学 会 等 発 表 実 績

委託業務題目「海外諸国の各医療制度の中での「統合医療」の使用実態・健康被害・エビデンスの調査および日本の医療機関での使用実態調査」

機関名　国立大学法人東京大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
RA治療ガイドラインにおける医療経済評価の位置付けと日本での展望（口頭）	津谷喜一郎, 五十嵐中, 宮坂信之, 山中寿	第58回日本リウマチ学会総会・学術集会	2014.4	国内
温泉医学と研究デザイン—1945年の長崎原爆被爆者に対する永井隆の比較研究から—（口頭）	津谷喜一郎	第79回日本温泉気候物理医学会総会・学術集会	2014.5	国内
Assessing the quality of study reports on spa therapy based on randomized controlled trials by the spa therapy checklist (SPAC)（口頭）	Kamioka H, Tsutani K, Maeda M, Hayasaka S, Goto Y	第79回日本温泉気候物理医学会総会・学術集会	2014.5	国内
Kampo medicines: is it a part of integrative medicine in Japan?（口頭）	Tsutani K	Integrated Medicine and Health 2014	2014.5	国外
一般人アンケートと医師アンケートからみた日本の統合医療の課題—平成24-25年度厚労科研調査から—（口頭）	津谷喜一郎	一般社団法人日本統合医療学会第3回教育セミナー	2014.5	国内
WHOによる健康の定義の歴史—東アジアの言語と政治—（口頭）	津谷喜一郎	第115回日本医史学会総会・学術大会	2014.5	国内
日本東洋医学界EBM委員会の活動の経緯（口頭）	津谷喜一郎	第65回日本東洋医学会学術総会	2014.6	国内
Structured abstract development of east Asian traditional medicine and health food（口頭）	Tsutani K	2014 Joint Meeting of WPRIM and APAME and APAME Convention	2014.8	国外
The Japanese association of medical journal editors (JAMJE)（ポスター）	Kitamura K, Tsutani K, Kitagawa M	APAME 2014	2014.8	国外
診療ガイドラインとCOI（口頭）	津谷喜一郎	第7回日本医学雑誌編集者会議(JAMJE)総会・シンポジウム	2014.11	国内
Use of Kampo diagnosis in randomized controlled trials of Kampo products in Japan: a systematic review.（ポスター）	Motoo Y, Arai I, Tsutani K	The 17th International Congress of Oriental Medicine	2014.11	国外
Cannabinoid-based medicines の歴史と本邦における規制について（口頭）	宮路天平, 山口拓洋, 津谷喜一郎	日本薬史学会2014年会	2014.11	国内
プラセボに関する日本人の知識や参加意識—2003年と2013年のインターネット調査—（口頭）	津谷喜一郎, 小出宏, 中野重行	第35回日本臨床薬理学会学術総会	2014.12	国内
日本東洋医学会EBM委員会の取り組み：漢方におけるエビデンスとアート（口頭）	津谷喜一郎	第18回日本統合医療学会	2014.12	国内

米国におけるdietary supplementとしての中薬製品 －流通品のラベル表示の評価－（ポスター）	唐文涛, 池田秀子, 新井一郎, 津谷喜一郎	日本薬学会第135年会	2015.3 (予定)	国内
ISO/TC249における伝統医学の国際標準化 –最近1年間の薬物分野の動向–（口頭）	新井一郎	和漢医薬学会	2014.8	国内
Industry of Kampo Medicines and Regulation on Herbal Drug Development in Japan（口頭）	Ichiro ARAI	Symposium hosted by BK21plus Korean Medicine Science Center,Institute of Oriental Medicine Kyung Hee Univ./Recent trends of new herbal medicine development, commercialization and regulation (Seoul, Korea)	2015.2.25	国外
Advancements and challenges relevant to integrative traditional and modern medicine in the world: Japan（口頭）	Motoo Y	2014 Integrative Traditional and Modern Medicine International Forum	2014.11	国外

２．学会誌・雑誌等における論文掲載

	掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
1	Use of Kampo Diagnosis in Randomized Controlled Trials of Kampo Products in Japan: A Systematic Review	Motoo Y, Arai I, Tsutani K	PLoS ONE	2014	国外
2	Effectiveness of horticultural therapy: A systematic review of randomized controlled trials	Kamioka H, Tsutani K, Yamada M, Hyuntae Park, Okuizumi H, Honda T, Okada S, Sang-Jun Park, Kitayuguchi K, Abe T, Handa S, Mutoh Y	Complementary Therapies in Medicine	2014	国外
3	診療ガイドラインとシステマティック・レビュー	唐文涛, 小島原典子, 河合富士美, 津谷喜一郎.	薬理と治療	2014	国内
4	EQUATOR Networkから得られる, 質の高い研究報告のための国際ルール③. STROBE: 疫学における観察研究報告のためのルール	上岡洋晴, 中山健夫, 津谷喜一郎	薬理と治療	2014	国内
5	食品の新たな機能性表示制度で求められるエビデンスのあり方	津谷喜一郎	薬理と治療	2014	国内
6	温泉医学と研究デザイン－1945年の長崎原爆被爆者に対する永井隆の比較研究から－	津谷喜一郎	日本温泉気候物理医学会雑誌	2014	国内
7	代替医療による間接的な健康被害の実態	津谷喜一郎, 湯川慶子, 長澤道行, 新井一郎, 五十嵐中, 折笠秀樹, 鶴岡浩樹, 福山哲,元雄良治, 山崎喜比古	薬理と治療	2014	国内
8	代替医療の利用状況・長所・主観的肯定的変化－慢性疾患患者の視点から－	湯川慶子, 津谷喜一郎, 石川ひろの, 山崎喜比古, 木内貴弘	薬理と治療	2015	国内
9	慢性疾患患者の代替医療による副作用への対処とヘルスリテラシーとの関連	湯川慶子, 石川ひろの, 山崎喜比古, 津谷喜一郎, 木内貴弘	日本健康教育学会誌	2015	国内
10	漢方製剤の記載を含む診療ガイドライン (KCPG)	新井一郎	漢方と最新治療	2014	国内
11	ISOにおける中国伝統医学の国際標準化	新井一郎	医薬品医療機器レギュラトリーサイエンス	2014	国内
12	Effect of Saikokeishito, a Kampo medicine, on hydrogen peroxide-induced premature senescence of normal human dermal fibroblasts	Takata T, Motoo Y, Tomosugi N	Journal of Integrative Medicine	2014	国外

13	Acupuncture and herbal medicine for cancer patients 2014	Efferth T, Lee S, Motoo Y, Schröder S	Evid Based Complement Alternat Med	2014	国外
14	インフルエンザ感染後に発症した慢性疲労症候群に漢方治療が有効であった1例	守屋 純二, 竹内 健二, 上西 博章, 赤澤 純代, 元雄 良治, 橘本 英樹, 金嶋 光男, 小林 淳二, 山川 淳一	日本東洋医学雑誌	2014	国内
15	がん治療と漢方～支持療法としての意義～	元雄 良治	Medicament News	2014	国内

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補完代替医療(CAM)総論	鶴岡浩樹, 津谷喜一郎	In: 八木剛平, 渡邊衡一郎(編). レジリアンス－症候学・脳科学・治療学	2014	国内

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Use of Kampo Diagnosis in Randomized Controlled Trials of Kampo Products in Japan: A Systematic Review

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Abstract

Background: The Committee for Evidence-based Medicine (EBM) of the Japan Society for Oriental Medicine started compiling Evidence Reports of Kampo Treatment (EKAT) in 2007. EKAT is a compilation of structured abstracts of randomized controlled trials (RCTs), along with comments by a third party reviewer. As of 31 December, 2012, there were 378 RCTs of Kampo medicines in Japan. The primary research question of this study is "How frequently is Kampo diagnosis used in RCTs of Kampo medicines?" The secondary research question is "When is Kampo diagnosis used in RCTs?"

Materials and Methods: The structured abstract (SA) of each RCT article was reviewed to examine how Kampo diagnosis was used in RCTs, especially how Kampo diagnosis was used in the randomization process.

Results: Kampo diagnosis was used before randomization in 27 RCTs (7.1%), after randomization in 31 RCTs (8.2%), and not used in 320 RCTs (84.7%). Before randomization, Kampo diagnosis was used as a criterion for inclusion in 10 RCTs, criterion for exclusion in 9 RCTs, and criteria for both inclusion and exclusion in 2 RCTs. Kampo formulas were determined according to Kampo diagnosis in 7 RCTs. After randomization, subgroup analyses according to Kampo diagnosis were done in 27 RCTs, and grade of disease severity at Kampo diagnosis was used for analysis as an endpoint in 4 RCTs.

Conclusions: Kampo diagnosis was used before randomization only in approximately 15% of RCTs, and the number of RCT articles using Kampo diagnosis after randomization was almost the same as that before randomization. Further studies to determine the good RCTs conforming to CONSORT requirements and good systematic reviews conforming to PRISMA requirements are needed to clarify the significance of Kampo diagnosis.

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Introduction

Kampo, traditional Japanese medicine, originated from ancient Chinese medicine, and greatly developed especially during the Edo era (1603-186 A.D.). Kampo has distinct characteristics such as abdominal diagnosis for therapeutic indications and useful formulas with smaller amounts of herbs, compared with Chinese medicine. In 1967, four Kampo formulas were covered by National Health Insurance, and since 1986, 148 Kampo formulas have been approved for ethical use [1]. From 1967 to 1986, the ethical Kampo product approval process was based on "a consensus-based monograph" written by the Federation of Pharmaceutical Manufacturers' Associations of Japan under the supervision of the Ministry of Health and Welfare (re-named as the Ministry of Health, Labor and Welfare [MHLW] in 2001) and not on clinical evidence. The indications on the label were based on symptoms, not traditional Kampo medicine theory or Western medicine diagnosis. The MHLW reevaluation of 1985 to 2014 led to a slight modification of these indications.

In general, Kampo formulations are extracts of herbal formulas and prepared as described in the classical Kampo literature [2–4]. The difficulty with implementing randomized controlled trials (RCTs) of Kampo medicines has often been attributed to the use of Kampo diagnosis. Since high-quality GMP- based extracts of Kampo formulas for ethical use have been prescribed in RCTs, the reproducibility of RCT results have been very high. In Japan, Kampo is used in a Western-style medical system, and is prescribed by medical doctors, educated in Western medicine, but having basic knowledge of Kampo. Doctors are required, not by law, but as professionals, to have a basic knowledge of the indications for each Kampo formula at the time of prescription as well as knowledge of Western medical diagnosis. According to a survey by the Japan Kampo Medicines Manufacturers' Association (JKMA) in 2011, 52% of Japanese medical doctors prescribe Kampo formulas based on Western medicine, 32% on Western medicine with consideration of Kampo diagnosis, 10% on both Western medicine and Kampo medicine, and 6% on Kampo diagnosis [5].

Kampo diagnosis is based on the results of a physical examination, especially on the results of abdominal palpation, which is specific for Kampo medicine. Kampo medicine is taught at all 80 medical schools in Japan and is part of the Model Core Curriculum for Medical Education of 2001 set by the Association

of Cooperative Researchers on Medical and Dental Education under the supervision of the Ministry of Education, Culture, Sports, Science and Technology of Japan. The Japan Society for Oriental Medicine (JSOM) has certified approximately 2,150 Kampo experts (medical doctors) as of March 2011. These experts have passed an examination and completed a training program. Indeed, ordinary physicians, not Kampo medicine experts, can prescribe Kampo drugs, and health insurance actually covers the cost of drugs prescribed for diseases as named in Western medicine name for the disease. Thus, Japanese doctors can prescribe Kampo formulas based on Western medical diagnosis. Since it is unclear that this system is adequate, evidence should be gathered from RCTs of Kampo medicines prescribed on the basis of Kampo diagnosis.

RCTs of Kampo medicines have been conducted in a variety of clinical fields such as gastroenterology, cardiology, respiratology, etc. The Committee for Evidence-based Medicine (EBM) of JSOM has investigated the description of Kampo products in the Japanese Clinical Practice Guidelines (CPGs), and presents the results of this investigation (in "Clinical Practice Guidelines Containing Kampo Products in Japan" [in Japanese]) to the public on the website (http://www.jsom.or.jp/medical/ebm/cpg/index.html). Analysis of the results indicates that CPG developers do not have sufficient access to the evidence on Kampo [3].

The first Evidence Reports of Kampo Treatment (EKAT) project started in 2001, and the first report was published in 2005. An Evidence Report Task Force (ER-TF) was established in 2005, and the EKAT project gathered momentum in 2007. The EKAT 2010 (which was published in 2010) contained the structured abstracts of 345 RCTs of Kampo formulas [6,7], and has been linked to the Cochrane Library (CENTRAL) as a Specialized Register. EKAT 2013 will be available by July 2014 and covers all previous structured abstracts archived. However, not all the articles on Kampo RCTs include comments from a Kampo perspective. In addition, how Kampo diagnosis is used in each RCT has not been studied.

The primary research question of this study is "How frequently is Kampo diagnosis used in RCTs of Kampo medicines?" The secondary research question is "When is Kampo diagnosis used in RCTs?" The long-term goal of this research is to improve the quality of RCTs of Kampo treatment by showing the relevance of Kampo diagnosis to the evaluation of Kampo formulations.

Materials and Methods

1. The process of compiling abstracts for EKAT 2010

Articles about RCTs of Kampo formulas (i.e., extract granules, tablets, and capsules, or pills, approved for prescription), published between 1986 and 2009, were included. References published before 1986 were excluded for the following reason: In 1986, the quality standard of Kampo products for ethical use was revised, and all the products needed to receive re-approval to meet the new standard. Therefore, all the Kampo products currently available on the market have the quality standards set in 1986. Kampo products meeting the old quality standard are no longer available, and information from clinical trials using these products is not applicable to current clinical practice. The data sources of EKAT were the Cochrane Library (CENTRAL), Igaku Chuo Zasshi (*Japana Centra Revuo Medicana* [JCRM], Ichushi) web, and the database offered by the Japan Kampo Medicines Manufacturers' Association (JKMA). The Cochrane Library (CENTRAL) includes PubMed/Medline-derived and EMBASE-derived RCTs. Studies on in-house formulas such as decoctions were excluded owing to their lesser reproducibility. Structured abstracts with comments by third parties were arranged in the order used in the International Classification of Diseases and Related Health Problems 10th Revision (ICD10). Finally, 416 references were reviewed, and SAs of articles on 345 RCTs and 1 meta-analysis were prepared. Information on the development process in detail can be obtained on the website of EKAT 2010 [7]. EKAT has been updated every year.

2. Review of EKAT

We reviewed EKAT 2010 [7] and its supplementary versions EKAT Appendix 2011 [8] and EKAT Appendix 2012 [9]. Finally, 378 RCTs, 1 meta-analysis, and 457 articles were subjected to our analysis. Fig. 1 shows the PRISMA flow diagram [10]. In this diagram, the number of studies included in qualitative synthesis is 375, whereas the number of RCTs is 378. This difference was caused by the fact that 3 articles included 2 RCTs, respectively. We organized all the SAs in EKAT 2010, Appendix 2011, and Appendix 2012 into one package, classifying them into subspecialties such as cancer, infectious diseases, cardiovascular diseases, etc.

3. Identification of Kampo diagnosis in each SA

We reviewed each SA and its original article to determine whether Kampo diagnosis was used in the RCT process, focusing especially on the relationship between the application of Kampo diagnosis and randomization. Since each SA stated whether a Kampo diagnosis was made, the description of the Kampo diagnosis was easily retrievable. Each abstract in EKAT contains an item known as "From a Kampo medicine perspective", which explains how Kampo diagnosis was used in the RCT.

4. The pre- and post-randomization uses of Kampo diagnosis

Each RCT was analyzed from the viewpoint of the pre-randomization and post-randomization uses of Kampo diagnosis. Kampo diagnosis was used at the design (pre-randomization) stage and data analysis (post-randomization) stage of RCTs. At the pre-randomization stage, Kampo diagnosis was used in the inclusion and/or exclusion criteria and description of Kampo diagnosis was included to make it understandable to prescribing physicians. At the post-randomization stage, subgroup analysis revealed a significant dependence of Kampo medicine effectiveness on Kampo diagnosis. We provided examples of how Kampo diagnosis was used at different stages of RCTs of Kampo treatments.

5. An example of a basic Kampo diagnosis

Kampo diagnosis of kidney deficiency requires the presence of 3 or more of the following 6 symptoms: 1) heaviness of the back; 2) heaviness in the lower legs with pain in the heels and lateral surface of the lower legs; 3) tinnitus/hearing loss; 4) loss of hair and hair luster; 5) looseness or loss of teeth; 6) sexual dysfunction (impotence, nocturnal emission).

Results

SAs were prepared for 378 selected RCT references and 1 meta-analysis reference. The numbers of study designs in SAs are shown in Table 1.

Use of Kampo diagnosis in 378 RCTs in EKAT 2010 (as well as appendices to EKAT 2010 [Appendix 2011 and 2012]) was analyzed. As shown in Table 2, Kampo diagnosis was used before randomization in 27 RCTs (7.1%) and after randomization in 31 RCTs (8.2%). There were 4 types of Kampo diagnosis use, i.e.,

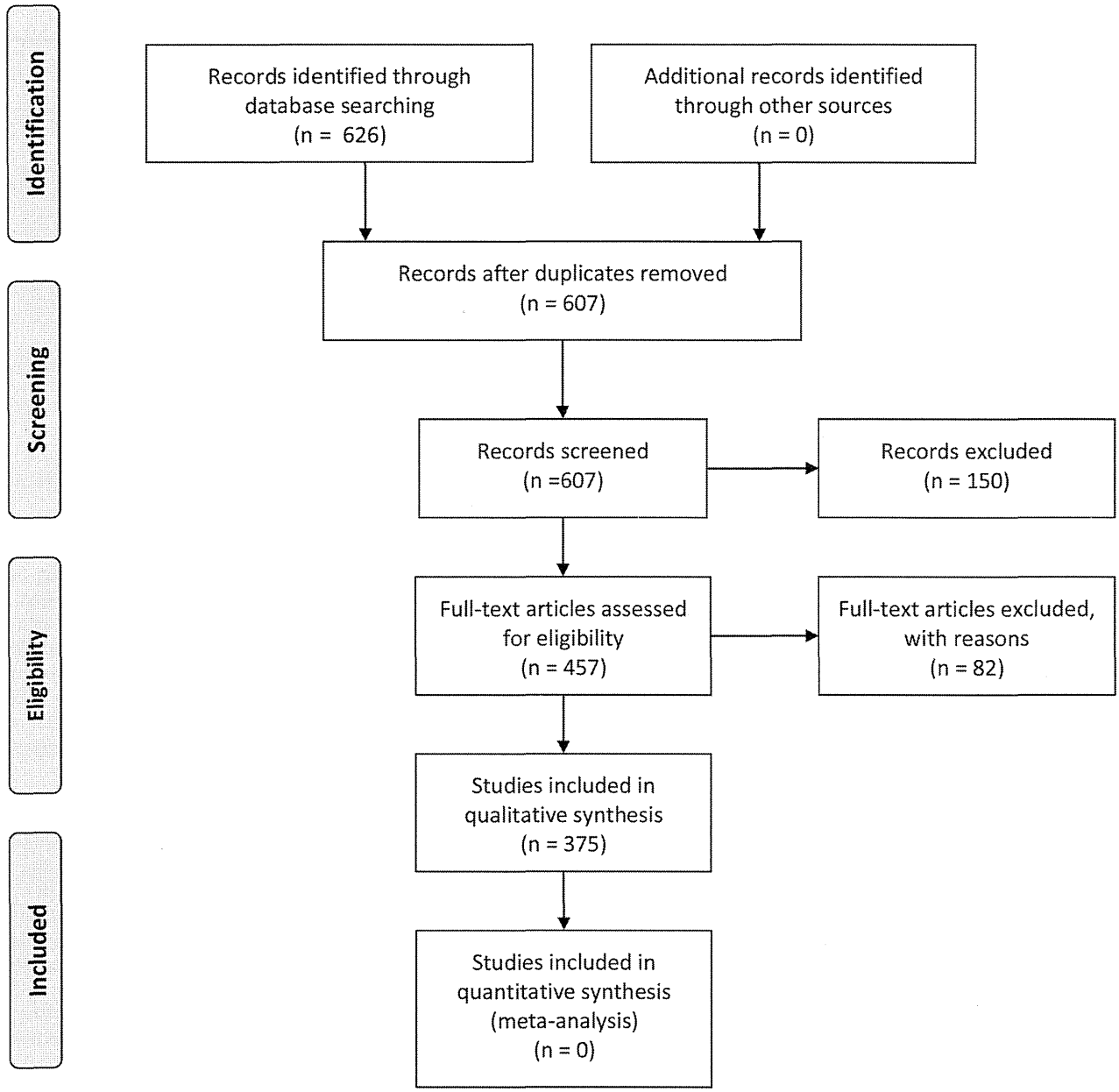

Figure 1. The PRISMA flow diagram.
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usage in inclusion criteria, in exclusion criteria, in both inclusion and exclusion criteria, and in the selection of Kampo formulas. Kampo diagnosis was used for randomization of only responders in two RCTs and only non-responders in one RCT. Post-randomization subgroup analyses were performed in 27 RCTs, and Kampo diagnosis was used to determine the efficacy of Kampo formulations in 4 RCTs.

Short descriptions including disease name, Kampo diagnosis, intervention (Kampo formula), and control are shown for each use category in Table 3. Further details can be found in each SA and its original article. Here, a typical RCT exemplifying a particular type of use is described below in narrative form.

1. Pre-randomization

1. Kampo diagnosis in inclusion criteria. Kobayashi et al. [11] used Kampo diagnosis in their inclusion criteria. Their objective was to assess the efficacy of hochuekkito for the treatment of atopic dermatitis. Patients with atopic dermatitis and *qi* deficiency (n = 77) were included and divided into a hochuekkito administration group (n = 37: arm 1), and a placebo group (n = 40: arm 2). No significant between-arm difference was found in the reduction of skin lesion score and change of *qi* deficiency score.

These authors used response or non-response to hochuekkito as inclusion criteria, and randomized responders and non-responders as follows.

Allocation of responders to the Kampo formulation. Odaguchi et al. [12] evaluated the efficacy of goshuyuto for relief of chronic

Table 1. Designs of 378 RCTs in EKAT.

Randomization	
Randomized controlled trial (RCT)	348
Quasi-RCT/controlled clinical trial (CCT)	30
Blinding	
Double-blinded	36
Single-blinded	5
Open	337
Assignment	
Parallel	330
Crossover	48
Total	378

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headache. Goshuyuto was administered for 4 weeks to 91 patients with chronic headache. Sixty patients responded to goshuyuto, 27 patients did not respond, and 4 patients withdrew. The 60 responders were randomly assigned either to arm 1 (goshuyuto, n = 28) or arm 2 (placebo, n = 25), and 53 patients completed this trial. The number of days with headache was significantly less in arm 1 than in arm 2. There was no significant between-arm difference in the dosage of analgesics taken.

Allocation of non-responders to the Kampo formulation. Ushiroyama et al. [13] reported the efficacy of switching to unkeito from treatment based on the traditional diagnostic criterion (i.e., "eight-principle pattern identification") in women with polycystic ovary syndrome (PCOS). Among the 64 patients diagnosed with PCOS and treated with keishibukuryogan or tokishakuyakusan according to Kampo diagnosis, 54 non-responders were randomly assigned either to arm 1 (continuous administration of keishibukuryogan or tokishakuyakusan; n = 27) or arm 2 (unkeito; n = 27). Switching to unkeito decreased blood levels of luteinizing hormone and significantly stimulated ovulation. Unkeito had an ovulation-inducing action, regardless of Kampo diagnosis.

2. Kampo diagnosis in exclusion criteria. Nakajima et al. [14] used Kampo diagnosis in their exclusion criteria. Their objectives were to assess the efficacy of shosaikoto for interferon-resistant chronic hepatitis C. There were 100 participants (i.e., patients with chronic active hepatitis C who completed interferon therapy) after exclusion of those with yin pattern and deficiency pattern and three assigned groups: squalene group (1500 mg/day, n = 33: arm 1), cepharanthine group (1 mg/kg body weight per day, n = 33: arm 2), and shosaikoto group (6.0 g/day, n = 34: arm 3). Efficacy was equivalent in all groups.

3. Kampo diagnosis in inclusion and exclusion criteria. Arakawa et al. [15] evaluated the efficacy and safety of orengedokuto in patients with hypertension symptoms in a double-blind, randomized, controlled trial (DB-RCT). A total of 204 out of 265 patients met the inclusion criteria (presence of high blood pressure and hypertension symptoms such as irritability, etc., indicating the need for orengedokuto) and exclusion criteria, i.e., presence of yin pattern and deficiency pattern. They were divided into an orengedokuto administration group (n = 103: arm 1), and a placebo group (n = 101: arm 2). Hypertension symptoms were significantly lower in the orengedokuto group.

4. Selection of Kampo formula according to Kampo diagnosis. Ohno [16] evaluated the efficacy of Kampo Medicine (as a system) in patients with Sjögren's syndrome. Sixty-four patients were assigned either to arm 1 (according to Kampo diagnosis, n = 30, after 2 dropped out) or arm 2 (n = 28; after 4 dropped out). Treatments included bakumondoto alone for kidney deficiency–negative (n = 23), bakumondoto plus rokumigan for kidney deficiency without coldness (n = 3), and bakumondoto plus hachimijiogan for kidney deficiency with coldness (n = 4) in arm 1 and hochuekkito in arm 2. The amount of increase in salivary secretions was significantly greater in arm 1 than in arm 2 ($P<0.005$).

2. Post-randomization

1. Subgroup analyses according to Kampo diagnosis. Miyamoto et al. [17] reported the efficacy and

Table 2. Use of Kampo diagnosis in 378 RCTs in EKAT.

1. Pre-randomization	**27 RCTs (7.1%)**
1) Kampo diagnosis in inclusion criteria	10 (37.0%)
2) Kampo diagnosis in exclusion criteria	9 (33.3%)
3) Kampo diagnosis in inclusion criteria & exclusion criteria	2 (7.4%)
4) Selection of Kampo formula according to Kampo diagnosis	6 (22.2%)
2. Post-randomization	**31 RCTs (8.2%)**
1) Subgroup analyses according to Kampo diagnosis	27 (87.1%)
2) Severity score of Kampo diagnosis as endpoint	4 (12.9%)

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Table 3. Short descriptions including disease name, Kampo diagnosis, intervention (Kampo formula), and control for each use category.

	Randomization	Disease	Kampo diagnosis	intervention	control	Author (year)
1	1 Inclusion criteria (n = 10)	Polycystic ovary syndrome	Sixty-four patients were randomly assigned to one of 2 groups using the diagnostic criteria "yin and yang, excess or deficiency, interior and exterior, cold and heat", to receive 8-week preliminary administration of either keishibukuryogan or tokishakuyakusan. Then, 54 non-responder patients were further assigned to receive either a continuation of the same treatment (n = 27) or unkeito (n = 27) for 8 weeks.	Unkeito (n = 27)	Keishibukuryogan or Tokishakuyakusan (n = 27)	Ushiroyama T, et al. (2006)
2	1 Inclusion criteria (n = 10)	Sleep disorders	Of 20 normal healthy men receiving yokukansankachimpihange before the start of the study, 7 with sleep disorders favorably affected were selected for the study.	Yokukansankachimpihange (n = 7)	Anchusan (n = 7)	Aizawa R, et al. (2002)
3	1 Inclusion criteria (n = 10)	Essential hypertension.	Excess pattern	Daisaikoto (n = 14)	No administration (n = 15)	Sasaki J, et al. (1993)
			Deficiency pattern	Chotosan (n = 24)	No administration (n = 30)	
4	1 Inclusion criteria (n = 10)	Common cold	Subject selection was made on the basis of persistent symptoms and discomfort in the mouth, which indicate "shosaikoto-sho"	Shosaikoto (n = 131)	Placebo (n = 119)	Kaji M, et al. (2001)
5	1 Inclusion criteria (n = 10)	Atopic dermatitis	*Qi*-deficiency was one of the inclusion criteria for enrollment in this trial.	Hochuekkito (n = 37)	Placebo (n = 40)	Kobayashi H, et al. (2010)
6	1 Inclusion criteria (n = 10)	Senile pruritus	intermediate pattern to excess pattern	Orengedokuto (n = 16)	Antihistamine (n = 16)	Ohkawara A, et al. (1991)
			deficiency pattern	Goshajinkigan (n = 25)	Antihistamine (n = 29)	
7	1 Inclusion criteria (n = 10)	Gonarthro sis	The *sho* concept was an inclusion criterion. Although "gonarthrosis complying with the *sho* for boiogitokabushi" was used as a criterion, the *sho* concept was not defined.	Boiogitoka shuchibushimatsu (n = 110)	Loxoprofen (n = 101)	Nishizawa Y, et al. (2007)
8	1 Inclusion criteria (n = 10)	Dysmeno rrhea	Forty females suffering from dysmenorrhea for at least 1 year, with all *qi* deficiency, *yin*, and static blood scores of 30 or more, without orthopedic disorders, and not receiving oral low-dose medications or prescribed anxiolytics.	Tokishakuyakusan (n = 20)	Placebo (n = 20)	Kotani N, et al. (1997)
9	1 Inclusion criteria (n = 10)	Climacteric complaints	Table 1, which shows the 7 target symptoms of climacteric disorder, was referred for selection of keishibukuryogan*.	Keishibukuryogan (n = 21)	Keishibukuryogan and tofisopam (n = 22)	Tanaka E, et al. (1997)

Table 3. Cont.

	Randomization	Disease	Kampo diagnosis	intervention	control	Author (year)
10	1 Inclusion criteria (n = 10)	Chronic headache	patients with chronic headache that responded to goshuyuto	Goshuyuto (n = 28)	Placebo(n = 25)	Odaguchi H, et al. (2005, 2006)
11	2 Exclusion criteria (n = 9)	Chronic hepatitis C	Patients with yin pattern and deficiency pattern were excluded before the allocation.	Shosaikoto (n = 49)	One of the commonly used liver protectors (n = 50)	Nakajima O et al. (1999)
12	2 Exclusion criteria (n = 9)	Interferon-resistant chronic hepatitis C	One patient with yin pattern and deficiency pattern was excluded before the allocation, and the study was actually conducted in 99 patients.	Shosaikoto (n = 39)	Squalene (n = 33) Cepharanthine (n = 40)	Nakajima O, et al. (2003)
13	2 Exclusion criteria (n = 9)	Spring nasal allergy (pollinosis)	Deficiency pattern patients were excluded.	Ryokankyomishingeninto (n = 15)	Shoseiryuto (n = 15)	Mori H, et al. (1996)
14	2 Exclusion criteria (n = 9)	Spring allergic rhinitis (pollinosis)	Since shoseiryuto is used in intermediate or excess pattern patients, and eppikajutsuto is used in physically strong patients, physically weak patients were excluded.	Eppikajutsuto (n = 49)	Shoseiryuto (n = 45)	Mori H, et al. (1997)
15	2 Exclusion criteria (n = 9)	Spring allergic rhinitis (pollinosis).	Since shoseiryuto is used in intermediate pattern to excess pattern patients, physically weak patients were excluded.	Daiseiryuto (Keishito + Makyokansekito) (n = 24)	Shoseiryuto (n = 45)	Mori H et al. (1998)
16	2 Exclusion criteria (n = 9)	Springtime nasal allergy and allergic conjuncti vitis	Patients with deficiency pattern were excluded*.	Keimakakuhanto (Keishito + Maoto) (n = 33)	Shoseiryuto (n = 32)	Mori, et al. (1999)
17	2 Exclusion criteria (n = 9)	Nasal allergy and allergic conjunctivi tis in spring	Subjects with deficiency pattern were excluded because shoseiryuto and gokoto are used to treat subjects with excess or intermediate patterns.	Gokoto (n = 58)	Shoseiryuto (n = 58)	Shimazaki Y, et al. (2001)
18	2 Exclusion criteria (n = 9)	Springtime nasal allergy and allergic conjunctivi tis	Patients with deficiency pattern were excluded*.	Maobushisaishinto (n = 32)	Shoseiryuto (n = 34)	Yoshimoto T, et al. (2002)
19	2 Exclusion criteria (n = 9)	Antibody production after influenza vaccination	Subjects not intending to use hochuekkito, as well as subjects with easy fatigability, a high susceptibility to colds, slow recovery from colds, a high susceptibility to other infections like herpes and wound infection, poor appetite, loose bowels, and somnolence especially after meals	Hochuekkito (n = 18)	Placebo (n = 18)	Hamazaki K, et al. (2007)
20	3 Inclusion & exclusion criteria (n = 2)	Hyper tension symptoms	The inclusion criteria were high blood pressure and presence of hypertension symptoms. Patients with cold/yin pattern or deficiency pattern were excluded. Patients with thin physique were also excluded.	Orengedokuto (n = 103)	Placebo (n = 101)	Arakawa K, et al. (2003, 2003)
21	3 Inclusion & exclusion criteria (n = 2)	Dyspepsia caused by dysfunction of the upper gastro intestinal tract	In this study, the inclusion criteria were deficiency pattern symptoms (i.e., decreased tone of abdominal wall, subjective/objective splashing sound, gastroptosis tendency, and mental/physical weakness) and the exclusion criteria were excess pattern symptoms (i.e., mental and physical strength, massive and muscular body, and reddish face).	Rikkunshito (n = 147)	low-dose (1:4 dilution) Rikkunshito (n = 133)	Harasawa S, et al. (1998, 1999)

Table 3. Cont.

	Randomization	Disease	Kampo diagnosis	intervention	control	Author (year)
22	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Aqueous flare elevation after small-incision cataract surgery	Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.	Orengedokuto (n = 14) Kakkonto (n = 10) Saireito (n = 10)	no medication (n = 20)	Ikeda N, et al. (2001)
23	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Aqueous flare elevation after complicated cataract surgery	Evaluation of sho and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic(now Department of Japanese Oriental Medicine)in the above-mentioned university hospital.	Kakkonto (n = 12)	Saireito (n = 10)	Ikeda N, et al. (2002)
24	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Common cold syndrome associated with fever	Kampo prescriptions were administered according to sho in patients with fever associated with common cold.	Kakkonto, Maoto, Keimakakuhanto, Chikujountanto, Shoseiryuto, Keishikashakuyakuto or Kososan (n = 35)	Fenoprofen (n = 45)	Homma Y, et al. (1995)
25	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Peptic ulcer	Based on the endoscopic findings, patients with marked redness and irregularity of gastric antral mucosa were assigned to the shigyakusan treatment, and patients with less evident findings to the saikokeishito treatment.	Shigyakusan or Saikokeishito (n = 7)	Sucralfate (n = 6)	Watanabe H, et al. (1995)
26	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Sjögren's syndrome	Arm 1 used Kampo diagnosis to allocate patients, specifically *jinkyo* (kidney deficiency). Kampo formulations for Arm 1 were selected based on the status of *jinkyo*: 1) bakumondoto alone for *jinkyo*-negative; 2) bakumondoto plus rokumigan for *jinkyo* without chills; and 3) bakumondoto plus hachimijiogan for *jinkyo* with chills.	Hochuekkito (n = 28)	Bakumondoto, Bakumondoto + Rokumigan or Bakumondoto + Hachimijiogan (n = 30)	Ohno S, et al. (2006)
27	4 Selection of Kampo formula according to Kampo criteria (n = 6)	Osteopenia in women during menopause	Keishibukuryogan for 6 patients with excess pattern, and tokishakuyakusan for 6 patients with deficiency pattern*.	Keishibukuryogan (n = 6) Tokishakuyakusan (n = 6)	no administration of Kampo drug (n = 6)	Ohta H, et al. (1990)

* described in the original article, not in SA.

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safety of shoseiryuto in the treatment of bronchitis. Patients with mild to moderate bronchitis and evaluable symptoms were randomly assigned to two arms (arm 1: shoseiryuto, n = 101; arm 2: placebo, n = 91). General improvement was moderate to marked and tended to be greater in arm 1 than in arm 2. Subgroup analyses revealed that patients without physical frailty and those with cough and watery sputum showed a significantly higher rate of general improvement in arm 1 than in arm 2.

2. Severity score of Kampo diagnosis as endpoint. Shimada [18] evaluated the efficacy and safety of tokishakuyakusan for the treatment of hypofunction and decreased independence in patients with post-stroke. Such patients were randomly assigned to two arms (arm 1: tokishakuyakusan, n = 16; arm 2: no administration of Kampo medicines, n = 15). There were statistical differences between the two arms in the Stroke Impairment Assessment Set and Functional Independence Measure scores at 12 months. These scores remained at baseline levels in arm 1 but were significantly decreased in arm 2. By additional exploratory analysis using severity scores of Kampo diagnosis such as blood stasis and kidney deficiency as endpoints in before and

after comparison, the authors found a significant improvement in blood stasis score and kidney deficiency score in arm 1 at 12 months. But, blood stasis score did not change and kidney deficiency score worsened in arm 2, resulting in significant differences between the two arms at 12 months.

Discussion

In this study, we described the current status of the use of Kampo diagnosis in RCTs of Kampo formulations. In EKAT, two Japanese-language databases (Ichushi [JCRM] and JKMA) and one English-language database (Cochrane Library CENTRAL) were searched. Addition of Chinese-language databases to the conventional systematic review (SR) increased the number of references retrieved by the search [19]. However, the quality of the RCTs of Kampo medicines is most important, and our SR revealed that EKAT provides us usable information on Kampo treatment. Our report is the first paper to divide the uses of Kampo diagnosis into pre- and post-randomization uses, to describe the four pre-randomization uses of Kampo diagnosis (in inclusion criteria, exclusion criteria, both inclusion and exclusion criteria, and in Kampo formula selection), and to describe the two post-randomization uses of this diagnosis (subgrouping of patients for analysis, use of a score for Kampo diagnosis severity as an endpoint).

Most RCTs of Kampo medicines were small and did not use Kampo diagnosis. This might imply that Kampo medicines show efficacy in the Western-style medical system and this information would be useful to clinicians whose practice is oriented toward Western medicine. To show the relevance of Kampo diagnosis to the conduct of RCTs on Kampo treatment, the quality and quantity of RCTs should be improved. If we could verify the relevance of the use of Kampo diagnosis to such RCTs, it is expected that their findings would be more significant and that Kampo medicine efficacy and safety would be increased. It is vitally important for traditional East Asian medicine to address this issue.

Clinical research on Kampo treatments, especially by researchers of Western medicine, is often criticized by Kampo traditionalists for not using Kampo diagnosis in the randomization process. However, no report has shown how Kampo diagnosis is used in RCTs. Most criticisms of RCTs that ignore Kampo diagnosis come from individuals who have poor understanding of modern evaluation methodology. The use of traditional diagnosis in RCTs or CPGs has been discussed [20,21]. The present study, however, does not discuss the superiority of Kampo-diagnosis use over its non-use. Kampo-diagnosis use and non-use were compared in only 4 RCTs (which is the fourth type of pre-randomization usage designated "Selection of Kampo formula according to Kampo diagnosis". When the number of RCTs using Kampo diagnosis for this purpose increases to a certain level, the research question "Is the use of Kampo diagnosis superior to its non-use?" can be answered by performing another SR. Preliminary analysis has revealed the poor quality of articles reporting RCTs. To show the superiority of Kampo diagnosis use with SRs, it will be necessary to improve the quality of these studies by using the CONSORT statement [22].

There are pros and cons to the use of Kampo diagnosis in RCTs. If the Kampo diagnosis is found to enhance the efficacy of Kampo treatment, it would broaden the applications of Kampo medicine in Western disease entities. If the Kampo diagnosis is not found to enhance the efficacy of a Kampo formula, it would mean that Kampo products can have favorable effects without the need to know complex concepts and techniques of Kampo diagnosis. However, the prescription of a Kampo formula based on Kampo diagnosis could increase the drug's safety and thereby lead to better clinical outcome.

It is too early to know the precise implications or interpretation of legal policy or the labeling of ethical Kampo products. More RCTs of drugs prescribed according to Kampo diagnosis are needed to compare with RCTs of drugs not prescribed according to Kampo diagnosis and show the superiority in both efficacy and safety of Kampo formulations. The current labeling policy in Japan is believed to be sufficient, based on the fact that Western medical diagnosis was used in over 90% of RCTs in our study. While Kampo traditionalists stress the importance of using the Kampo diagnostic system, they lack interest in regulatory systems and emphasize educational systems.

As for the limitations of the SR, firstly, there was possible publication bias. Clinical trial registration (the tool to prevent publication bias) was developed in 2005 in Japan [23]. The number of articles about the RCTs in this study is as follows: 1986-89: 11 (2.9%), 1990s: 180 (47.6%), 2000s: 157 (41.5%), 2010-11s:30 (7.9%). There were 261 RCT articles from 1986 to 2004, and 117 RCT articles from 2005 to 2011. Thus, 69.0% of RCTs were published before the problem of publication bias was addressed. Secondly, the motivations for conducting RCTs were not clearly stated; some were of purely academic interest, and some were of industrial interest. The CONSORT statements of 1996, 2001, and 2010 have been translated into Japanese but were ignored by those interested in Kampo medicine. And only the statement of 2010 addresses the role of the funding agency in the conduct of the study. Kampo industry may have more interest in RCTs that involve the use of Western medicine diagnosis because reporting them increases sales. PRISMA guidelines [24] should be used when preparing systematic reviews of RCTs with low risk of biased information.

Conclusions

Kampo diagnosis before randomization was used only in approximately 15% of RCTs, and the number of RCT articles using Kampo diagnosis after randomization was almost the same as that before randomization. To clarify the importance of Kampo diagnosis in the conduct of RCTs, the CONSORT statement should be used in the reporting of good RCTs and the PRISMA statement should be used in the reporting of systematic reviews.

Supporting Information

Checklist S1 PRISMA Checklist
(DOC)

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Author Contributions

Conceived and designed the experiments: YM IA KT. Performed the experiments: YM IA KT. Analyzed the data: YM IA KT. Contributed reagents/materials/analysis tools: YM IA KT. Wrote the paper: YM IA KT.

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Effectiveness of horticultural therapy: A systematic review of randomized controlled trials

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KEYWORDS
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Randomized controlled trial;
Rehabilitation effect

Summary
Aim: To summarize the evidence from randomized controlled trials (RCTs) on the effects of horticultural therapy (HT).
Methods: Studies were eligible if they were RCTs. Studies included one treatment group in which HT was applied. We searched the following databases from 1990 up to August 20, 2013: MEDLINE via PubMed, CINAHL, Web of Science, Ichushi-Web, GHL, WPRIM, and PsyclNFO. We also searched all Cochrane Database and Campbell Systematic Reviews up to September 20, 2013.
Results: Four studies met all inclusion criteria. The language of all eligible publications was English and Korean. Target diseases and/or symptoms were dementia, severe mental illness such as schizophrenia, bipolar disorder, and major depression, frail elderly in nursing home, and hemiplegic patients after stroke. These studies showed significant effectiveness in one or more outcomes for mental health and behavior. However, our review especially detected

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omissions of the following descriptions: method used to generate randomization, concealment, blinding, and intention-to-treat analysis. In addition, the results of this study suggested that the RCTs conducted have been of relatively low quality.
Conclusion: Although there was insufficient evidence in the studies of HT due to poor methodological and reporting quality and heterogeneity, HT may be an effective treatment for mental and behavioral disorders such as dementia, schizophrenia, depression, and terminal-care for cancer.

Introduction

Over the years, recreation activity and relaxation in a forest environment, called "forest therapy" or "Shinrin-yoku" (e.g., forest-air bathing, and forest-landscape watching and walking) have become a kind of climatherapy or nature therapy, and are popular methods for many urban people with mental stress conditions.[1] The fields of preventive and alternative medicine have also shown an interest in the therapeutic effects of forest therapy.[2] The green landscape may help one recover from stress by causing lowered blood pressure, higher alpha brain wave amplitude, and reduced muscle tension.[3] In addition, a recent study reported that forest bathing trips increased natural killer (NK) cell activity, which was mediated by increases in the number of NK cells and the levels of intracellular anti-cancer proteins and phytoncides released from trees. The decreased production of stress hormones may also partially contribute to the increased NK cell activity.[4]

Among nature therapies, horticultural therapy (HT), which is easily implemented, has been very popular for treatment and rehabilitation for patients and for positive health enhancement of elderly people. The fields of preventive and alternative medicine have also shown an interest in the therapeutic effects of HT.

A study reported that an intervention in a hospital horticultural garden was expected to influence healing, alleviate stress, increase feelings of well-being and promote participation in social life and re-employment for patients with brain damage.[5] A non-randomized controlled cohort trial reported that the addition of HT to a pain management program improved participants' physical and mental health and their coping ability with respect to chronic musculoskeletal pain.[6] A systematic review of controlled and observational studies for nature-assisted therapy reported that significant improvements were found for varied outcomes in diverse diagnoses, spanning from obesity to schizophrenia.[7]

It is well known in research design that evidence grading is highest for a systematic review (SR) with meta-analysis of randomized controlled trials (RCTs). Although several studies have reported the treatment and rehabilitation effects of HT, there is no SR of the evidence based on RCTs. We checked the Cochrane Review protocol HT for schizophrenia,[8] but it is not published at present. We focused on all treatment and rehabilitation effects in accordance with the International Classification of Diseases-10 (ICD-10). The objective of this review was to summarize the evidence from RCTs on the effects of HT.

Methods

Criteria for considering studies included in this review

Types of studies
Studies were eligible if they were RCTs.

Types of participants
There was no restriction on patients.

Types of intervention and language
Studies included at least one treatment group in which HT was applied. The definition of the HT was complex, and 'therapeutic horticulture' was also considered to have the same meaning. The American Horticultural Therapy Association defined HT as the engagement of a person in gardening-related activities, facilitated by a trained therapist, to achieve a specific treatment goal.[9] On the other hand, Gonzalez defined therapeutic horticulture as an open program, "a process that uses plant-related activities through which participants strive to improve there well-being through active and passive involvement", which can be easy implemented and performed by a variety of health-care providers.[10] We focused on all cure and rehabilitation effects in accordance with the ICD-10 and attached importance to feasibility and external validity. Therefore, in this study, we adopted the later as HT. There was no restriction on the basis of language.

Types of outcome measures
We focused on all cure and rehabilitation effects in accordance with the ICD-10. There was no restriction on secondary outcomes.

Search methods for studies identification

Bibliographic database
We searched the following databases from 1990 up to August 20, 2013: MEDLINE via PubMed, CINAHL, Web of Science, Ichushi Web (in Japanese), the Global Health Library (GHL), the Western Pacific Region Index Medicus (WPRIM), and PsycINFO. The International Committee of Medical Journal Editors (ICMJE) recommended uniform requirements for manuscripts submitted to biomedical journals in 1993. We selected articles published (that included a protocol) since 1990, because it appeared that the ICMJE recommendation had been adopted by the

relevant researchers and had strengthened the quality of reports.

We also searched the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Methodology Register (Methods Studies), the Health Technology Assessment Database (Technology Assessments), the NHS Economic Evaluation Database (NHS EED), The Cochrane Collaboration databases (Cochrane Groups), the Campbell Systematic Reviews (the Campbell Collaboration), and all Cochrane up to August 20, 2013.

All searches were performed by a specific searcher (hospital librarian) who was qualified in medical information handling, and who was sophisticated in searches of clinical trials.

Search strategies

The special search strategies contained the elements and terms for MEDLINE, CINAHL, Web of Science, Ichushi Web, GHL, WPRIM, PsycINFO, and All Cochrane databases (Table 1). Only keywords relating to the above intervention were used for the searches. First, titles and abstracts of identified published articles were reviewed in order to determine the relevance of the articles. Next, references in relevant studies and identified RCTs were screened.

Registry checking

We searched the International Clinical Trials Registry Platform (ICTRP), the International Prospective Register of Systematic Review (PROSPERO), Clinical Trials.gov, and the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) up to August 20, 2013.

ICTRP in the WHO Registry Network meets specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary registries meet the requirements of the ICMJE. Clinical Trials.gov is a registry of federally and privately supported clinical trials conducted in the United States (US) and around the world. UMIN-CTR registers clinical trials conducted in Japan and around the world.

Handsearching, reference checking, and other

We handsearched abstracts published on HT and relevant journals in Japan. We checked the references of included studies for further relevant literature.

Review methods

Selection of trials

In order to make the final selection of studies for the review, all criteria were applied independently by four review authors (e.g., TH, JK, SP, TA) to the full text of articles that had passed the first eligibility screening (Fig. 1). Disagreements and uncertainties were resolved by discussion with other authors (e.g., HK, KT, YM).

Studies were selected when (i) the design was a RCT and (ii) one of the interventions was a form of HT. Trials that were excluded are presented with reasons for exclusion (Appendix).

Quality assessment of included studies

In order to ensure that variation was not caused by systematic errors in the study design or execution, eight review authors (HP, SO, HO, SH, SP, JK, TA, and TH) independently assessed the quality of articles. A full quality appraisal of these papers was made using the Cochrane's criteria list for the methodological quality assessment.[11] Disagreements and uncertainties were resolved by discussion with other authors (e.g., HO, SO, and HK).

Each item was scored as "yes" (y), "no" (n), "do not know or unclear" (?), or "not applicable" (n/a). Depending on the study design, some items were not applicable. The "n/a" was excluded from calculation for quality assessment. We displayed the percentage of present description on all 11 check items for the quality assessment of articles. Then, based on the percentage of risk of poor methodology and/or bias, each item was assigned to the following categories: good description (80—100%), poor description (50—79%), or very poor description (0—49%). Inter-rater reliability was calculated on a dichotomous scale using percentage agreement and Cohen's kappa coefficient (k).

Summary of studies and data extraction

Eight review authors (HP, SO, HO, SH, SP, JK, TA, and TH) described the summary from each article based on the recommended structured abstracts.[12,13]

Benefit, harm, and withdrawals

The GRADE Working Group[14] reported that the balance between benefit and harm, quality of evidence, applicability, and the certainty of the baseline risk were all considered in judgments about the strength of recommendations. Adverse events, withdrawals, and cost for intervention were especially important information for researchers and users of clinical practice guidelines, and we presented this information with the description of each article.

Analysis

Pre-planned stratified analyses were: (a) trials comparing HT with no treatment or waiting list controls, (b) trials comparing different types of general method (e.g., physical therapy, occupational therapy), and (c) trials comparing HT with other different intervention(s) (e.g., music therapy and animal-assisted therapy). We planned to express the results of each RCT, when possible, as relative risk (RR) with corresponding 95 percent confidence intervals (95%CI) for dichotomous data, and as standardized or weighted mean differences (SMD) with 95%CI for continuous data. Heterogeneous results of studies that provided by inclusion criteria were not combined. All analyses were computed with the "R version 2.15.1", a free software environment for statistical computing and graphics (URL:http://www.r-project.org/). It compiles and runs on a wide variety of UNIX platforms, and Window.

Research protocol registration

We submitted and registered our research protocol to the PROSPERO database (no. CRD42013005340),[15] an international database of prospectively registered SRs

Table 1 The special search strategies.

1 MEDLINE
#1 Search ("Horticultural Therapy"[Mesh] OR "horticultural"[TW] OR "horticulture"[TW])
#2 Search (("Gardening"[Mesh] OR "gardening"[TW] OR "Agriculture"[Mesh] OR "Agriculture"[TW]) AND ("therapy"[TW] OR "therapeutics"[TW] OR "therapeutic"[TW]))
#3 Search (#1) OR #2
#4 Search ("Randomized Controlled Trial" [Publication Type] OR ("randomized"[All] OR "randomised"[All]))
#5 Search (#3) AND #4
#6 Search (#3) AND #4 Filters: Publication date from 1990/01/01

2. CINHAL
#1 (MH "Horticulture") OR TI horticultur* OR AB horticultur*
#2 (MH "Agriculture+") OR TI (agricultur* OR gardening) OR AB (agricultur* OR gardening)
#3 TI (therap* OR activit* OR intervention*) OR AB (therap* OR activit* OR intervention*)
#4 #2 AND #3
#5 #1 OR #4
#6 (MH "Randomized Controlled Trials") OR TI (randomized OR randomised) OR AB (randomized OR randomised)
#7 #5 AND #6

3. Web of Science
#1 (horticultur* OR gardening) AND トピック=(therap* OR activit* OR intervention*)
#2 (random*)
#3 #2 AND #1

4. Ichushi Web
#1 園芸/TH or 園芸/TA or 園芸療法/TH or ガーデニング/AL
#2 (農業/TH or 農業/TA) and (作業療法/TH or 作業療法/TA)
#3 #1 or #2
#4 ランダム/AL or 無作為/AL or 対照/AL or 比較/AL
#5 (#3 and #4) and (DT=1990:2013) and (PT=原著論文)

5. Global Health Library
All Indexes: (horticulture OR horticultural OR gardening) AND (randomized OR randomised)

6. WPRIM
#1 Abstract:animal% and Abstract:therap% -Limits:1990-2012; Humans
#2 All:animal assisted therapy or All:animal-assisted
#3 #1 or #2

7. PsycINFO
#1 SU.EXACT.EXPLODE("Horticulture Therapy")
#2 ti(horticultur* OR gardening OR agricultur*) OR ab(horticultur* OR gardening OR agricultur*)
#3 #1 OR #2
#4 ti(random*) OR ab(random*)
#5 #3 AND #4
#6 #5 AND Journal, Journal Article, 1990-2013

8. All Cochrane
#1 MeSH descriptor: [Horticultural Therapy] explode all trees
#2 MeSH descriptor: [Gardening] explode all trees
#3 MeSH descriptor: [Agriculture] explode all trees
#4 horticultur*:ti,ab,kw (Word variations have been searched)
#5 agricultur* or garden or gardens or gardening:ti,ab,kw (Word variations have been searched)
#6 therap* or activit*:ti,ab,kw (Word variations have been searched)
#7 #1 or #2 or #4
#8 (#3 or #5) and #6
#9 #7 or #8 from 1990 to 2013 (Word variations have been searched)

9. Campbell Systematic Reviews
(horticulture OR horticultural OR agriculture OR gardening) AND therap* [search in All text]

10. ICTRP
horticulture OR horticultural OR gardening

11International Prospective Register of Systematic Reviews
horticulture [Interventions/Exposure] OR horticultural [Interventions/Exposure] OR Gardening [Interventions/Exposure]

12. Clinical Trials. gov
[Basic Search]: horticulture OR horticulral OR gardening

13. UMIN-CTR
園芸 [自由記載語]

in health and social care. Key features from the review protocol are recorded and maintained as a permanent record in PROSPERO. This provided a comprehensive listing of SRs registered at inception, and enabled comparison of reported review findings with what was planned in the protocol. PROSPERO is managed by CRD and funded by the UK National Institute for Health Research (NIHR). Registration was recommended because it encourage full publication of the review's findings and transparency in changes to methods that could bias findings.[16]

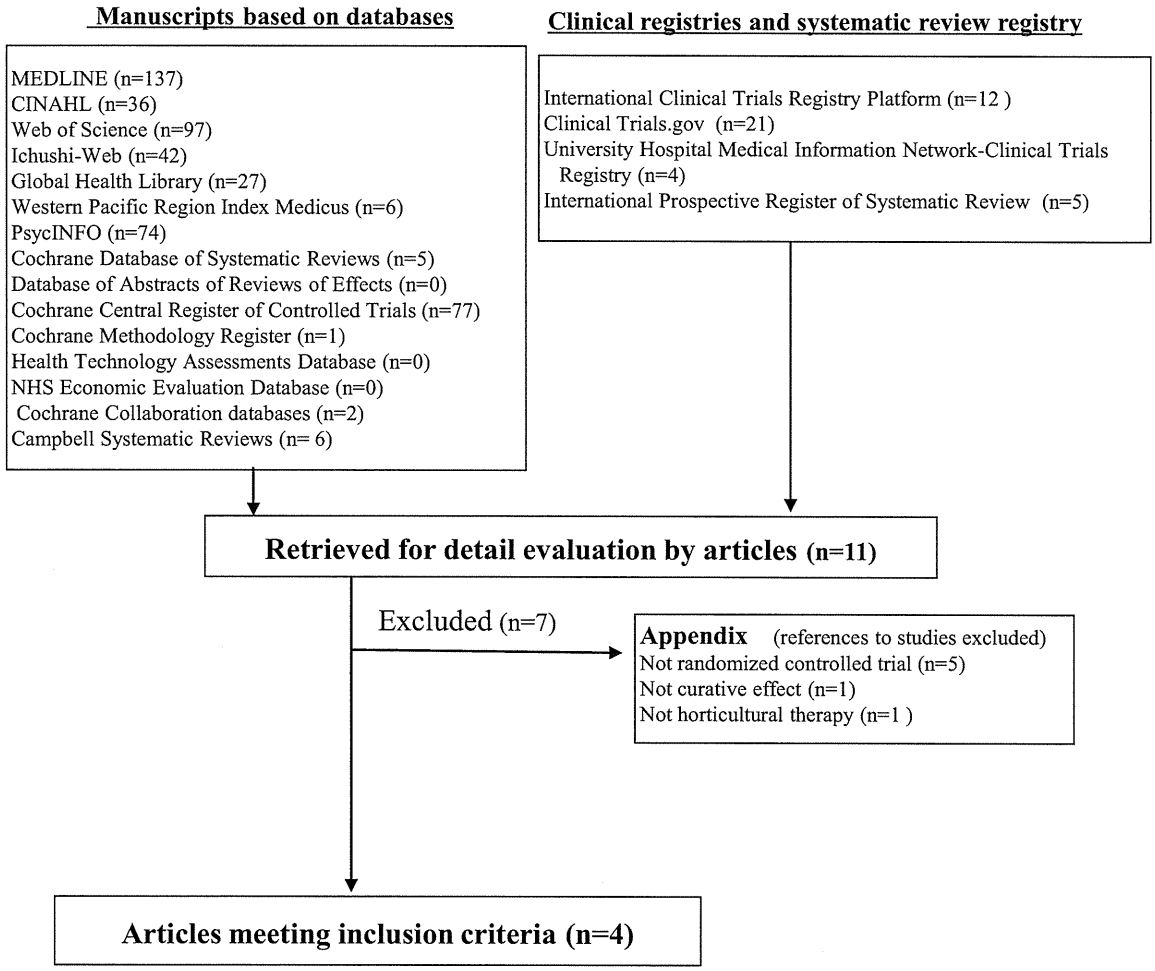

Figure 1 Flowchart of trial process.

Results

Study selection

The literature searches based on databases included potentially relevant articles (Fig. 1). Abstracts from those articles were assessed, and 11 papers were retrieved for further evaluation (checks for relevant literature). Seven publications were excluded because they did not meet the eligibility criteria (see Appendix). Four studies[17–20] met all inclusion criteria (Table 1).

Study characteristics

The language of all eligible publications was English[17–19] and Korean.[20] Target diseases and/or symptoms (Table 2) were dementia,[17] severe mental illness such as schizophrenia, bipolar disorder, and major depression,[18] frail elderly in nursing home,[19] and hemiplegic patients after stroke.[20] Based on ICD-10, we identified a disease targeted in each article (Table 3). Among four studies, two studies were about "Mental and behavioral disorders (F00-01,[17] F20,30-33[18])". There was one study in "Disease of the nervous system (G31)".[20] Because there were a variety of target diseases, there was one article for which we could not identify a single disease.[19]

Jarrott et al. reported that HTs were viable and desirable choices for dementia-care programs because they successfully engaged groups of participants who were often difficult to engage in activities that elicit high levels of adaptive behavior.[17]

Kam et al. reported that the horticultural activity program was effective in reducing stress of persons with psychiatric illness, but did not have a significant impact on work behavior and quality of life.[18]

Tse reported that an indoor gardening program for older people living in nursing homes improved life satisfaction and social network, and decreased perception of loneliness.[19]

Kim et al. reported that HT had effects on the improvement of mental health such as self-esteem, powerlessness, depression, and perceptual function for hemiplegic patients after stroke.[20]

Quality assessment

We evaluated 11 items from the Cochrane's criteria list in more detail (Table 4). Inter-rater reliability metrics for the