Review Article

Traditional Japanese Kampo Medicine: Clinical Research between Modernity and Traditional Medicine—The State of Research and Methodological Suggestions for the Future

Kenji Watanabe,1 Keiko Matsuura,1 Pengfei Gao,1 Lydia Hottenbacher,2 Hideaki Tokunaga,1 Ko Nishimura,1 Yoshihiro Imazu,1 Heidrun Reissenweber,3 and Claudia M. Witt2

1 Center for Kampo Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
2 Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, 10098 Berlin, Germany
3 Research Unit for Japanese Phytotherapy (Kampo), Department of Internal Medicine, University of Munich, Munich, Germany

Correspondence should be addressed to Claudia M. Witt, claudia.witt@charite.de

Received 12 October 2009; Accepted 13 May 2010

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The Japanese traditional herbal medicine, Kampo, has gradually reemerged and 148 different formulations (mainly herbal extracts) can be prescribed within the national health insurance system. The objective of this article is to introduce Kampo and to present information from previous clinical studies that tested Kampo formulae. In addition, suggestions on the design of future research will be stated. The literature search was based on a summary, up until January 2009, by the Japanese Society of Oriental Medicine and included only those trials which were also available in either Pubmed or ICHUSHI (Japan Medical Abstracts Society). We included 135 studies, half of these studies (n = 68) used a standard control and 28 a placebo control. Thirty-seven trials were published in English [all randomized controlled trials (RCTs)] and the remaining articles were in Japanese only. The sample size for most studies was small (two-third of the studies included less than 100 patients) and the overall methodological quality appeared to be low. None of the studies used Kampo diagnosis as the basis for the treatment. In order to evaluate Kampo as a whole treatment system, certain aspects should be taken into account while designing studies. RCTs are the appropriate study design to test efficacy or effectiveness; however, within the trial the treatment could be individualized according to the Kampo diagnosis. Kampo is a complex and individualized treatment with a long tradition, and it would be appropriate for further research on Kampo medicine to take this into account.

1. Background

1.1. Historical Background. Japanese traditional herbal medicine (Kampo medicine) obtained the unique features observed today during its phase of long historical development in Japan. In Japan, the administration of crude herbal drug formulations dates back by more than 1500 years. Recent decades have seen a revival of Kampo medicine in medical practice, accompanied by a scientific reevaluation and critical examination of its relevance in modern health care [1].

The term “Kampo”, which literally means “method from the Han period (206 BC to 220 AD) of ancient China”, refers to its origin from ancient China. The basic therapeutic handbook for the application of herbal prescriptions was the Shang han lun. During the Edo-period from 1600 onwards, the specific Japanese characteristics of Kampo took shape. The seclusion of Japan from the outside world led to ever increasing differences from the predominantly Chinese concepts. The huge variety of the thousands of Chinese crude drugs was reduced to ~300, those being the most efficacious drugs which were subsequently combined into ~300 prescriptions. From a pragmatic point of view, Japanese physicians criticized the highly theoretical and speculative nature of Chinese medicine as being inadequate to meet the problems of everyday practice. The strongest critique came from Yoshimasu Todo in the 18th century who wrote: “In clinical medicine, we should only rely on what we actually have observed by examination of the patient”. For Yoshimasu Todo, one way to gain data on
The results of the abdominal palpation should give additional clinical information in order to select the most appropriate herbal prescription for the patient. Yoshimasa Todo's pragmatic attitude and his abdominal palpation as a diagnostic procedure has had a strong influence on Kampo therapy right up until the present day [3].

It is not surprising that many Japanese physicians were drawn towards medical techniques from the West to improve their therapeutic options in surgery, but most of them continued to use traditional Kampo prescriptions for treating problems of internal medicine until the 19th century. At the end of the 19th century, it became obvious that for the urgent medical problems of that time, infectious diseases and acute surgical problems, Western medicine had better tools. The German system of medical education was adopted. In 1876, the government passed a regulation that all physicians were required to study Western medicine. The practice of Kampo was not forbidden but greatly inhibited and gradually declined [4]. However, after the Second World War, the first modern Kampo specialists carried on the traditions from the Edo-period. This revival of Kampo took place within a context dominated by modern Western medicine. The pragmatic and reductive approach of restricting Kampo therapy to clinically meaningful components helped to facilitate its gradual integration into modern medicine. Modern industrial society, in combination with longer life expectancy, has caused a shift in the predominant disease patterns, bringing to the therapeutic forefront chronic and degenerative diseases, functional and psychosomatic disorders and the multimorbidity of the elderly. These provide the main indications for the use of herbal drugs, not only with respect to treatment, but also for prevention [5].

Although rooted in Chinese tradition, Kampo medicine is not the same as modern traditional Chinese medicine (TCM). TCM emphasizes the traditional concepts of East Asian natural philosophy, such as Yin and Yang and the theory of the five elements. Japanese Kampo favors diagnostic methods that directly relate the symptoms to the therapy, bypassing speculative concepts. The vast array of crude drugs has been reduced in Kampo and also the quantity of each drug in the formulation is much lower. While Kampo still uses traditional prescriptions, TCM also tends to create new drug combinations [6].

1.2. Usage and Integration into Modern Medicine. Kampo traditional prescriptions have been included in the Japanese National Health Insurance drug list since 1971. A total of 148 Kampo herbal prescriptions are able to be funded to date. The application of Kampo has steadily increased and according to a survey by the Journal Nikkei Medical, more than 70% of physicians prescribe Kampo drugs today [7]. The Japan Society for Oriental Medicine is the biggest society for Kampo medicine and has 8600 members and 2600 certified board members. In 2001, Kampo education for medical students was incorporated into ‘the model core curriculum’ by the Japanese Ministry of Education, Culture, Sports, Science and Technology [6].

The development of modern ready-to-use forms was directly related to the enormous increase in Kampo usage, mainly as spray-dried granular extracts of the original formulae. They have increasingly replaced the traditional decoction of the crude drugs, even though they are also covered by the national insurance system. Besides being simple to administer, industrial production has enabled several other advantages. The quality control of the purity as well as toxicity is standardized in Japan, following the Japanese pharmacopoeia and internationally established regulations for Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP). The standardization of the main components has become possible and this is a precondition of clinical research. Today, extract preparations make up to 95% of the Japanese Kampo market.

In Western countries, herbal therapies originating in other cultural areas, mainly Chinese herbal medicine as part of TCM, are receiving increasing interest. In the USA, TCM is still far more visible than Kampo. The practitioners practice herbal therapy often in combination with acupuncture, which is often a mixture of Chinese, Japanese and Korean acupuncture styles. Kampo drugs are only available over the counter, meeting Japanese GMP criteria. Since Japanese pharmaceutical companies have started clinical trials in the USA, several drugs have already been registered as investigational new drugs (IND) by the Food and Drug Administration. Safety and toxicity data from Japan are generally accepted by the US and European agencies.

In Europe, especially in Germany, there is a long-term tradition of herbal medicine, and there is growing interest in Chinese phytotherapy and Japanese Kampo is also getting more and more attention. However, there is a shortage of doctors specialized in Japanese Kampo.

1.3. Background of Kampo. Kampo is an individualized treatment system where the overall condition of the patient and their constitution are of real importance; additionally, Kampo has a holistic therapeutic approach, as the mind and body are seen as one entity. The therapeutic aim is to relieve symptoms and to restore harmony in bodily functions. The treatment regime is based on symptoms. For the determination of the appropriate herbal prescription, the physician carries out a thorough investigation of the complaints and symptoms of the patient, including taking their temperature, examining sensation, weakness or sweating, symptoms which are not often primarily taken into account in conventional medicine. The physical examination includes abdominal palpation, tongue inspection and pulse diagnosis. This provides additional information concerning the state of the disease, by gathering the amount and distribution of ki (vital energy), ketsu (blood) and sui (body fluid). The subjective complaints and the symptoms observed by the physician are combined to an individual symptom profile, a Kampo diagnosis (sho), which leads to the selection of the appropriate prescription [8]. It may happen that patients...
with the same conventional diagnosis obtain different pres-
scriptions (same diagnosis but different treatments), or 
patients with different conventional diagnoses are prescribed 
the same formula (same treatment for different diagnoses). 

Japanese physicians with limited education in Kampo
diagnostics tend to apply the formulations according to 
conventional Western diagnoses. This makes sense for some 
limited indications, if the formula for the Kampo sho is close 
to the conventional diagnosis. However, in most cases, the 
traditional individual approach, where each patient receives 
their appropriate prescription, is the preferred option. For 
example, diseases that are expected to respond to the formula 
Kakkonto are diagnosed as Kakkonto-sho and it naturally 
follows that Kakkonto is prescribed in such cases.

These special conditions have made clinical research in 
the field of Kampo medicine more complex than the research 
on conventional drugs. The World Health Organization West 
Pacific Regional Office (WHO/WPRO) has put considerable 
efforts into standardizing East Asian traditional medicine 
[9]. WHO headquarters is considering incorporating the 
international classification of Traditional Medicine, East Asia 
(ICTM EA) into International Classification of Diseases 
(ICD)-11. ICD-11 is planned to be finalized in 2014 and 
scheduled to be approved by the WHO assembly in 2015. 
Japan proposes a double coding system of the ICD codes, 
that is, the conventional diagnosis code together with the 
traditional diagnosis (or pattern) code. This will allow 
integration into the conventional medical system without 
loosing the traditional information. The Kampo pattern 
(sho) codes have already been published in Japanese [10].

|                      | RCT | Quasi-RCT | Cross-over design | Comparative study (non-randomized) | Total |
|----------------------|-----|-----------|-------------------|-----------------------------------|-------|
| Kampo versus either  | 31  | 1         | 4                 | 3                                 | 39    |
| no treatment or a    |     |           |                   |                                   |       |
| different Kampo      |     |           |                   |                                   |       |
| formula              |     |           |                   |                                   |       |
| Kampo versus placebo | 22  | 0         | 2                 | 4                                 | 28    |
| Kampo versus standard| 53  | 5         | 4                 | 6                                 | 68    |
| treatment            |     |           |                   |                                   |       |
| Total                | 106 | 6         | 10                | 13                                | 135   |

Table 1: Summary of Kampo clinical studies (1987–2007).

Our search was based on an evidence report of Kampo 
treatment made by the Japanese Society of Oriental Medicine 
(JSOM) which included 320 clinical trials between 1986 and 
2008. [11]. This report includes Kampo trials available in 
the Cochrane register [12], ICHUSHI (Japan Medical Abstracts 
Society) [13] and the database from the Japan Kampo 
Medicines Manufacturer Association [14]. In this review 
only those studies were included, which used granulate 
formulations and were based on the drug regulation 
that was introduced in 1986. Liquid formulations and decoctions 
were excluded. Only peer-reviewed research from the JSOM 
database were included, which were also available in PubMed 
[15] or ICHUSHI [13]. A total of 135 trials, published 
between 1988 and 2007, were identified and summarized 
Table 1. These publications were extracted by two researchers 
fluent in both English and Japanese. Subsequently, they were 
discussed with two senior researchers (a Kampo specialist 
from Japan and a research methodologist from Germany). We 
classified Kampo clinical studies into three categories 
(Tables 2, 3, and 4):

(i) Kampo compared with either no treatment or differ-
ent Kampo formula.

(ii) Kampo compared with placebo.

(iii) Kampo compared with standard treatment.

Among the 135 clinical studies, 106 were randomized 
controlled trials (RCTs), 6 quasi-RCTs and 10 were cross-
over studies. There were 13 non-randomized comparative 
studies. Among the 106 RCTs, 23 studies were placebo-
controlled. More than two thirds of the studies used only 
Kampo as verum, whereas in 38 studies, Kampo was used 
in addition to the standard treatment. Almost half of the 
studies (n = 68) used a standard control, 28 used a placebo 
control, 24 had no treatment control and in 15, another 
Kampo formula was used as a control Table 1.

The sample size varied between 4 patients in the smallest 
study and 2069 patients in the largest. Most of the studies 
were small. Two thirds included less than 100 patients 
and the overall quality was low. Thirty-five trials were 
published in English and the remaining studies were in 
Japanese. The spectrum of diagnoses was diverse. The most 
common diagnosis was asthma (ICD J 45.0 and J 45.9), 
which was evaluated in nine studies. Many of the trials had 
low methodological quality (small sample size and unclear 
concealment) and thus a publication bias is to be expected. 
With respect to the methodology, it is interesting to note 
that in all studies summarized here, the treatment was based 
on the Western diagnosis only. A Kampo diagnosis was not 
mentioned in any of the trials. However, one trial seemed 
to be more individually based, using seven different Kampo 
formula in the verum group [134].

3. Suggestions for Future Research

3.1. Relevant Research Questions. The research available 
followed a Western approach and concentrated on single 
Western diagnoses treated with one Kampo formula. Since 
Kampo is a comprehensive and complex treatment system

2. Information Available on Clinical Research
Table 2: Kampo clinical studies comparing Kampo either with no treatment or with a different Kampo formula.

| Author (year)            | Reference | Language | ICD 10 code (disease name)                                      | Design  | N   | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment      |
|--------------------------|-----------|----------|----------------------------------------------------------------|---------|-----|---------------|----------|-------------|--------------|----------|----------------------|
| Seki et al. (1999)       | [16]      | J        | A49.0 (MRSA colonization infection)                              | RCT     | 95  | E             | No       | 2           | K            | NT       | hochuekkito          |
| Konno et al. (1997)      | [17]      | J        | C16.9 (gastric cancer)                                           | RCT     | 23  | E             | No       | 2           | SK           | NT       | juzentaihoto         |
| Saito et al. (2006)      | [18]      | J        | C80 (gastroenteric cancer)                                       | RCT     | 48  | E             | No       | 2           | K            | NT       | hochuekkito          |
| Suzuki et al. (1995)     | [19]      | J        | C80 (leukopenia with chemotherapy)                               | RCT     | 90  | E             | No       | 2           | SK           | NT       | juzentaihoto         |
| Higuchi et al. (2002)    | [20]      | J        | D37.6 (liver cirrhosis)                                          | RCT     | 52  | E             | No       | 2           | K            | NT       | juzentaihoto         |
| Ushiroyama et al. (2001) | [21]      | E        | E22.9 (endocrine function)                                       | RCT     | 100 | E             | No       | 2           | K            | NT       | unkeito              |
| Ushiroyama et al. (2006) | [22]      | E        | E28.2 (polycystic ovary syndrome)                                | RCT     | 64  | E             | No       | 2           | K            | NT       | unkeito              |
| Ushiroyama et al. (2003) | [23]      | E        | E28.3 (primary ovarian failure)                                  | RCT     | 197 | E             | No       | 2           | K            | NT       | unkeito              |
| Namiki (2007)            | [24]      | J        | E66.9 (obesity)                                                  | RCT     | 55  | E             | No       | 2           | SK           | NT       | bofutsusho-san       |
| Iwasaki et al. (2005)    | [25]      | E        | F05.1 (delirium superimposed on dementia)                        | RCT     | 52  | R             | Yes      | 2           | K            | K        | yukukansanhenge, anchusan |
| Higuchi et al. (2007)    | [26]      | E        | G30.9 (alzheimer's disease)                                      | RCT     | 75  | R             | No       | 3           | K            | NT       | kihito, goshajinkigan |
| Ikeda et al. (2002)      | [27]      | E        | H25.9 (senile cataract)                                          | RCT     | 27  | R             | No       | 2           | K            | K        | Kakkonto, saireito, orenegedokuto, kakkonto, saireito |
| Ikeda (2001)             | [28]      | E        | H25.9 (senile cataract)                                          | RCT     | 54  | R             | No       | 4           | K            | NT       | goshajinkigan         |
| Abe (2002)               | [29]      | J        | I89.0 (lymphoedema)                                             | RCT     | 80  | R             | No       | 2           | K            | NT       | maobushisaishinto, shoseiryuto |
| Yoshimoto et al. (2002)  | [30]      | J        | J30.1 (allergic rhinitis due to pollen)                          | RCT     | 66  | no            | No       | 2           | K            | K        | Kakkonto, saireito, shoseiryuto, keimakakuhanto |
| Mori et al. (1999)       | [31]      | J        | J30.1 (allergic rhinitis due to pollen)                          | Case Control | 88  | no            | No       | 2           | K            | K        | Kakkonto, saireito, shoseiryuto, keimakakuhanto |
| Nishizawa et al. (2003)  | [32]      | J        | J45.0 (predominantly allergic asthma)                            | RCT     | 139 | R             | DB       | 2           | K            | K        | saibokuto, shoseiryuto |
| Mizuno et al. (2001)     | [33]      | J        | K21.0 (reflux oesophagitis)                                      | RCT     | 46  | R             | No       | 2           | K            | NT       | rikkunshito          |
| Nishida (2006)           | [34]      | J        | K30 (dyspepsia)                                                 | RCT     | 11  | no            | No       | 2           | K            | K        | rikkunshito          |
| Oyabu et al. (1995)      | [35]      | J        | K56.5 (intestinal adhesions)                                     | RCT     | 53  | E             | No       | 2           | K            | NT       | daikenchuto         |
| Mori et al. (2003)       | [36]      | J        | K39.1 (functional diarrhoea)                                     | RCT     | 41  | E             | No       | 2           | K            | NT       | hangeshashinto       |
| Okabayashi et al. (1998) | [37]      | E        | K83.1 (obstruction of bile duct)                                 | RCT     | 24  | E             | SB       | 2           | SK           | NT       | inchinkoto          |
| Endo et al. (2006)       | [38]      | E        | K91.9 (postprocedural disorder)                                  | RCT     | 17  | no            | No       | 2           | SK           | K        | daikenchuto         |
| Author (year) | Reference | Language | ICD 10 code (disease name) | Design | N Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment |
|--------------|-----------|----------|-----------------------------|--------|----------------|----------|------------|--------------|---------|----------------|
| Ohno (2006)  | [40]      | J        | M35.0 (sicca syndrome)      | quasi-RCT | 64 no | No 2 | K | K | bakumondoto, rokumigan, hachimijiogon, hochuekkito hachimijiogon, goshajinkigan, shuchibushimatsu |
| Maejima et al. (2004) | [41] | J | M48.02 (spine deformity) | RCT | 24 R | No 3 | K | K |
| Yoshikawa et al. (1997) | [42] | J | N02.8 (childhood IgA nephropathy) | RCT | 101 E | No 2 | K | NT | saireito |
| Yoshikawa et al. (1998) | [43] | J | N04.9 (nephrotic syndrome) | RCT | 171 E | No 2 | SK | NT | saireito |
| Oribe et al. (2006) | [44] | J | N81.4 (postoperative discomfort for uterine prolapse) | RCT | 19 No | No 2 | K | NT | hachimijiogon |
| Takamatsu et al. (2002) | [45] | J | N95.8 (climacteric disorders) | Case Control | 67 No | No 2 | K | K | tokishakuyakusan, keishibukuryogan, kamishoyosan, juzentaihoto |
| Kawakami et al. (2003) | [46] | J | O92.5 (feeling of lactation deficiency) | RCT | 72 R | No 6 | K | K | kakkonto, juzentaihoto, kyukichoketsuin |
| Usihroyama et al. (2005) | [47] | E | O99.3 (maternity blues) | RCT | 268 E | No 2 | K | NT | kyukichoketsuin |
| Yoshida (2000) | [48] | J | R11 (vomiting in children) | RCT | 34 R | DB 2 | K | K | goreisan and hochuekkito suppositorium shakuyakukanzoto, goshajinkigan |
| Nishizawa et al. (2000) | [49] | J | R25.2 (cirrhosis) | RCT | 75 R | No 2 | K | K | |
| Yoshikawa et al. (1997) | [50] | J | R31 (essential microscopic hematuria) | RCT | 68 R | No 3 | K | NT | kyukikyogaito, saireito |
| Kishida et al. (2007) | [51] | E | R60.9 (postoperative edema and inflammation) | RCT | 17 R | No 2 | K | NT | saireito |
| Hasegawa et al. (2002) | [52] | J | T45.1 (paclitaxel-induced myalgia) | RCT-crossover | 15 R | No 2 | SK | K | shakuyakukanzoto |
| Ueda et al. (1999) | [53] | J | Z22.8 (MRSA) | RCT | 22 R | No 2 | K | NT | Hochuekkito |
| Okawa et al. (1995) | [52] | J | Z51.0, D70 (leucopenia with radiotherapy of malignancies) | RCT | 126 R | No 2 | K | NT | ninjinyoito |

J: Japanese; E: English; R: randomization; E: envelopes; DB: double blind; SB: single blind; K: Kampo; SK: Standard + Kampo; S: Standard; NT: no treatment; P: placebo; ICD: International Classification of Diseases; Kampo treatment includes only formulae produced after 1986. ICD codes details: [http://apps.who.int/classifications/apps/icd/icd10online/](http://apps.who.int/classifications/apps/icd/icd10online/), dosage of the Kampo formulae: [http://www.jsom.or.jp/medical/ebm/index.html](http://www.jsom.or.jp/medical/ebm/index.html).
Table 3: Kampo clinical studies comparing Kampo with placebo.

| Author (Year) (N)           | Reference | Language | ICD 10 code (disease name)                | Design    | Cases (N) | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment                  |
|-----------------------------|-----------|----------|------------------------------------------|-----------|-----------|---------------|----------|------------|--------------|---------|------------------------------------|
| Suzuki et al. (2002) [54]   | J         | A49.0 (MRSA) | RCT                                      | 13        | R         | DB 2          | K        | P          | hochuekkito  |         |                                   |
| Hioki et al. (2004) [55]    | E         | E66.9 (obesity) | RCT                                      | 81        | R         | DB 2          | K        | P          | bofutsushosan |         |                                   |
| Suzuki et al. (2005) [56]   | E         | F03 (dementia) | RCT                                      | 30        | R         | DB 3          | K        | P          | goshajinkigan, chotosan |         |                                   |
| Iwasaki et al. (2004) [57]  | E         | F03 (dementia) | RCT                                      | 33        | R         | DB 2          | K        | P          | hachinjikigan |         |                                   |
| Nagaki et al. (2003) [58]   | E         | H16.1 (keratitis) | RCT                                      | 75        | R         | DB 3          | K        | P          | goshajinkigan |         |                                   |
| Arakawa et al. (2006) [59]  | E         | I10 (essential hypertension) | RCT                                      | 204       | R         | DB 2          | K        | P          | orengedokuto  |         |                                   |
| Nakamura et al. (2000) [60] | J         | I95.1 (Orthostatic hypotension) | RCT-cross over                           | 10        | R         | SB 2          | K        | P          | goreisan      |         |                                   |
| Kaji et al. (2001) [61]     | J         | J00 (acute nasopharyngitis) | RCT                                      | 250       | R         | DB 2          | K        | P          | shosaikoto    |         |                                   |
| Baba (1995)                 | J         | J30.4 (allergic rhinitis) | RCT                                      | 217       | E         | DB 2          | K        | P          | shoseiryuto   |         |                                   |
| Miyamoto et al. (2001) [63] | J         | J40 (bronchitis) | RCT                                      | 192       | R         | DB 2          | K        | P          | shoseiryuto   |         |                                   |
| Urata et al. (2002) [64]    | E         | J45.0 (bronchial asthma) | RCT-cross over                           | 33        | R         | DB 2          | K        | P          | saibokuto     |         |                                   |
| Nishizawa et al. (2001) [65] | J         | J45.0 (bronchial asthma) | RCT                                      | 32        | R         | DB 2          | K        | P          | Saibokuto inhalation |         |                                   |
| Nishizawa et al. (2001) [66] | J         | J45.0 (bronchial asthma) | RCT                                      | 74        | R         | DB 2          | K        | P          | Saibokuto inhalation |         |                                   |
| Iwasaki et al. (2007) [67]  | E         | J69.0 (pneumonitis) | RCT                                      | 95        | R         | DB 2          | K        | P          | hangenkoubokuto |         |                                   |
| Harasawa et al. (1998) [68] | J         | K31.9 (dysmotility-like dyspepsia) | RCT                                      | 296       | R         | DB 2          | K        | P          | rikunshito    |         |                                   |
| Sasaki et al. (1998) [69]   | J         | K58 (irritable bowel syndrome) | RCT                                      | 204       | E         | DB 2          | K        | P          | keishikashakuyakuto |         |                                   |
| Miyoshi et al. (1994) [70]  | J         | K59.0 (constipation) | RCT                                      | 146       | E         | DB 3          | K        | P          | daikoan-zoto  |         |                                   |
| Itoh et al. (2002) [71]     | E         | K91.3 (post-operative ileus) | RCT                                      | 24        | R         | SB 2          | K        | P          | daiken-chuto  |         |                                   |
| Takagaki et al. (2000) [72] | J         | K91.3 (paralytic ileus) | RCT                                      | 21        | R         | SB 2          | K        | P          | daiken-chuto  |         |                                   |
| Nishizawa et al. (2004) [73] | E/J      | M35.0 (Sicca syndrome) | RCT-cross over                           | 229       | R         | DB 2          | K        | P          | bakumondoto   |         |                                   |
| Aoki et al. (2001) [74]     | E         | N39.9 (urodynamic studies) | RCT-cross over                           | 19        | R         | SB 2          | K        | P          | maobushisaishinto |         |                                   |
| Author (Year)          | Reference | Language | ICD 10 code (disease name) | Design    | Cases (N) | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment        |
|-----------------------|-----------|----------|----------------------------|-----------|-----------|---------------|----------|------------|--------------|---------|------------------------|
| Kumada et al. (1999)  | [75]      | J        | R25.2 (muscle cramps)      | RCT       | 126       | R             | DB       | 2          | K            | P       | shakuyakukanzoto       |
| Odaguchi et al. (2006)| [76]      | E/J      | R51 (headache)             | RCT       | 53        | R             | DB       | 2          | K            | P       | goshuyuto             |
| Satoh et al. (2005)   | [77]      | E        | R54 (senile muscle weakness)| RCT       | 13        | R             | DB       | 3          | K            | P       | hochuekkito           |
| Hamazaki et al. (2007)| [78]      | E        | Z01.8 (adjuvant effect to vaccination) | RCT       | 36        | R             | DB       | 2          | K            | P       | hochuekkito           |
| Takahashi et al. (2007)| [79]   | E        | Z01.8 (serum amino acid concentration) | RCT-crossover | 18       | R             | SB       | 3          | K            | P       | rokumigan             |
| Saruwatari et al. (2004)| [80] | E        | Z01.8 (COPD)               | RCT-crossover | 26       | R             | DB       | 2          | K            | P       | bakumondoto           |
| Isobe et al. (2003)   | [81]      | E        | Z01.9 (retinal blood flow)  | RCT-crossover | 12       | R             | DB       | 2          | K            | P       | hachimijiohan         |

J: Japanese; E: English; R: randomization; E: envelops; DB: double blind; SB: single blind; K: Kampo; SK: Standard + Kampo; S: Standard; NT: no treatment; P: placebo; ICD: International Classification of Diseases, Kampo treatment includes only formulae produced after 1986, ICD codes details [http://apps.who.int/classifications/apps/icd/icd10online/](http://apps.who.int/classifications/apps/icd/icd10online/), dosage of the Kampo formulae [http://www.jsom.or.jp/medical/ebm/index.html](http://www.jsom.or.jp/medical/ebm/index.html).
| Author (Year)          | Reference | Language | ICD 10 (disease)                           | Design     | Cases (N) | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment                  |
|-----------------------|-----------|----------|-------------------------------------------|------------|-----------|---------------|----------|------------|--------------|---------|----------------------------------|
| Sasaki et al. (2006)  | [82]      | J        | C18.9 (gastroenteric cancer)              | RCT        | 168       | No            | No       | 2          | SK           | S, K    | juzentaihoto                      |
| Sasaki et al. (2007)  | [83]      | J        | C18.9 (cancer chemotherapy)               | RCT        | 168       | No            | No       | 2          | SK           | S, K    | juzentaihoto                      |
| Adachi (1988)         | [84]      | J        | C50.9 (advanced breast cancer)            | RCT        | 74        | E             | No       | 2          | SK           | S       | juzentaihoto                      |
| Yamamoto et al. (2003)| [85]      | J        | D25.9 (uterine adenomyosis)               | RCT        | 24        | R             | No       | 2          | SK           | S       | keishibukuryogan                  |
| Akase et al. (2003)   | [86]      | J        | D50.0 (anemia due to uterine myoma)       | RCT        | 25        | R             | No       | 2          | K            | S       | tokishakuyakusan                  |
| Aoe (2007)            | [87]      | J        | D50.8 (iron deficiency anemia)            | RCT        | 120       | R             | No       | 3          | SK           | S       | juzentaihoto                      |
| Yanagibori et al. (1995)| [88]   | J        | D50.9 (Iron deficiency anemia,)           | RCT        | 39        | E             | SB       | 2          | SK           | S       | ninjinyoito                       |
| Aoe et al. (2000)     | [89]      | J        | D62 (acute posthaemorrhagic anemia)       | RCT        | 57        | R             | No       | 2          | SK           | S       | juzentaihoto                      |
| Aoe et al. (1999)     | [90]      | J        | D62 (acute posthaemorrhagic anemia)       | RCT        | 90        | R             | No       | 3          | SK           | S       | juzentaihoto, ninjinyoito         |
| Azuma et al. (1994)   | [91]      | J        | E10-E14 (non-insulin-dependent diabetes mellitus) | RCT          | 18        | E             | No       | 2          | SK           | S       | seishinrenshii                   |
| Yamano et al. (1995)  | [92]      | J        | E78.5 (hyperlipidaemia)                   | RCT        | 92        | E             | No       | 3          | SK           | S, NT  | daisaikoto                       |
| Sasaki et al. (1991)  | [93]      | J        | E78.5 (hyperlipidaemia)                   | RCT        | 40        | R             | No       | 3          | SK           | S       | daisaikoto                       |
| Ishida et al. (1999)  | [94]      | J        | F41.9 (anxiety disorder, unspecified)     | RCT        | 15        | R             | No       | 2          | SK           | S       | saibokuto                        |
| Yamagiwa and Fujita (2007)| [95] | J        | F45.3 (abnormal sensation)               | quasi-RCT  | 86        | R             | No       | 2          | K            | S       | rikkunshito                      |
| Maruyama (2006)       | [96]      | J        | G43.9 (migraine, unspecified)             | RCT-cross  | 28        | R             | No       | 2          | K            | S       | goshuyuto                        |
| Kimura et al. (1991)  | [97]      | J        | G51.3 (facial spasm)                     | RCT        | 20        | R             | No       | 2          | SK           | S       | shakuyakukanzoto                 |
| Sekine et al. (2003)  | [98]      | J        | G54.4 (lumbosacral root disorders)        | RCT-cross  | 20        | R             | No       | 2          | K            | S       | goshajinkigan                    |
| Inoue (2001)          | [99]      | J        | H65.0 (acute serous otitis media)         | Case Control | 34    | No            | No       | 2          | K            | S       | shoseiryuto, eppikajutsuto      |
| Matsushita et al. (1995)| [100]  | J        | I67.9, I67.8, I10 (cerebrovascular disease, hypertension) | RCT        | 22        | E             | No       | 2          | K            | S       | chosotsn                         |
| Akiyama et al. (2001) | [101]     | J        | I73.0 (Raynaud's syndrome)                | Case Control | 49    | No            | No       | 2          | SK           | S       | tokishakuyakusan, orengedokuso   |
| Author (Year) | Reference | Language | ICD 10 (disease) | Design | Cases (N) | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment |
|--------------|-----------|----------|------------------|--------|-----------|--------------|----------|------------|--------------|---------|----------------|
| Fujimori et al. (2001) | [102] | J | J00 (postinfections cough) | RCT | 25 | R | No | 2 | K | S | bakumondoto |
| Kimoto and Kuroki (2005) | [103] | J | J10 (influenza) | Case Control | 19 | No | No | 2 | SK | S | maoto |
| Kubo et al. (2007) | [104] | E | J10.1 (type A influenza infection) | quasi-RCT | 37 | No | No | 2 | SK | S | maoto |
| Kato et al. (2005) | [105] | J | J44.9 (chronic obstructive pulmonary disease) | RCT | 31 | E | No | 2 | SK | S | seihaito |
| Tatsumi et al. (2009) | [106] | E | J44.9 (chronic obstructive pulmonary disease) | RCT | 71 | E | No | 2 | K | S | hochuekkito |
| Nishizawa et al. (2004) | [107] | J | J45.0 (bronchial asthma) | RCT | 161 | R | No | 2 | K | S | shinbito inhalation |
| Nishizawa et al. (2003) | [108] | J | J45.0 (bronchial asthma) | RCT | 114 | R | No | 2 | K | S | shinbito inhalation |
| Nishizawa et al. (2002) | [109] | J | J45.0 (bronchial asthma) | RCT | 107 | R | No | 2 | K | S | saibokuto |
| Nishizawa et al. (2002) | [110] | J | J45.0 (bronchial asthma) | RCT | 94 | R | No | 2 | K | S | saibokuto inhalation |
| Egashira and Nagano (1993) | [111] | E | J45.9 (bronchial asthma) | RCT | 112 | E | SB | 2 | SK | S | saibokuto |
| Mikamo et al. (2007) | [112] | J | J98.9 (respiratory infection) | RCT | 116 | No | No | 3 | SK | S | jumihaidokuto, kakkoto, keishito, kososan, shosaikoto, hochuekkito |
| Umemoto et al. (2007) | [113] | J | K11.7 (dry mouth) | RCT | 100 | No | No | 3 | K | S | bakumondoto |
| Yamada et al. (1998) | [114] | J | K14.6 (glossodynia) | RCT | 104 | R | No | 2 | K | S | saibokuto |
| Kato et al. (2005) | [115] | J | K21.0 (gastro-oesophageal reflux disease with oesophagitis) | RCT | 19 | E | No | 2 | SK | S | hangekobokuto |
| Koide (2006) | [116] | J | K21.9 (gastro-oesophageal reflux disease without oesophagitis) | RCT | 118 | No | No | 3 | SK, K | S, K | rikkunshito |
| Higuchi et al. (1999) | [117] | E | K26.9 (Helicobacter pylori) | RCT | 63 | R | No | 2 | SK | S | goshuyuto |
| Yamaguchi and Koide (2007) | [118] | J | K30 (dyspepsia) | RCT | 120 | E | No | 3 | K | S | rikkunshito |
| Nishizawa et al. (2004) | [119] | J | K59.0 (constipation) | RCT | 318 | R | No | 2 | SK | S | kumibinroto |
| Nakajima et al. (2003) | [120] | J | K73.9 (chronic hepatitis) | RCT | 100 | E | No | 3 | K | S, K | shosaikoto |
| Nakajima et al. (1999) | [121] | J | K73.9 (chronic hepatitis) | RCT | 99 | R | No | 2 | SK | S | shosaikoto |
| Author (Year)               | Reference | Language | ICD 10 (disease)                  | Design       | Cases (N) | Randomization | Blinding (N) | Intervention | Control | Kampo treatment                          |
|----------------------------|-----------|----------|----------------------------------|--------------|-----------|---------------|--------------|--------------|---------|------------------------------------------|
| Tarao (2007)               | [122]     | J        | K73.9 (chronic hepatitis)        | RCT          | 156       | No            | No           | 2            | K       | K                                        |
| Okuma (1993)               | [123]     | J        | L70.0 (cne vulgaris)             | RCT          | 268       | R             | No           | 5            | K       | S, K                                     |
| Nishizawa et al. (2004)    | [124]     | J        | M35.0 (sicca syndrome)           | RCT          | 847       | R             | No           | 2            | K       | S                                        |
| Nishizawa et al. (2003)    | [125]     | J        | M35.0 (sicca syndrome)           | RCT          | 756       | R             | No           | 2            | K       | S                                        |
| Nishizawa et al. (2002)    | [126]     | J        | M35.0 (sicca syndrome)           | RCT          | 105       | C             | No           | 2            | K       | S                                        |
| Hayashi et al. (1994)      | [127]     | J        | M48.0 (spinal stenosis)          | Quasi-RCT    | 27        | R             | No           | 2            | K       | S                                        |
| Maejima and Katayama (2004)| [128]     | J        | M48.02 (chronic lumbar pain)     | RCT          | 89        | R             | No           | 3            | K       | S, K                                     |
| Nishizawa et al. (2007)    | [129]     | J        | N32.8 (overactive bladder)       | RCT          | 704       | No            | No           | 2            | K       | S                                        |
| Iwabuchi (2000)            | [130]     | J        | N93.9 (dysfunctional uterine bleeding) | Case Control | 183       | No            | No           | 2            | K       | S                                        |
| Takamatsu (2006)           | [131]     | J        | N95.1 (menopausal syndrome)      | Quasi-RCT    | 170       | No            | No           | 2            | K       | S                                        |
| Ushiroymama et al. (2005)  | [132]     | E        | N95.8 (menopausal syndrome)      | RCT          | 131       | R             | No           | 2            | K       | S                                        |
| Matsuo et al. (2005)       | [133]     | J        | N95.8 (menopausal syndrome)      | RCT-cross over | 24       | R             | No           | 2            | SK      | S                                        |
| Ota et al. (2001)          | [134]     | J        | N95.8 (menopausal syndrome)      | RCT          | 96        | R             | No           | 2            | K       | S                                        |
| Ushiroymama et al. (2006)  | [135]     | J        | O03.9 (uterine hemorrhage)       | RCT          | 72        | R             | No           | 2            | K       | S                                        |
| Wada et al. (2003)         | [136]     | J        | O90.9 (postpartum condition)     | RCT          | 60        | R             | No           | 2            | K       | S                                        |
| Sakuma et al. (2002)       | [137]     | J        | O90.9 (postpartum psycho-physical condition) | RCT          | 171       | R             | No           | 2            | K       | S                                        |
| Author (Year) | Reference | Language | ICD 10 (disease) | Design | Cases (N) | Randomization | Blinding | Groups (N) | Intervention | Control | Kampo treatment |
|---------------|-----------|----------|-----------------|--------|-----------|---------------|----------|------------|--------------|---------|----------------|
| Takushima and Inoguchi (2001) | [138] | J | O90.9 (puerperium) | Case Control | 47 | No | No | 2 | K | S | kyukichoketsuin |
| Nishizawa et al. (2003) | [139] | J | R05 (cough) | RCT | 2069 | R | No | 2 | K | S | bakumondoto |
| Motoo et al. (2005) | [140] | E | T37.5 (ribavirin-induced anemia) | RCT | 23 | R | No | 2 | K | S | ninjinnyoito |
| Hushiki et al. (2003) | [141] | J | T45.4 (gastritis due to oral iron) | RCT | 120 | R | No | 2 | SK | S | rikkunshito |
| Imazato et al. (1998) | [142] | J | Z01.8 (pretreatment of barium enema) | RCT | 60 | R | No | 2 | SK | S | shakuyakukanzoto |
| Yokota et al. (1990) | [143] | J | Z01.8 (pretreatment of barium enema) | RCT | 60 | R | No | 2 | K | S | daiokanzoto |
| Saida et al. (2003) | [144] | J | Z01.8 (pretreatment for bowel endoscopy) | RCT | 70 | E | No | 2 | SK | S | shakuyakukanzoto |
| Ohnishi et al. (1999) | [145] | E | Z01.9 (pharmacokinetics with carbamazepine) | RCT-crossover | 4 | R | No | 2 | SK | S | shoseiryuto |
| Saida et al. (2005) | [146] | E | Z03.1 (pretreatment of colonoscopy) | RCT | 285 | E | No | 2 | SK | S | daikenchuto |
| Sugihara (1999) | [147] | J | Z03.1 (gastric endoscopy) | Case Control | 58 | No | No | 2 | SK | S | shakuyakukanzoto |
| Mizukami et al. (2007) | [148] | J | Z03.8 (pretreatment of colonoscopy) | Quasi-RCT | 42 | No | No | 2 | SK | S | shakuyakukanzoto |
| Ai et al. (2006) | [149] | E | Z03.8 (pretreatment of colonoscopy) | RCT | 110 | R | No | 2 | K | S | shakuyakukanzoto |

J: Japanese; E: English; R: randomization; E: envelops; DB: double blind; SB: single blind; K: Kampo; SK: Standard+Kampo; S: Standard; NT: no treatment; P: placebo; ICD: International Classification of Diseases, Kampo treatment includes only formulae produced after 1986, ICD codes details http://apps.who.int/classifications/apps/icd/icd10online/, dosage of the Kampo formulae http://www.jsom.or.jp/medical/ebm/index.html.
with a traditional approach, many research questions still need to be investigated. Kampo has been used for hundreds of years and is well integrated into the Japanese health care system, therefore it should be taken into account using an appropriate research strategy. When performing clinical research identical questions must be addressed for every new treatment, as well as for traditional treatments, which are already on the market:

(i) For whom and what is it used to treat?
(ii) Is it safe?
(iii) Is it superior to placebo?
(iv) Is it superior or equivalent to conventional standard treatment?

For traditional treatments, the order of research questions should differ from conventional drug research, because traditional treatments are already widely available [150]. First, knowledge is needed regarding who will benefit from the treatment and which diseases the treatment is intended to treat, as well as how it is to be administered. In addition, it would be helpful to get an idea as to whether the patients improve under the treatment not to mention the essential safety assessment.

All of these questions could be answered using a prospective observational study which evaluates these aspects in usual care. This has been done for other traditional treatments such as homeopathy [151–153], and is currently being carried out for Kampo at the Keio University [154]. This computer-based self-assessment system is divided into two domains. One is the patients’ self-assessment at every visit using a visual analogue scale (VAS) and the other domain is an assessment by the physician. Data from both sources are combined and analyzed using data mining. The advantage of this system is that data is collected in a real-life setting. Also, Kampo values subjective complaints. This computer-based, self-assessment system, allows data incorporation of patient’s subjective outcome measures.

Objective outcome measures which are often used in experimental RCTs are sometimes separated from subjective feelings. Kampo physicians value subjective complaints and diagnose sho not only based on objective findings, but also from the subjective complaints. The evaluation of the Kampo treatment by the physician is sometimes decided based on the subjective symptoms. Current Kampo clinical research has not taken this aspect into account. Due to the individualized treatment approach of Kampo, subjective outcome measures are relevant and should always be considered while planning a study. In addition to databases, some authors have also suggested that more individual single-case research including N of one trials would be suitable to reflect Kampo medicine [155, 156]. The main motivation to perform clinical research on traditional treatments is for justification purposes, most placebo-controlled trials on Kampo do not reflect the use of Kampo in usual practice and are therefore not helpful when making medical decisions in daily practice.

3.2. Testing for Superiority over Placebo. Previous research has followed the principles of conventional drug research by testing the superiority of a single Kampo formula over a placebo for a clearly defined conventional diagnosis. An RCT from 1998, for example, compared Rikkunshito with a kind of placebo (low dose of the same formula) for the treatment of dyspepsia [68]. Results from this kind of trial are helpful for the integration of a single formula into conventional care. A formula that has proven efficacy in a conventional drug trial could be used in the future without any Kampo knowledge. However, this provides no information about Kampo as a whole treatment system.

Nevertheless, this kind of research does not represent the traditional Kampo treatment. A traditional treatment is led from the Kampo diagnosis (by taking a patient history, abdominal examination, tongue and pulse diagnosis). If the aim of a clinical trial is to ask whether Kampo treatment in a traditional way is efficacious or not, the traditional treatment system has to be taken into account. For this purpose, an additional Kampo diagnosis with the conventional diagnosis could be used for choosing the appropriate Kampo medicine. There are two options; the first excludes the influences of the Kampo diagnostic procedure and the study could be performed in a similar way as suggested for the placebo-controlled study. When this design is used, the Kampo diagnosis is performed for all patients before randomization, although it is only needed for the group that actually receives Kampo.

The first design is that Kampo diagnoses and an appropriate treatment could be used for stratification within the randomization process (see Figure 1). This design is especially useful for pilot trials or smaller studies to prove Kampo as an individualized treatment system. This trial design allows for an individual Kampo treatment according to the Kampo diagnosis. However, it also means that a range of different formulae will be administered. In order to ensure blinding, it might be necessary to prepare an adequate placebo for each formula, if they differ in appearance, smell and taste. In this type of trial, the patients should not only be blinded for the treatment, but they should also not receive any information about their Kampo diagnosis. Designs like this have already been used for homeopathy [157].

For many Western diagnoses, more than two Kampo diagnoses are common. Different patterns would result in a larger number of subgroups and some of these might be too small to have enough statistical power for subgroup analysis. For this reason, it makes sense to use the pooled patterns for primary analysis and to pre-specify subgroup analysis for the more common patterns. Another possibility, which might be easier to handle for the trial process, is to use the Kampo diagnosis as additional inclusion criteria and to recruit only those patients with relevant Kampo diagnosis for the formula under research. An example for this can be seen in the study by Kobayashi [158]. When using this design, it must be recognized that a large number of patients may need to be screened. In addition, the results are less representative for the Western diagnosis and integration into conventional care might be more difficult, because Western
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Placebo 2 (n = 50)

Placebo 1 (n = 50)

Kamishoyosan (n = 50)

Keishibukuryogan (n = 50)

Verum

Figure 1: Combining the Western and Kampo diagnosis for a placebo-controlled trial: to evaluate the efficacy of Kampo drug treatment, for example, for menopausal symptoms (ICD N95.1).

Standard

Placebo 1 (n = 100)

Kamishoyosan (n = 50)

Keishibukuryogan (n = 50)

Diagnosis: qi stagnation/depression pattern (n = 100)

Stagnant blood pattern (n = 100)

Figure 2: Combining the Western and Kampo diagnosis for a standard care controlled trial: to evaluate the effectiveness of Kampo as a whole treatment system, for example, for menopausal symptoms (ICD N95.1).

3.3. Testing for Non-Inferiority or Superiority over Standard Care. Doctors and patients want to know whether it is better to use Kampo instead of, or in addition to conventional treatment. Depending on its causality or external validity, the main focus of these studies could be performed more experimentally (homogenous patients and clearly defined treatment protocols) or more pragmatically (heterogeneous patients and a treatment which represents usual care) [159]. Especially for chronic diseases where a more complex treatment is needed [160], a pragmatic study design to test Kampo as an additional treatment could provide useful information for decision making. Similarly for the suggested placebo-controlled study designs, it is possible to use an individualized Kampo treatment within these studies.

The second possibility is to see the diagnostic procedure as part of the Kampo treatment, and the diagnostic procedure be used only on the Kampo group after randomization Figure 2. Study designs shown in Figures 1 and 2 are used to answer different research questions. The first option focuses on the treatment effects of the drug, whereas the second option provides a broader picture and evaluates Kampo as a whole treatment system, which consists of both the diagnostic procedure and the drug treatment.

3.4. Taking Patient Expectations into Account. Patient preferences and patient expectation can play a role in complementary and alternative medicine trials. Two systematic reviews suggest that the influence of patient expectations on outcomes is related to both within-group changes and between-group differences [161, 162]. This has already been shown for acupuncture [163]. If the patients in a Kampo
trial have higher expectations of a positive outcome than the "average" patient, then this could result in within-group changes that are larger than in a more representative sample. High expectations might also be associated with high response rates and improved outcomes in the placebo-controlled group. This could result in a ceiling effect making it more difficult to detect a significant difference between verum and placebo. Different strategies are available to deal with this problem, such as: including a run-in phase, stratification for randomization and measuring expectation. A simple tool for measuring aspects of expectations at baseline is to ask questions such as: "How effective do you expect the treatment to be?" with responses such as "very effective", "effective", "slightly effective", "not effective" or "don't know". These data could be used to make adjustments in the primary data analysis.

4. Conclusion

Kampo is a holistic and individualized treatment with a long tradition and future research is required to take this into account. RCT is the appropriate study design for testing efficacy or effectiveness, however within such a study, the treatment should be individualized according to the Kampo diagnosis.

Funding

This work was supported by Grant-in-Aide for Research on Applied Use of Statistics and Information, Health and Labour Sciences Research and Clinical Research for Development of Preventive Medicine and New Therapeutics from Ministry of Health, Labour and Welfare of Japan. This work was also supported by the Center for Clinical Trials, Japan Medical Association. Claudia Witts' Chair for Complementary Medicine is endowed by the Carstens-Trials, Japan Medical Association. This work was also supported by the Center for Clinical Development of Preventive Medicine and New Therapeutics and Labour Sciences Research and Clinical Research for Grant-in-Aide for Research Funding. RCT is the appropriate study design for testing efficacy or effectiveness, however within such a study, the treatment should be individualized according to the Kampo diagnosis.

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