted. In addition, the development plan that briefly describes the overall plan to be carried out at least in the first year and the next year is needed.⁴

3.1.2.7. Data requirements for clinical trials of herbal medicine used for more than 3 years with 200 cases. In the case of the investigator-initiated clinical trials with frequently used herbal medicine in KM hospitals, certification that the study drug (herbal medicine) has been used in the KM hospital for more than 3 years with 200 cases is essential for the application. To prove that the study drug has enough clinical cases for patients with target indications, an anonymous patient list with a medical record of the target disease and

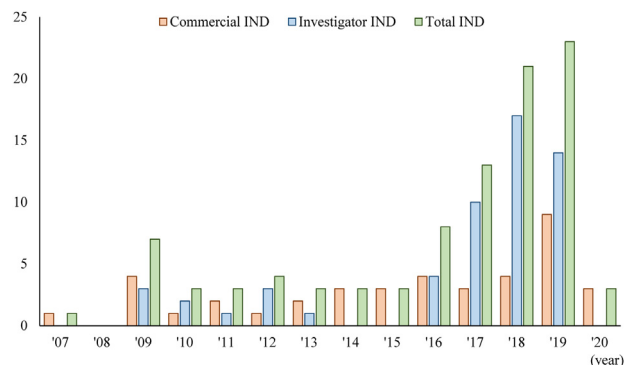


Fig. 3. The number of herbal medicine clinical trials approved by the KMFDS from 2007 to April 2020.

Data were searched from the clinical trial information on the website of the Korean Ministry of Food and Drug Safety (<https://nedrug.mfds.go.kr/searchClinic>, search date: April 26, 2020). Clinical trials of herbal medicine conducted in Korean medicine hospitals were counted.

herbal medicine is required. Additionally, IRB approval and a recommendation from the Minister of Health and Welfare or related organizations are required. Nonclinical data, including pharmacological and toxicology data, are not required, which are necessary for the clinical trial of a newly developed drug. However, certification of investigational herbal medicine produced by the GMP facility is also required.² The IND approval casebook of the investigator's clinical trial of herbal medicine used for more than 3 years with 200 cases is available at the website of the NCKM.¹¹

3.2. Current status of herbal medicine clinical trials in the Republic of Korea

3.2.1. Herbal medicine clinical trials approved by KMFDS (2007~2020.04)

A total of 126 clinical trials were searched on the KMFDS website. Nine herbal medicine clinical trials that were not conducted in KM hospitals were included in the additional search. Forty clinical trials were excluded that were conducted in KM hospitals but were not herbal medicine clinical trials. As a result, 95 herbal medicine clinical trials were included in the analysis (Fig. 2).

The number of herbal medicine clinical trials approved by the KMFDS is gradually increasing over time, as presented in Fig. 3. In 2017, the number of investigator INDs increased remarkably, and the number of commercial INDs increased significantly in 2019. Of the total approved clinical trials, the proportion of investigator IND was the highest at 57.9% (n = 55). Most of the commercial INDs were phase 2 trials, including phase 2a and phase 2b. With regard to the applicants, 61.1% (n = 58) of the total clinical trial applicants were KM hospitals, followed by 20.0% (n = 19) that were pharmaceutical companies and 14.7% (n = 14) that were KM universities. Refer-

Table 2
Characteristics of herbal medicine clinical trials approved by KMFDS from 2007 to April 2020.

Phase	N	%
Phase 1	4	4.2%
Phase 1/2	1	1.1%
Phase 2	24	25.3%
Phase 2a	3	3.2%
Phase 2b	4	4.2%
Phase 2b/3	1	1.1%
Phase 3	3	3.2%
IIT	55	57.9%
Category of CTA holder		
Korean Medicine hospital	58	61.1%
Western Medicine hospital	2	2.1%
Korean Medicine University	14	14.7%
Korea Institute of Oriental Medicine	2	2.1%
Pharmaceutical Company	19	20.0%
CTA holder ^a		
Kyunghee University Korean Medicine Hospital	14	14.7%
Daejeon University Korean Medicine Hospital	14	14.7%
Kyunghee University	11	11.6%
Hanpoong Pharm & Foods Co.,Ltd.	9	9.5%
Busan University Korean Medicine Hospital	7	7.4%
Wonkwang University Korean Medicine Hospital	7	7.4%
Others	33	34.7%
Characteristic of study drug		
Approved drugs (pharmacokinetic, drug interactions)	12	12.6%
Approved drugs for a new indication	41	43.2%
Herbal medicine used for more than 3 years/200 cases	3	3.2%
Newly developed drugs (new composition)	39	41.1%

CTA, clinical trial application; KMFDS, Korean ministry of food and drug safety; IIT, investigator-initiated trial.

^a Names of the holders with a ratio of 5% or more were presented.

ring to the characteristics of the study drug, clinical trials targeting new indications for approved drug were the most common (n=41, 43.2%), followed by those targeting newly developed drugs (new composition) (n=39, 41.1%). There were 12 clinical trials (12.6%) on the pharmacokinetic or drug interactions of approved drugs, and three clinical trials (3.2%) targeting herbal medicine used for more than 3 years with 200 cases (Table 2).

3.2.2. Herbal medicine clinical trials registered in CRIS (2010.02.~2020.04.)

Among a total of 396 registered clinical trials searched from the CRIS, observational studies (n=91) and interventional studies of non-herbal medicine such as acupuncture, electroacupuncture, moxibustion, and dietary supplements (n=197) were excluded. Finally, 108 herbal medicine clinical trials were included in the analysis (Fig. 2).

The number of herbal medicine clinical trials registered in CRIS is gradually increasing, as presented in Fig. 4. In particular, the number of KMFDS-regulated studies increased significantly in 2018 and 2019. The characteristics of registered herbal medicine clinical trials are shown in Table 3. According to the registered information, the proportion of KMFDS-regulated studies was 38.0% (n=41). Approximately 51.9% (n=56) of registered clinical trials were funded by the Ministry of Health and Welfare, followed by 22.2% (n=24) funded by the Korea Institute of Oriental Medicine (KIOM). Several pharmacokinetic studies were funded by the Jeollanamdo Development Institute of Korean Traditional Medicine. Regarding the disease category of the clinical trials, diseases of the musculoskeletal system, including chronic low back pain and knee osteoarthritis, accounted for 14.8% (n=16), followed by diseases of the nervous system (11.1%, n=12), including ischemic stroke and Parkinson's disease, and mental and behavioral disorders (9.3%, n=10), including Hwa-byung, major depressive disorder, and sleep disorders. Clinical trials were conducted on various herbal medicines; Bojungiki-gang and Ojeok-san were tested frequently,

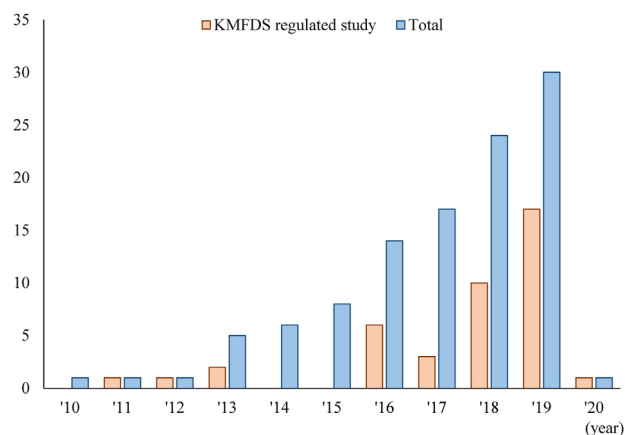


Fig. 4. The number of herbal medicine clinical trials registered in CRIS from February 2010 to April 2020.

Data were searched from the clinical trials information on the website of the Clinical Research Information Service (<https://cris.nih.go.kr/>, search date: April 23, 2020). Clinical trials of herbal medicine conducted in Korean medicine hospitals were counted.

with five trials (4.6%) each. Referring to the characteristics of the study drugs especially in KMFDS-regulated trials, clinical trials targeting approved drugs for a new indication (n=20, 48.8%) were the most common, followed by clinical trials targeting newly developed drugs (new composition) (n=12, 29.3%). There were six clinical trials (14.6%) evaluating the pharmacokinetic and drug interactions of approved drugs and three clinical trials (7.3%) targeting herbal medicines used for more than 3 years with 200 cases.

Details of the study design of the registered herbal medicine clinical trials are summarized in Table 4. There were 15.7% (n=17) pharmacokinetic studies, 10.2% (n=11) before-after studies, 71.3% (n=77) parallel design clinical trials, and 2.8% (n=3) cross-over design studies. Pharmacokinetic studies were conducted for the standardization and modernization of herbal formulas, and commonly used herbal products were tested. Two of the pharmacokinetic studies were cross-over designs comparing extract powder and soft extract of identical herbal formulas. Most clinical trials were parallel design, and placebo comparators were used frequently. There were a few active comparator clinical trials, including conventional medications, cognitive behavioral therapy, and another herbal formula. For mild Alzheimer's disease, ischemic stroke, and amyotrophic lateral sclerosis, herbal medicines were tested for add-on therapy in addition to standard medication. A parallel design with two groups comparing herbal medicine and placebo was the most common, and some parallel designs used three groups to compare low and high doses of herbal medicine and placebo to find the appropriate dose. A few cross-over design clinical trials were registered for the participants with hangovers from drinking, stress due to lack of sleep, and muscle soreness induced by exercise. A total of 7 studies (6.5%) considered pattern identification, which is one of the characteristics of KM, in conducting herbal medicine clinical trials. Five clinical trials suggested inclusion criteria for the pattern identification of each disease: insomnia with heart deficiency, polycystic ovarian syndrome with phlegm pattern, acne vulgaris with wind-heat pattern, functional dyspepsia with liver-spleen disharmony pattern, and functional dyspepsia with excess pattern. Additionally, one clinical trial was planned to be conducted for patients with spleen qi deficiency. There was a clinical trial that tested two different herbal medicines based on KM pattern identification. In this study, Gyegibokryung-hwan was planned to be used for dysmenorrhea-accompanied acne vulgaris patients with excess syndrome, whereas Dangguijagyag-san was planned to be used for patients with deficiency syndrome.

Table 3
 Characteristics of herbal medicine clinical trials registered in CRIS from February 2010 to April 2020.

	Total(N = 108)	KMFDS regulated(N = 41)	KMFDS non-regulated(N = 67)
Principal organization			
Kyunghee University Korean Medicine Hospital	32 (29.6%)	13 (31.7%)	19 (28.4%)
Daejeon University Korean Medicine Hospital	18 (16.7%)	7 (17.1%)	11 (16.4%)
Wonkwang University Korean Medicine Hospital	9 (8.3%)	5 (12.2%)	4 (6.0%)
Korea Institute of Oriental Medicine	6 (5.6%)	2 (4.9%)	4 (6.0%)
Busan University Korean Medicine Hospital	5 (4.6%)	3 (7.3%)	2 (3.0%)
Gachon University Korean Medicine Hospital	5 (4.6%)	0 (0.0%)	5 (7.5%)
Others	33 (30.6%)	11 (26.8%)	22 (32.8%)
Source of research fund			
Ministry of Health & Welfare	56 (51.9%)	21 (51.2%)	35 (52.2%)
Korea Institute of Oriental Medicine	24 (22.2%)	10 (24.4%)	14 (20.9%)
Jeollanamdo Development Institute of Korean Traditional Medicine	9 (8.3%)	0 (0.0%)	9 (13.4%)
National Development Institute of Korean Medicine	6 (5.6%)	6 (14.6%)	0 (0.0%)
Others	13 (12.0%)	4 (9.8%)	9 (13.4%)
Category of diseases			
Neoplasms			
Endocrine, nutritional and metabolic diseases	6 (5.6%)	3 (7.3%)	3 (4.5%)
Mental and behavioral disorders	7 (6.5%)	3 (7.3%)	4 (6.0%)
Diseases of the nervous system	10 (9.3%)	4 (9.8%)	6 (9.0%)
Diseases of the circulatory system	12 (11.1%)	6 (14.6%)	6 (9.0%)
Diseases of the respiratory system	1 (0.9%)	1 (2.4%)	0 (0.0%)
Diseases of the digestive system	7 (6.5%)	2 (4.9%)	5 (7.5%)
Diseases of the skin and subcutaneous tissue	9 (8.3%)	4 (9.8%)	5 (7.5%)
Diseases of the musculoskeletal system and connective tissue	5 (4.6%)	4 (9.8%)	1 (1.5%)
Diseases of the genitourinary system	16 (14.8%)	8 (19.5%)	8 (11.9%)
Pregnancy, childbirth and the puerperium	4 (3.7%)	0 (0.0%)	4 (6.0%)
Symptoms, signs and abnormal clinical and laboratory findings	1 (0.9%)	0 (0.0%)	1 (1.5%)
Not applicable	8 (7.4%)	1 (2.4%)	7 (10.4%)
Frequently used study drug (Herbal medicine)			
Bojungikgi-tang	22 (20.4%)	5 (12.2%)	17 (25.4%)
Ojeok-san	5 (4.6%)	3 (7.3%)	2 (3.0%)
Gyejibokryeong-hwan	5 (4.6%)	2 (4.9%)	3 (4.5%)
Kami-Guib-tang	4 (3.7%)	2 (4.9%)	2 (3.0%)
Dangguijakyak-san	4 (3.7%)	0 (0.0%)	4 (6.0%)
Hwangryunhaedok-tang	4 (3.7%)	1 (2.4%)	3 (4.5%)
Others	82 (75.9%)	31 (75.6%)	51 (76.1%)
Characteristic of study drug			
Approved drugs within the approved indication	73 (67.6%)	6 (14.6%) ^a	67 (100%)
Approved drugs for a new indication	20 (18.5%)	20 (48.8%)	0 (0%)
Herbal medicine used for more than 3 years/200 cases	3 (2.8%)	3 (7.3%)	0 (0%)
Newly developed drugs (new composition)	12 (11.1%)	12 (29.3%)	0 (0%)

CRIS, Clinical Research Information Service; KMFDS, Korean ministry of food and drug safety.

^a Pharmacokinetic and drug interactions studies.

Table 4
 Study designs of herbal medicine clinical trials registered in CRIS from February 2010 to April 2020 (Total number = 108).

Design	Number of Arms	Comparator
Pharmacokinetic study	17 (15.7%)	1 group
		2 group(cross-over)
Before-after study	11 (10.2%)	1 group
		2 groups
Parallel design	77 (71.3%)	15
		2
		11
		63
		49
		5
		1
		3
		3
		2
Cross-over design	3 (2.8%)	12
		9
		2
		1
2 group	3	3
		1
		3

CRIS, clinical research information service; HM, herbal medicine; N/A, not applicable.

4. Discussion

As the importance of EBM is emphasized, there is increasing demand for evidence regarding the effectiveness and safety of herbal medicines frequently used in clinical settings. Therefore, we reviewed the regulation and current status of herbal medicine clinical trials in the Republic of Korea to identify current situations and suggest future directions for the trials.

Throughout this study, we found that strict standards were applied for IND approval of herbal medicine clinical trials outside of indication, although herbal medicine is already used frequently in KM clinical practice. These regulations can ensure the safe

and effective use of herbal medicine in clinical settings. In addition, we found that despite the strict regulations, the number of IND-approved herbal medicine clinical trials increases every year. Interestingly, in the case of investigator-initiated clinical trials for herbal medicines that have been used for more than 3 years with 200 cases at the clinical trial institution, there is a regulation that exempts nonclinical data by acknowledging the clinical experience even if they were not previously approved by KMFDS. This regulation was first listed in the “Guidelines for Approving Clinical Study Plans on Drugs” implemented in 2009, but no related clinical trials were conducted until recently. Through analysis of the current status of herbal medicine clinical trials, we confirmed that three clinical trials were recently approved by IND for new herbal formulations that are frequently used in KM institutions but not previously developed by pharmaceutical companies and not approved for commercial use. The trials were approved in 2018 based on the above guidelines as part of the recent KM research and development project from the Ministry of Health and Welfare. Currently, in the clinical field of KM, individualized herbal medicine is used with various dosage forms and compositions, and it is important to gather evidence related to real-world clinical settings for herbal medicine. Therefore, it is necessary to conduct clinical trials on herbal medicines that are used frequently in KM clinical settings but were not previously approved by KMFDS and are not sold by pharmaceutical companies by actively using regulation involving herbal medicines used for more than 3 years with 200 cases. To facilitate this, it is necessary to expand GMP facilities capable of producing and testing new herbal drugs. In addition, it is necessary to accumulate systematic medical records of excellent herbal medicines held by KM hospitals.

In addition, we confirmed that most of the clinical trials were funded by the government (Ministry of Health and Welfare or Ministry of Science and ICT) through analysis of the current status of clinical trials. Unlike conventional medicine, pharmaceutical companies are not actively participating in herbal medicine clinical trials due to various institutional conditions, such as the lack of a separation between prescribing and dispensing herbal medicine. Therefore, to expand the base of herbal medicine, it is necessary to expand support to pharmaceutical companies through related projects from the government and various incentive systems.

Investigation of the study designs for herbal medicine clinical trials showed that there have been a large proportion of clinical trials comparing herbal medicine and placebo to evaluate the efficacy of herbal medicine. However, recently, as part of the KM research and development project of the Ministry of Health and Welfare, strengthening the health insurance coverage of herbal medicine has emerged as a major issue. Accordingly, clinical trials comparing non-benefit herbal medicine and an active control, a standard treatment, have been conducted for the economic evaluation of herbal medicine. In particular, a clinical trial comparing one herbal medicine approved for coverage by the national health insurance and another non-benefit herbal medicine to strengthen the basis for non-benefit herbal medicine coverage was noted.¹² A survey on the awareness of KM doctors regarding the expansion of health insurance benefits for herbal medicines in 2018 revealed that 87.0% of the respondents agreed with the necessity.¹³ In addition, according to the Ministry of Health and Welfare Report on Usage and Consumption of KM in 2017, there is an increasing demand to strengthen the health insurance coverage for herbal medicines from both the general public and outpatients and inpatients of KM hospitals.¹⁴ Therefore, there is a need to benchmark the designs of existing clinical trials and conduct clinical trials targeting the reinforcement of the health insurance coverage for herbal medicines. For this purpose, the safety and effectiveness of herbal medicines should be ensured first and this increased demand should be taken into consideration in planning herbal medicine clinical trials.

Interestingly, 17 studies (15.7%) related to the pharmacokinetic properties of herbal medicine were confirmed through CRIS searching. In particular, 2 studies evaluated the pharmacokinetics and safety of herbal medicine extract powder and soft extract. Clinical trials comparing various dosage forms of herbal medicine could be used as basic data to activate the herbal medicine industry through the development of modern formulations. In addition, considering that patients with chronic disease frequently use both conventional medication and herbal medicine and that there are concerns about safety issues of herb-drug interactions, it is necessary to identify the effect of herbal medicines on the pharmacokinetic changes of conventional medications through clinical trials.

Traditional KM is characterized by pattern identification, a system of diagnosis with its own theoretical basis and practical experience.¹⁵ In a survey of 400 KM doctors, a utilization rate of pattern identification in clinical settings for 18 chronic diseases (chronic fatigue, pain, metabolic diseases, dementia, tumors, etc.) reached 87.8%-97.1%.¹⁶ However, among the KM research papers published in domestic journals related to KM, the use of pattern identification in randomized controlled trials (RCTs) was insufficient.¹⁷ The utilization rate of pattern identification in RCTs performed in Japan was only 15.3%.¹⁸ In China, among 296 clinical trials using Chinese herbal medicines for depression, only 105 studies (35.5%) used pattern identification for diagnosis.¹⁹ In accordance with the CRIS search results in our study, only 6.5% of herbal medicine clinical trials considered pattern identification. According to a consensus document on clinical research in Chinese medicine, it is recommended to recruit participants according to conventional medicine diagnosis and then to perform pattern identification before randomization. Recruiting participants based on pattern identification can be considered if a clear and limited number of pattern identifications exist.²⁰ Accordingly, various clinical trial designs have been proposed to apply pattern identification to clinical trials²¹ and can be considered when planning clinical trials for herbal medicine.

The limitation of our study is that on the KMFDS and CRIS websites, we searched for herbal medicine clinical trials in which the phrase “*Korean Medicine*” was included in the name of the institution to confirm the current status of the herbal medicine clinical trials. Therefore, we could not identify herbal medicine clinical trials that were not conducted in KM hospitals because of limited publicly available information and the number of included trials was lower than that of herbal medicine clinical trials reported in the KMFDS’s press releases (**Supplementary Fig. 1**). Clinical trials conducted in Korea may be registered on *clinicaltrials.gov* as well as on CRIS. In our study, we only searched CRIS, which is more accessible because the homepage is organized in the Korean language. This implies that our results may not cover all herbal medicine clinical trials in Korea. In addition, clinical trial information may not be disclosed for reasons such as new drug development. These factors may have contributed to the differences between the number of clinical trials found on KMFDS and the number of IND-approved protocols registered on CRIS.

Nevertheless, we analyzed the relevant regulation and current status of herbal medicine clinical trials for the first time to identify the current situation and suggest future directions. This study can help improve the understanding of the regulation and status of herbal medicine clinical trials in Korea for herbal medicine clinical researchers around the world and facilitate global clinical trials. In addition, by reviewing the current status of herbal medicine clinical trials, we found that clinical trials are being actively conducted and that herbal medicine clinical trials to elucidate the characteristics of KM are being conducted using relevant regulations as part of the KM research and development project. In the future, based on this study, it is necessary to accumulate scientific evidence on herbal medicine and to expand the base of herbal medicine through

well-designed clinical trials. We especially hope that high-quality clinical trials will be conducted to develop new drugs that reflect the clinical setting for KM based on regulations regarding herbal medicines used for more than 3 years with 200 cases. In addition, clinical trials that not only evaluate the efficacy and safety of herbal medicines but also promote the expansion of insurance coverage for them should be conducted. To do this, it is important to prepare a foundation for the active participation of pharmaceutical companies through the improvement of various systems and to conduct collaborative research among academics, researchers, industry, hospitals, and governments.

Author contributions

Conceptualization: MSL. Methodology: BL, YC, and PWK. Data Curation: BL and YC. Formal Analysis: BL and YC. Writing-Original Draft: BL and YC. Writing-Review & Editing: PWK, CY, and MSL. Supervision: MSL. Funding Acquisition: MSL.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Funding

This work was supported by the Korea Institute of Oriental Medicine (KSN2013210).

Ethical statement

Not applicable

Data availability

Not applicable

Supplementary materials

The number of herbal medicine trials approved by the KMFDS from 2004 to 2018 based on the KMFDS's press release, can be found, in the online version, at doi:<https://doi.org/10.1016/j.imr.2020.100688>.

References

1. Lee YM. Introduction to evidence based medicine. *Korean J Vasc Endovasc Surg* 2003;19(2):212–9.
2. Guideline for Approving Clinical Study Plans on Drugs. MFDS Notification No. 2019-146. December 30, 2019. <http://www.law.go.kr/admRulLsInfoP.do?admRulSeq=2100000185510>. Accessed September 10, 2020.
3. National Institute of Food and Drug Safety Evaluation. *Global drug development and evaluation trends*. Cheongju, Korea: National Institute of Food and Drug Safety Evaluation; 2012.
4. Regulation on Safety of Medicinal Products, etc. Ordinance of the Prime Minister No. 1641. September 7, 2020. <http://www.law.go.kr/lsInfoP.do?lsiSeq=221475&efYd=20200907&ancYnChk=0#0000>. Accessed September 10, 2020.
5. Regulation on Approval and Notification of Herbal (crude) Medicinal Preparations, Etc. MFDS Notification No. 2019-143. December 30, 2019. <http://www.law.go.kr/admRulLsInfoP.do?chrClsCd=&admRulSeq=2100000185655>. Accessed September 10, 2020.
6. 2010 Korea Research-based Pharmaceutical Industry Association. *KOREA IND booklet*. Seoul, Korea: Korea Research-based Pharmaceutical Industry Association; 2011.
7. Dai L, Cheng CW, Tian R, et al. Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018). *Chin J Integr Med* 2019;25(1):71–9.
8. Cheng CW, Wu TX, Shang HC, et al. CONSORT extension for chinese herbal medicine formulas 2017: Recommendations, explanation, and elaboration. *Ann Intern Med* 2017;167(2):112–21.
9. National Institute of Food and Drug Safety Evaluation. *Complementary casebook of investigational new drug application*. Cheongju, Korea: National Institute of Food and Drug Safety Evaluation; 2019.
10. US Food Drug Administration. *Guidance for industry: Estimating the maximum safe starting dose in adult healthy volunteer*. US Food and Drug Administration: Rockville, MD; 2005.
11. Guideline center for Korean Medicine. *IND approval Casebook for the Investigator's Clinical Trials - focusing on herbal medicine used for more than 3 years / 200 cases -*. Gyeonggi-do: Korean Studies Information Co., Ltd.; 2019.
12. Woo HL, Ji HR, Kim S, et al. Efficacy and safety of herbal medicine (Dangguijagyag-san) for primary dysmenorrhea: study protocol for a randomized, double-blind, placebo-controlled, parallel-group, multi-center trial. *Integr Med Res* 2020;9(2):100394.
13. Joo YJ, Kim JC, Lee EK, et al. Survey on the Korean medicine doctor's awareness of the extension and activation of herbal medicine preparations insurance benefits. *Journal of Society of Preventive Korean Medicine* 2018;22(3):31–44.
14. Kim YJ. *Usage and consumption of Korean medicine Report in 2017*. Seoul, Korea: National Institute for Korean Medicine Development; 2018.
15. Kim HJ, Bae HS, Park SU, Moon SK, Park JM, Jung WS. Clinical approach to the standardization of oriental medical diagnostic pattern identification in stroke patients. *Evid Based Complement Alternat Med* 2011;2011.
16. Yeo M, Park K, Lee Y. A national-wide survey on utilization of pattern identification for chronic diseases among Korean medicine doctors. *Journal of Society of Preventive Korean Medicine* 2017;21(2):23–34.
17. Jin HJ, Lee J, Jang E. Research trends of pattern identification of Korean medicine using the network analysis. *J Korea Contents Assoc* 2014;14(12):1037–46.
18. Motoo Y, Arai I, Tsutani K. Use of Kampo diagnosis in randomized controlled trials of Kampo products in Japan: a systematic review. *PLoS One* 2014;9(8):e104422.
19. Yeung WF, Chung KF, Ng KY, Yu YM, Zhang SP, Ng BF, et al. Prescription of Chinese herbal medicine in Pattern-Based traditional Chinese medicine treatment for depression: A systematic review. *Evid Based Complement Alternat Med* 2015;2015:160189.
20. Witt CM, Aickin M, Cherkin D, et al. Effectiveness guidance document (EGD) for Chinese medicine trials: A consensus document. *Trials* 2014;15:169.
21. Watanabe K, Matsuura K, Gao P, et al. Traditional Japanese Kampo Medicine: Clinical Research between Modernity and Traditional Medicine-The State of Research and Methodological Suggestions for the Future. *Evid Based Complement Alternat Med* 2011;2011:513842.