



Review article

Clinical studies of traditional Japanese herbal medicines (Kampo): Need for evidence by the modern scientific methodology

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ABSTRACT

Background: Japanese Kampo medicine is a traditional medicine with roots in ancient Chinese medicine. Because traditional physicians had been abolished in Japan, the present mainstream of Kampo treatment is that physicians who learned modern Western medicine prescribe Kampo extract products based on Western medical diagnosis. This situation is different from that in other east Asian countries, and the physicians require scientific clinical evidence.

Methods: Clinical studies were searched from literature databases, clinical trial registry sites, and “Evidence Reports of Kampo Treatment (EKAT)” published by the Japan Society for Oriental Medicine.

Results: At the approval of Kampo products, scientific clinical evidence was not required because they have a long-period experience as a decoction. However, in the 1990s, Kampo products became a subject for national reevaluation; double-blind and placebo-controlled clinical trials. At the time, a methodological foundation for conducting clinical assessments of Kampo medicines was established. From 2000 onwards, with the evidence-based medicine era, the field of Kampo medicine also saw many randomized controlled trials, and their evidence was collected and published as EKAT. In the 2010s, post-marketing clinical trials of Kampo products also had to be conducted in this environment due to the need for ethical and scientific assurance. Currently, there are numerous clinical trials of Kampo products being conducted with high-grade trial designs.

Conclusion: The situation of Kampo clinical studies reflects the unique history and position of Kampo medical system and Kampo products in Japan.

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1. Introduction

Kampo medicine is a traditional medicine with roots in ancient Chinese medicine, which was introduced to Japan in the ancient age and subsequently modeled into a Japanese variant. The origins of Kampo medicine are the same as those of traditional Chinese and Korean medicine. However, in their current forms, traditional Chinese and Korean medicine are in different circumstances than their Japanese counterparts, although there is a difference between China and Korea in terms of the legally permitted interventions and the interventions paid by health insurance (Table 1).

Among the Japanese practitioners with national licenses, only physicians are allowed to diagnose and treat patients according to

various types of traditional medicine in addition to Western medical treatment (Supplement 1). However, in universities, physicians receive only limited education regarding Kampo medicines for traditional medicine, and there is an extremely small number of individuals who practice traditional treatment other than the prescription of Kampo medicines based on Western medical diagnosis. Currently, Kampo treatment in Japan mostly consists of physicians prescribing Kampo extract products for prescription either independently or alongside modern drugs without a traditional medical diagnosis for diseases.^{1,2} In Japan, there are unique circumstances concerning the background of how clinical research on Kampo medicine is conducted in accordance with modern medicine. This means that individuals who conduct clinical research on Kampo medicines and those who use these research results are all physicians using Kampo medicines based on Western medicine.

Kampo medicines used in Japan are all handled under the same regulations as those applicable to standard Western medical prod-

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Table 1

The present situation of Kampo medicine and other traditional medicine derived from ancient Chinese medicine

	Traditional Japanese herbal medicine (Kampo)	Traditional Chinese herbal medicine / Korean herbal medicine
Main prescriber	Western medical doctor	Traditional medical doctor
Main dosage form of herbal medicines	Dry extracted products	Decoction
Main diagnosis for prescription	Modern diagnosis	Traditional diagnosis
Main dosage manner	Together with modern Western medicinal products	Solely traditional medicines

ucts.¹ Among these, Kampo formulations prescribed by physicians are covered by the National Health Insurance. Many of these are dried extract granules in modern dosage form, with a single dose in an aluminum pouch. For this reason, physicians prescribe these as “general drugs” without much awareness of the fact that these are traditional drugs. However, Kampo formulations for prescription are different from those of other medicines covered by insurance. This is with respect to the indications of Kampo formulations for the prescriptions that are seen as already assured by the Japanese through experience as decoctions, and also that these formulations have been approved without clinical trials. In other words, Kampo formulations for prescription do not have the clinical data that “general drugs” would have with pre-launch trials for commercially available doses.³ This has been seen as a problem since shortly after Kampo formulations for prescription became commercially available in the late 1970s. For these reasons, each time the financial resources for medical treatment become constrained, Kampo extract products for prescription have always been at risk of being excluded from health insurance coverage.³ In order to fill this gap in clinical data at the time of approval, Kampo medicine manufacturers and physicians who work in Kampo treatment conducted clinical trials of Kampo formulations for prescription with the objective of maintaining insurance coverage. Furthermore, Kampo medicine manufacturers have recently taken up the strategy of proposing new modern usage methods of previously approved Kampo based on clinical evidence (Supplement 2). These are the reasons for conducting clinical trials of Kampo medicines by Kampo medicine manufacturers in Japan.

This review outlines the clinical trials of Kampo medicines conducted in the context of this distinct Japanese environment.

2. Methods

Literatures of clinical studies on Kampo medicines was searched by Ichushi Web and PubMed. Search of Ichushi Web was performed on 11 May 2020 using the following search formula; ((Kampo medicines/TH)) and (DT=1965:2010 and (PT="exclude case report") and (PT=Original Literature) and CK=human and SH=Therapeutic Use,Treatment,Medication). Search of PubMed was performed on 27 May 2020 using the following search formula; ("medicine, kampo"[MeSH Terms] OR "medicine, chinese traditional"[MeSH Terms]) AND "clinical study"[Publication Type] AND "Japan"[Affiliation] (Supplement 3). The literatures searched in both Ichushi Web and PubMed were counted as ones of PubMed.

The reevaluation of Kampo extracted products was searched on the website "The reevaluation collection" of The Federation of Pharmaceutical Manufacturers' Associations of JAPAN.⁴

Randomized controlled trials and meta-analysis of Kampo products are analyzed data of Evidence Reports of Kampo Treatment (EKAT) 2016 and its Appendix 2017 and 2018^{5,6} published by the Japan Society for Oriental Medicine.

Clinical registration on Kampo medicines was searched in the UMIN Clinical Trials Registry (UMIN-CTR),⁷ Japan Clinical Trials Information (JAPIC-CTR),⁸ Center for Clinical Trials, Japan Medical Association (JMA-CCT),⁹ the Japan Registry of Clinical Trials (jRCT),¹⁰ and ClinicalTrials.gov.¹¹ on 3 June 2020.

3. Results

3.1. Clinical studies of Kampo medicines

The status of all clinical trials on Kampo medicines to date is shown in Fig. 1. The number of clinical trials on Kampo medicines by year as searched by Ichushi-Web and PubMed is shown in Fig. 1A. The number of publications and reports on Kampo medicines gradually increased from its initial report date of 1982, peaked in 1992, after which it decreased before gradually increasing from the 2000s onwards. The top ten Kampo prescriptions used in clinical research are shown in Fig. 1B.

3.2. Reevaluation of prescription Kampo products

The reevaluations for eight products were specified on Feb 1, 1991, and final notifications for results were published on Apr 7, 2014. As the result, the indications of these products were revised, and some indications were removed (Supplement 4).

3.3. Randomized controlled trials and meta-analysis of Kampo products

An outline of the RCT publications of Kampo products was included in the EKAT 2016 Appendix 2017 and 2018 is shown in Fig. 2. The number of publications by year is shown in Fig. 2A, a peak is observed at the beginning of the 1990s, after which it briefly declines, with a trough in 2000, before rising a second time. The current number of RCT publications has returned to levels similar to those in the 1990s. However, the number of RCT publications declined after 2016. The reporting language of RCT publications was in Japanese for a majority of cases in the 1990s, though recently, over half have been in English.

It can be observed that many of the Kampo prescriptions used in RCTs were rikkunshito and daikenchuto (Fig. 2B). Cancer was the most common topic in the field of RCT research (Fig. 2C).

Eight meta-analyses¹²⁻¹⁹ have been reported (Supplement 5).

3.4. Registration of clinical studies of Kampo medicines

Survey results of clinical trial registrations of Kampo medicines using Japanese registration sites including UMIN-CTR, JAPIC-CTR, JMA-CCT and jRCT, and ClinicalTrials.gov of United States are shown in Fig. 3. The number of registered clinical trials on Kampo medicines increased since 2009, but this has decreased since 2017 (Fig. 3A). It can be observed that many of the Kampo prescriptions which were registered in these sites were daikenchuto and rikkunshito (Fig. 3B).

4. Discussion

4.1. Clinical studies of Kampo medicines

The number of publications and reports on Kampo medicines was shown in Fig. 1A. Parallels can be seen between these transitions in the number of clinical trials and publications and the transitions in the production value of Japanese Kampo medicines,

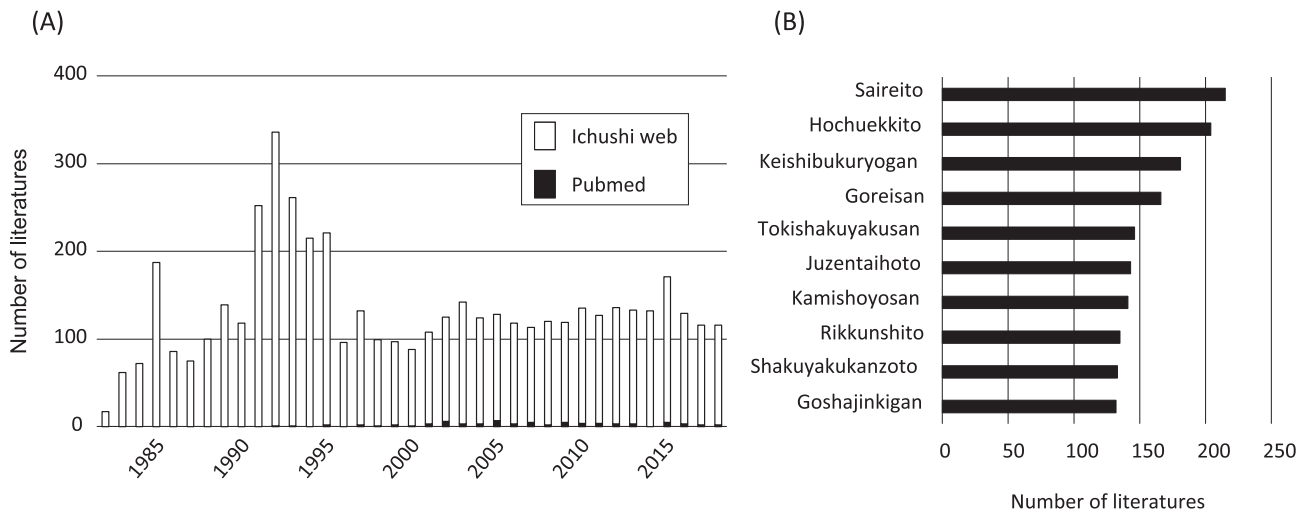


Fig. 1. Literature number of clinical studies on Kampo medicines. (A) Literature number by year, (B) Evaluated Kampo formulations.

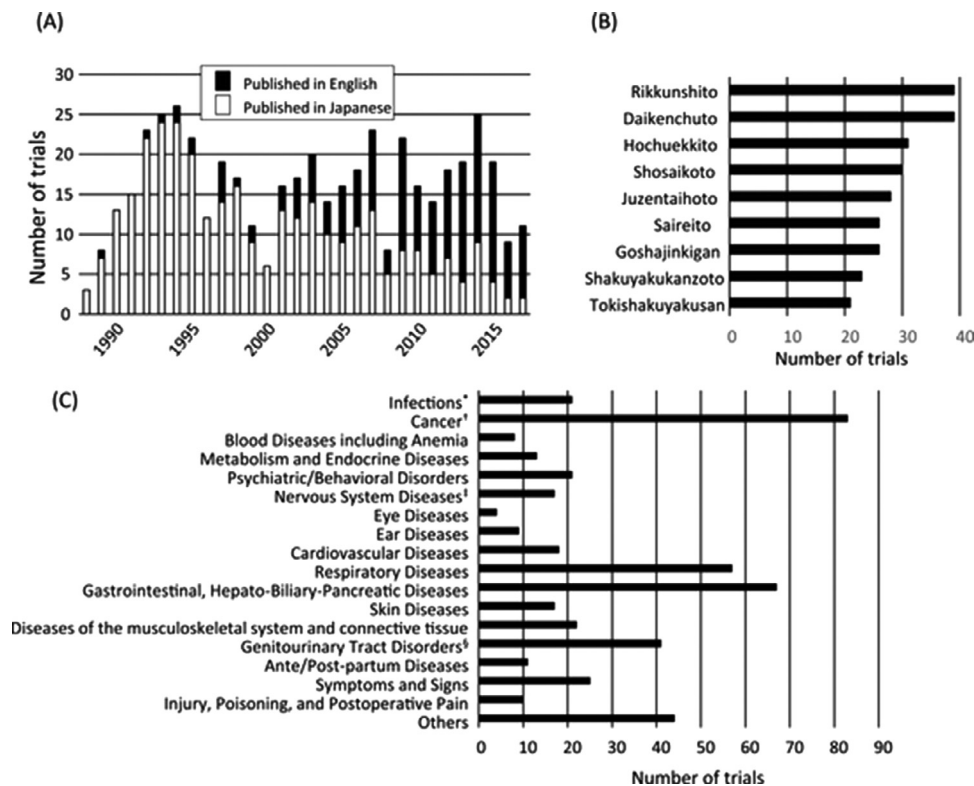


Fig. 2. Study number of Kampo RCTs in "Evidence Reports of Kampo Treatment" (EKAT) . (A) Study number by year, (B) Evaluated Kampo formulations, (C) Evaluated diseases. *including viral hepatitis, †including condition after cancer surgery and unspecified adverse drug reactions of anti-cancer drugs, ‡ including Alzheimer's disease, §including climacteric disorders.

particularly Kampo formulations for prescription.²⁰ The spread of Kampo extract products for prescription in the 1980s resulted in their explosive expansion in the market, centered on shosaikoto, which was used for chronic hepatitis. By 1996, as there were 10 deaths due to interstitial pneumonia²¹ which was an adverse reaction to shosaikoto, the market for all Kampo medicines rapidly decreased. By 2000, more 8 deaths were reported.²² Since the 2000s, clinical research uncovered a number of new uses for Kampo medicine, which led to the second and gradual recovery of its market. As can be seen, by the small number of publications in PubMed, most clinical research was published in Japanese journals in the native Japanese language.

Prescriptions, where many clinical trials have been conducted (Fig. 1B), are those with high usage in Japan.²⁰ There were case reports in the 1980s that stated that shosaikoto and saireito were effective against chronic hepatitis and nephrotic syndrome, respectively, and a large volume of clinical research was conducted to verify these results (Supplement 6). The fact that these two prescriptions had high drug prices in the national health insurance, and this led to manufacturers' profits is another reason for the large volume of clinical research with many of these trials being funded by manufacturers. However, most studies were small-scale research trials. By the early 1990s, the deaths due to interstitial pneumonia caused by shosaikoto dramatically decreased the sales

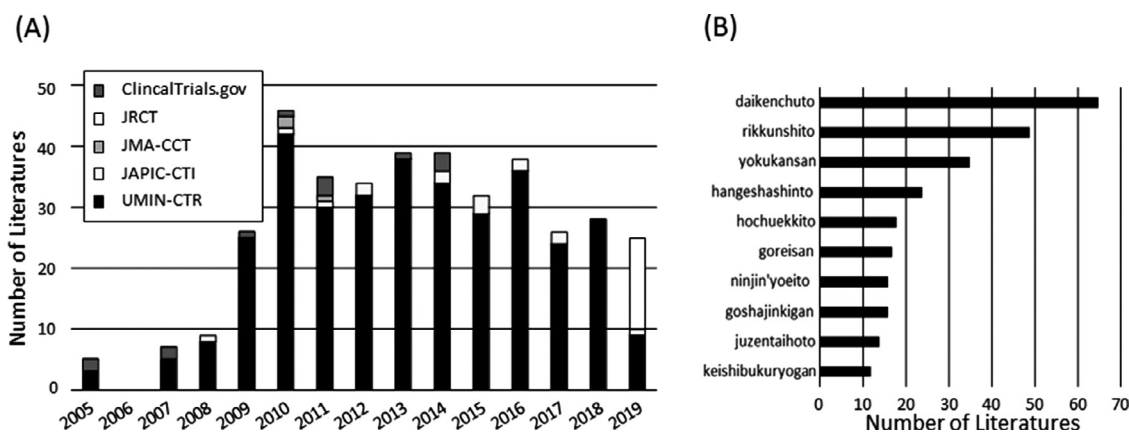


Fig. 3. Number of clinical registrations on Kampo Medicines (A) Registration number by year, (B) Evaluated Kampo formulations.

of shosaikoto and saireito. Therefore, manufacturers no longer had sufficient funds to conduct clinical research. As a result, the number of clinical research trials on Kampo medicines, including other prescriptions, dramatically decreased in the late 1990s (Fig. 1A). By the 2000s, case reports indicating that daikenchuto was effective against post-operative ileuses²³ were published, and clinical research on daikenchuto was initiated based on these results. Furthermore, following these results, the clinical effects of yokukansan against behavioral and psychological symptoms of dementia²⁴ and rikunshito against functional dyspepsia²⁵ were found, which resulted in a large volume of clinical research. During this time, the “promotion of clinical research based on multi-center, double-blind controlled trials of Kampo products and fundamental research to support its effects” was raised as a medium-term target for shareholders of the top Kampo medicine manufacturer.²⁶ A recent report indicated that goreisan resulted in the elimination of chronic subdural hematomas²⁷ and that there has been a rapid increase in the number of clinical research reports on goreisan.

The Clinical Trials Act (Supplement 7) was established in Japan in April 2017, which was enacted in April of the following year.²⁸ Based on this law, clinical research funded by pharmaceutical companies must present the research proposal to the national government in advance and must comply with implementation practices that are close to GCP (Good Clinical Practice). Consequently, post-marketing clinical research of medical products in Japan became even more difficult to implement in a procedural and financial sense. The number of publications and registrations of clinical trials on Kampo medicines has declined since 2017 (Fig. 1A, Fig. 2A, Fig. 3A). This indicates that pharmaceutical manufacturers had been involved in clinical research on Kampo medicines up to this point in time.

4.2. Reevaluation of prescription Kampo products

In Japan, there is a reevaluation system in which previously approved medical products have their quality, efficacy, and safety confirmed according to the current academic standards of medicine and pharmaceutical science. Depending on the reevaluation results, approval may be rescinded, and indications may be removed or modified accordingly.

Kampo formulations for prescription were approved based on experience as decoctions among the Japanese; therefore, no clinical trials were conducted with dried extract prior to approval. Hence, there were no clear clinical data that showed its efficacy. With the considerable increase in sales of Kampo formulations for prescription in the 1980s, there was a growing concern over whether these products should still be covered under the national health

insurance despite a lack of clinical data, and thus, Kampo formulations for prescription were selected for reevaluation. However, there were several conservative opinions which stated that clinical trials of Kampo extract products were impossible, with statements such as “Kampo medicines were administered using *Sho* (pattern of symptoms assessed by Kampo diagnosis); hence their efficacy cannot be proven by administering them according to Western medical diagnosis”; “because the color, smell, and taste of Kampo medicines are distinct, and it is difficult to make indistinguishable placebos, double-blind controlled clinical trials cannot be conducted”; and “Kampo is a tailor-made treatment, to begin with, therefore this is not suited for evaluations with statistical methodologies, and the results of trials are not useful for the individual patient”. With these in mind, the Ministry of Health and Welfare implemented “Research for the specification of reevaluation of Kampo products extract” in order to resolve these issues.²⁹ As a result, the following conclusions were made: *Sho* can be specified using inclusion and exclusion criteria, it is not impossible to create indistinguishable placebos for Kampo extract products, and if it can be confirmed efficacy in one disease/symptom of the groups consisting of similar multiple diseases/symptoms in the indications of the Kampo product, all the indications in this group will be deemed as effective. Furthermore, the quality of the medical products used needs to be assured for clinical evaluation. However, Kampo extract products for prescription had already undergone quality reset and assurance in 1986,¹ and hence, they were deemed eligible for clinical evaluation.

Based on these results, Kampo extract products for prescription were divided into several drug efficacy groups. First, eight prescriptions representing eight of these drug efficacy groups were specified for reevaluation in February 1991, and documents regarding their efficacy and safety were requested accordingly.³⁰ These of the three formulations were proven and their notifications were sent until 1996 (Supplement 4).

A notification of the results of the remaining prescriptions/indications was sent in April 2014, and their indications were revised and unified across all companies. Several indications were removed at that time. This was thought to be a comprehensive evaluation that included the results of many randomized controlled trials (RCTs) discussed later. Note that reevaluations of other Kampo products were not subsequently conducted therein.

4.3. Randomized controlled trials of Kampo products

With the era of evidence-based medicine (EBM) in the 1990s, there was an increased awareness regarding evidence for Kampo medicines, even among Japanese Kampo researchers. The Japan So-

ciety for Oriental Medicine (JSOM), which is the largest academic organization specializing in Kampo medicine in Japan, established a special committee for evidence-based medicine in 2001 and began collecting pieces of evidence for Kampo medicines. As previously mentioned, Kampo formulations for prescription in Japan were approved without clinical trials; thus, many individuals had doubts about their efficacy, and there had been many movements to remove their approval from the National Health Insurance. Consequently, the collection of clinical evidence on Kampo medicines by the JSOM began with the objective of insurance measures.

The special committee for evidence-based medicine collected high-grade clinical evidence on Kampo medicines and recommendations made. An interim report³¹ was published in 2002, and a final report, "Evidence Reports of Kampo Treatment",³² was published in 2005. For the final report, 95 out of 905 clinical publications on Kampo treatment were selected, and evidence-based recommendations were made. Of the 95 clinical trials selected, approximately one-third of the reports were at an RCT level or higher, and the rest was evidence at a lower level. Although this report was groundbreaking at the time, the publication selection method was not published, and the stance of JSOM, who supported Kampo treatment, was evident in the recommendations made.

Thus, for the second phase of the special committee for EBM starting in 2005 (standing committee with the "special" designation removed from 2009 onwards), this was changed to a policy of creating evidence reports from a position based on EBM methods. In other words, RCTs of Kampo products were comprehensively searched and selected after clearly showing the publication search/selection methods, after which structured abstracts were created from a critical appraisal standpoint and published. Recommendation levels for each therapy were not assigned because it was not the case for a majority of the publications where assessments were conducted by comparing with non-Kampo modern therapies (Supplement 8). These policy changes were implemented, and every year from 2007 to the present, these have been published on the JSOM website as Evidence Reports of Kampo Treatment (EKAT) in Japanese⁵ and English⁶. A total of 488 RCTs and 5 meta-analyses were included from 595 publications up to the EKAT 2016 Appendix 2018, published in June 2020. In EKAT, decoctions have not undergone quality assurance in their final dosage form for human use, and their reproducibility cannot be assured, and hence, their RCTs are not included.

An outline of the RCT publications on Kampo products (Fig. 2A) was similar to that of all clinical publications including non-RCT (Fig. 1A). The total number of the latter has not yet returned to its peak in the 1990s, however, that of the former returned to its peak. This shows that higher-quality RCT publications, in particular, have increased in Japan recently. However, the number of RCT publications declined after 2016. As previously mentioned, this was thought to be due to the influence of the Clinical Trials Act.²⁸

It can be observed that many of the Kampo prescriptions used in RCTs were prescriptions where manufacturers conducted clinical trials as part of sales strategies²⁶ (Fig. 2B). The most common topic in the field of RCT research was "Cancer" (Fig. 2C), although few expected actions on the cancer cells themselves, and a majority sought to reduce the various symptoms from surgical procedures or side effects of anti-cancer drugs. These types of trials are conducted because in Japan, Western physicians use Kampo medicines and routinely combine them with modern medicines.

An English version of the EKAT has been published from the outset.⁶ It was decided that English abstracts would be written on RCT publications on Kampo medicines that do not have English abstracts. In 2011, all RCT publications on Kampo medicines were included in the Cochrane Library (Central Register of Controlled Trials: CENTRAL) based on data up to EKAT 2010, and Japanese publications without an English abstract were linked to structural ab-

stracts with the English version of EKAT from CENTRAL.³³ Furthermore, EKAT 2010 was translated into Korean and published there.³⁴ Based on these actions, RCTs on Kampo medicines can be accessed in languages other than Japanese. Unfortunately, these works have not been updated since then.

An analysis of 378 RCTs included in EKAT 2010, Appendix 2011, and Appendix 2012 for whether the traditional medical diagnosis was conducted showed that only 27 RCTs (7.1%) used the concepts of *Sho*, which is the traditional medical diagnosis used in Japan for identifying patient selection/exclusion criteria and for selecting Kampo prescriptions.³⁵ Furthermore, only 31 RCTs (8.2%) were included in the post-trial subgroup analyses conducted with the concepts of *Sho*. In other words, a majority of RCTs did not use traditional medical diagnoses and were assessed using only Western medical disease names and Western medical diagnosis (Supplement 9).

There has been an increase in meta-analyses on Kampo medicines with the recent rise in RCT reports (Supplement 5). Therefore, assessments of Kampo product efficacy continue to be conducted at even higher levels.

Furthermore, JSOM has been established various environments for publications of RCT results (Supplement 10).

4.4. Registration of clinical studies of Kampo medicines

Currently, registration must be carried out prior to commencing a clinical trial. The three clinical trial registration sites in Japan since 2005 are the UMIN-CTR,⁷ JAPIC-CTR,⁸ and JMA-CCT.⁹ The jRCT¹⁰ was newly added in 2018 in order to register clinical trials based on the Clinical Trials Act. Currently, these four sites of information registration are collected in the Japan Primary Registries Network (JPRN)³⁶ and sent to the WHO International Clinical Trial Registry Platform (ICTRP).³⁷ As shown in Fig. 3, the number of registered clinical trials on Kampo medicines increased since 2009 due to the spread of clinical trial registration regulations, but this has decreased since 2017. This decrease after 2017 was also seen in both the number of clinical publications on Kampo medicines (Fig. 1) and the number of RCT reports on Kampo products (Fig. 2), and these are thought to be due to the Clinical Trials Act.²⁸ The majority of registrations were conducted in UMIN-CTR up to 2018, but the number of registrations was higher in jRCT than in UMIN in 2019. Clinical research trials that were submitted to the Clinical Trials Act, and obligated registration with jRCT, are those that received funding from pharmaceutical companies. In other words, over half of the clinical trials of Kampo medicines registered in 2019 were trials funded by pharmaceutical companies, and it is also estimated that a majority of clinical trials conducted before 2018, when the jRCT was not yet established, received funding from pharmaceutical companies as well. For the past several years, the top Kampo medicine manufacturer in Japan has emphasized the collection of basic and clinical data on daikenchuto, rikkunshito, and yokukansan,³⁸ the top three prescriptions in the registration (Fig. 4B). Furthermore, the Kampo medicine daikenchuto has seen ongoing development in the United States, and these trials have been registered in ClinicalTrials.gov. Unfortunately, however, the results of most registered Kampo clinical trials have not been reported (Supplement 11).

4.5. Impact of the results from clinical studies of Kampo products on their approved matter

Of the 369 trials that compared efficacy with placebos, non-drug groups, and modern drugs among the RCTs included in EKAT (up to Appendix 2018), 272 (74%) showed statistically significant effects in some form of results, while the remaining trials did

not show any statistically significant results. However, these negative reports would not affect the indications of Kampo extracted products immediately. The indications of Kampo medicines are expressed with the symptom names and the disease names, which can be applied in modern medicine, or just the symptom names. Most often, both the symptom and disease names use vague expressions that can be widely interpreted. Therefore, even if the one effect of the Kampo medicine was negative in the clinical study, it cannot completely disallow the indications and it does not affect the indications of Kampo medicines (Supplement 12).

4.6. Problems in conducting clinical studies of Kampo medicines

There are several problems in conducting clinical studies of Kampo medicines (Supplement 13). With regulatory changes after 1980, clinical trials equivalent to new modern drug applications were needed to approve new Kampo formulations for prescription. Japanese Kampo medicine manufacturers conducted clinical trials as part of their development of new Kampo formulations for prescription, such as with onpito, though they were not successful³⁹. Furthermore, procedures for expanding the existing indications of drugs are the same as those for developing new Kampo formulations for prescription, and discovery of a new usage method outside of the range of approved indications by a clinical researcher does not result in expansion of the stated indications without clinical trials being conducted. Thus, clinical trials by Kampo manufacturers were conducted only to prove the already obtained indications (and their expanded interpretations). Kampo medicine manufacturers also conduct clinical trials overseas in order to acquire approval for Kampo products outside of Japan; however, no positive results have been achieved to date⁴⁰⁻⁴².

Considering the above-mentioned special circumstances in Japan, as long as there are no major regulatory changes, Kampo clinical trials are thought to consist of either small-scale clinical research by clinical physicians for research purposes or medium-scale clinical trials conducted by Kampo medicine manufacturers to promote Kampo medicines. In Japan, Kampo medicines were developed with the advantage of being covered by insurance as a Kampo product for prescription. This led to the imposition of regulations similar to those imposed on other modern drugs, making the development of new prescriptions and addition of further indications difficult. However, at the same time, this made it difficult for new manufacturers to enter this market, and the manufacturers in existence got to occupy this market. The future of clinical studies of Kampo medicines depends on these manufacturers.

5. Conclusion

The situation of Kampo clinical studies reflects the unique history and position of Kampo medical system and Kampo products in Japan, which is different from other countries using traditional medicine with roots in ancient Chinese medicine.

Author contribution

This is the sole author's work.

Conflict of interest

The author declares no conflict of interest.

Funding

None.

Ethical statement

Not applicable.

Data availability

The data will be made available upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100722.

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