



Efficacy of daikenchuto, a traditional Japanese Kampo medicine, for postoperative intestinal dysfunction in patients with gastrointestinal cancers: meta-analysis

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Abstract

Background The Japan Society for Oriental Medicine makes a compilation of structured abstracts of randomized controlled trials (RCTs) of Kampo medicines available on its Evidence Reports of Kampo Treatment (EKAT) website.

Methods Using EKAT, we conducted a systematic review and meta-analysis on the efficacy of using daikenchuto (<https://mpdb.nibiohn.go.jp/stork>) for bowel dysfunction after surgery for gastrointestinal cancer. The primary outcomes were the time to first postoperative flatus and the time to first postoperative bowel movement (BM).

Results We found nine relevant RCTs. The mean differences between the daikenchuto group and control group (daikenchuto was not administered) were -0.43 (95% CI: -0.77 to -0.09) days for the time to first postoperative flatus, -0.29 (95% CI: -0.59 to 0.01) days for the time to first postoperative BM, and -0.95 (95% CI: -1.70 to -0.21) days for the length of postoperative hospital stay, and the risk ratio of the incidence of intestinal obstruction was 0.60 (95% CI: 0.35 – 1.03). The time to first postoperative flatus and the length of postoperative hospital stay were significantly shorter in the daikenchuto group than those in the control group ($P=0.01$). However, only double-blind studies were evaluated; the results turned to be non-significant.

Conclusion As a result of meta-analysis by all retrieved according to the registered protocol, daikenchuto was efficacious in improving postoperative bowel dysfunction in patients with gastrointestinal cancers. However, limiting to articles with description of COI and blindness, significance disappeared.

Keywords Daikenchuto · Kampo · Gastrointestinal cancers · Postoperative intestinal dysfunction · Meta-analysis

Introduction

Kampo medicine has its origin in ancient Chinese medicine, which evolved differently as it spread through various Asian countries, depending on the local cultural environment. Its history is unlike that of Western drugs that

have developed in contemporary medical environments. In Japan, Kampo medicine, although at first heavily influenced by Chinese medicine, has advanced in unique ways over time. For example, the diagnosis “abdominal diagnosis” (termed “Fukushin” in Japanese) is of Japanese origin [1]. For pharmaceutical formulations, Japan mainly uses

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standardized dried extract formulations, whereas China and Korea use mainly decoctions as traditional medicine. Accordingly, the efficacy of traditional medicines derived from ancient Chinese medicine needs to be evaluated separately for each country.

However, as most reports on clinical research on these medicines are of non-Japanese origin, little has been reported on the evidence of Kampo medicine in Japan. Therefore, the Japan Society for Oriental Medicine (JSOM) established an Evidence-Based Medicine (EBM) committee in 2001, and subsequently published “EBM in Kampo 2002, Interim Report” [2] and “Evidence Reports of Kampo Treatment 2005” [3]. After repeated revisions and renewals, the JSOM published “Evidence Reports of Kampo Treatment 2009: 320 RCTs (EKAT 2009)” (<https://www.jsom.or.jp/medical/ebm/ere/pdf/EKATE2009.pdf>), a structured abstract (SA) list, and the current version of “EKAT 2016” (<https://www.jsom.or.jp/medical/ebm/er/index.html>), which was published on the web in 2018. It is likely that EKAT could be actively used as a database for disseminating evidence for Japanese Kampo formulations.

Daikenchuto is a formulation that was first introduced in *Jinkuiyaolue* (金匱要略) in China in the third century, then in *Ishimpo* (医心方) in Japan in the tenth century, although the ingredients in these accounts differed. Afterwards, daikenchuto was developed separately in Japan. From the seventeenth century in particular, its use as a prescription for abdominal symptoms spread rapidly [4]. Japanese public health insurance now covers its use for poor circulation, abdominal pain, and a feeling of abdominal distension.

The ingredients of daikenchuto in Japan are explained in the Standards of Reporting Kampo Products (STORK, <https://mpdb.nibiohn.go.jp/stork>) and it should be regarded as a different prescription from that of China. Therefore, we have here focused on articles of the Japanese prescription only.

The efficacy of Kampo formulations as supportive therapy for cancer has recently begun to be evaluated in clinical trials and in meta-analyses [5, 6]. Although the efficacy of daikenchuto for patients with functional bowel disorder after cancer has been evaluated in a systematic review by Ishizuka et al. [7], this study did not comply with the PRISMA statement [8], did not evaluate the bias risk of each article, did not register in advance with PROSPERO (<https://www.crd.york.ac.uk/prospéro/>), etc. Furthermore, a recent Korean study that examined the efficacy of daikenchuto for improving intestinal dysfunction after abdominal surgery [9] did not search Japanese databases. Therefore, in this study, we aimed to improve the systematic review and meta-analysis of the efficacy of daikenchuto for postoperative functional bowel disorder after surgery for gastrointestinal cancer, using the EKAT database.

Materials and methods

Advance registration of protocol

The present study was conducted in accordance with the protocol registered in PROSPERO (Registration no. [International prospective register of systematic reviews] CRD42017068380) and in compliance with the PRISMA-P [10], PRISMA statement [8], Cochrane Handbook [11], and STORK.

Characteristics of databases

The EBM committee of the JSOM has compiled a list of SAs of randomized controlled trials (RCTs) using medical Kampo formulations available in Japan as “Evidence Reports on Kampo Treatment (EKAT)” and published on the web. EKAT includes the Cochrane Central Register of Controlled Trials (CENTRAL), the Japan Medical Abstracts Society (JAMAS)’s Igaku Chuo Zasshi (Ichushi)-web, with additional bibliographic data provided by the Japan Kampo Medicine Manufacturers’ Association. A search of EKAT, and a non-systematic manual-search, was performed on 04/04/2018 by several investigators. MEDLINE was not searched since all RCTs in MEDLINE are included in CENTRAL.

Eligibility criteria

The eligibility criteria were established by adding our own criteria to the EKAT criteria (inclusion criteria 1–3 and exclusion criteria 1–5 below). Studies that satisfied all of the following criteria were included: (1) use of Kampo formulations receiving marketing authorization in Japan; (2) RCT, quasi-RCT, crossover trial, or meta-analysis; (3) publication in 1986 or thereafter; and (4) cancer study by the ICD-10 classification in EKAT, or (5) study of visually identified cancer, including non-cancer studies by ICD-10 classification. Studies with any of the following criteria were excluded: (1) non-RCT or non-meta-analysis clinical study; (2) use of Kampo medicines that have not received marketing authorization in Japan (Kampo decoction, Chinese formulations, etc.); (3) use of Kampo medicines formulated before 1985 (differing from the current formulations in quality); (4) citation of existing articles on RCTs; (5) a description that is insufficiently clear for preparing an SA; (6) non-clinical research; and (7) use of Kampo formulations as combination therapy in any subjects in the control group.

Search strategy

The EKAT 2013, EKAT Appendix 2014, and EKAT Appendix 2015 were searched as follows.

CENTRAL was searched using the search terms shown in Table 1, for the period 1986–2014. For the Ichushi-web, RCTs of Kampo medicines were searched using search terms in Japanese (Table 2; words in square brackets indicate equivalent English words).

Additionally, we searched CENTRAL and the Ichushi-web using the same search strategies as for EKAT, but limited this search to publications from January 2015 to March 2018.

Article selection

Articles were selected using EKAT 2013, EKAT Appendix 2014 (https://www.jsom.or.jp/medical/ebm/pdf/EKATE_Appendix_2014.pdf), EKAT Appendix 2015, and were additionally searched from January 2015 to March 2018. First, 37 articles in EKATs classified according to ICD-10 as a cancer study (postoperative cancer, unidentified adverse drug reactions of anti-cancer drugs) were selected and combined with 11 cancer-related articles visually extracted from other classifications, making a total of 48 + 17 = 65 articles, which were compiled as advanced EKAT SAs. Next, nine

Table 2 Search formulae in Ichushi-web

No.	Search formulae
#1	漢方薬 [Kampo medicine]/TH
#2	漢方 [Kampo]/AL)
#3	(メタアナリシス [meta-analysis]/RD
#4	ランダム化比較研究 [randomized controlled trial]/RD
#5	準ランダム化比較研究 [quasi-randomized controlled trial]/RD
#6	DT= 1986: 2014
#7	(#1 or #2) and (#3 or #4 or #5) and #6

articles on the use of daikenchuto in postoperative functional bowel disorder after surgery for gastrointestinal cancers were extracted from among the 65 identified articles. In cases in which any pertinent data were omitted, we contacted the corresponding author by e-mail to request that the data be provided.

Data extraction and outcomes

First, an author (MH) extracted the following data: author, year, language, study design, cancer types, participants in Kampo group, participants in control group, and outcomes.

Table 1 Search formulae in CENTRAL

No.	Search formulae
#1	MeSH descriptor medicine, East Asian Traditional explode all trees
#2	MeSH descriptor medicine, Kampo explode all trees
#3	MeSH descriptor medicine, Chinese Traditional explode all trees
#4	MeSH descriptor drugs, Chinese Herbal explode all trees
#5	MeSH descriptor herb–drug interactions explode all trees
#6	MeSH descriptor herbal medicine explode all trees
#7	MeSH descriptor plants, medicinal explode all trees
#8	MeSH descriptor plant structures explode all trees
#9	MeSH descriptor plant extracts explode all trees
#10	MeSH descriptor Materia Medica explode all trees
#11	MeSH descriptor phytotherapy explode all trees
#12	(Kampo): ti,ab,kw
#13	(Kanpo): ti,ab,kw
#14	(Japanese): ti,ab,kw
#15	(Oriental): ti,ab,kw
#16	(Traditional): ti,ab,kw
#17	(East Asia): ti,ab,kw
#18	(East-Asia): ti,ab,kw
#19	(Herb*): ti,ab,kw
#20	(Chinese): ti,ab,kw
#21	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20), from 1986 to 2014

Subsequently, two co-authors (TN and YM) checked the process and the extracted results.

The primary outcomes were the time to first postoperative flatus and the time to first postoperative BM, as indices of subjective symptoms, and the planned secondary outcomes were the incidence of intestinal obstruction, length of postoperative hospital stay, survival rate, quality of life (QOL), and adverse events. Continuous outcomes were combined using mean differences (MDs), and dichotomous outcome was risk ratio (RR).

Statistical analysis

The significance level was set at 5%. Publication bias was visually evaluated using funnel plots. Statistical heterogeneity was evaluated based on the P value in the Cochrane Q test and I^2 . A fixed-effects model was used if statistical heterogeneity was low, and a random-effects model was used if statistical heterogeneity was moderate or high. Data were analysed using Review Manager 5.3.5 (Cochrane Collaboration software).

In accordance with the protocol, cancer types were classified into oesophageal cancer, gastric cancer, and colorectal cancer, and previously specified subgroup analysis was performed. We added subgroup analyses according to language, description of COI and blindness. The safety of daikenchuto was evaluated based on descriptions in articles.

Evaluation of article quality

Each article was evaluated for seven items of bias risk according to the Cochrane Handbook [11]. Three of seven authors checked risk of bias of 65 articles independently. Articles with high or unclear risk for at least five of the six items, not including “Other bias,” were judged to be “Unclear” for the risk of “Other bias.” YI, TI, YS, TN, and YM shared this evaluation task, which was followed by independent evaluation of all articles by MH, YMa and TNa. Any conflict of opinions was resolved by discussion to consensus.

Articles were also examined for the presence or absence of a description of safety, funding source, and financial conflict of interest (COI).

Results

Characteristics of studies analysed

After the literature search using EKAT, nine articles extracted from 38,774 articles were subjected to meta-analysis. A flowchart of the article selection is shown in Fig. 1, and characteristics of each RCT are shown in Table 3. One

trial included patients with oesophageal cancer [12], two involved gastric cancer [13, 14] and six involved colorectal cancer [15–20]. Seven trials were RCTs and two were quasi-RCTs. For a breakdown of quasi-RCTs, one trial was an alternate study [17]. For the definition of quasi-RCT is used some quasi-random method of allocation such as alternation. In another one [16], patients were assigned by month randomly. Therefore, we considered “month” as a cluster and modified the result considering design effect of cluster-RCT [11, 21]. Three trials included a placebo arm and six did not include a placebo arm. All trials originated from Japan: seven were written in English and two in Japanese. After e-mail contact with the authors of four studies, all authors responded and provided us the data necessary for meta-analysis. For other five studies, necessary data were mentioned in each article.

Primary outcomes

The time to first postoperative flatus was evaluated based on six articles (oesophageal, one; gastric cancer, one; colorectal cancer, four) (Fig. 2). The MD was -0.43 (95% CI: -0.77 to -0.09) days, showing a significantly shorter time to first postoperative flatus among the daikenchuto group than the control group ($P=0.01$). Since statistical heterogeneity was high, with $P=0.002$ and $I^2=73\%$, the random-effects model was used. In addition, the funnel plots were asymmetric, indicating that the risk of publication bias was not low (Fig. 3).

The time to the first postoperative BM was evaluated based on six articles (oesophageal, one; gastric, two; colorectal, three) (Fig. 4). The MD was -0.29 (95% CI: -0.59 to 0.01) days, showing that differences were not significant. Since statistical heterogeneity was moderate, with $P=0.03$ and $I^2=61\%$, the random-effects model was used. In addition, the funnel plots were asymmetric, indicating that the risk of publication bias was not low.

Secondary outcomes

Although the pre-planned secondary outcomes were the incidence of intestinal obstruction, the length of postoperative hospital stay, survival rate, and QOL, data on survival rate and QOL could not be integrated due to an insufficient number of articles reporting these items. This left the incidence of postoperative intestinal obstruction and the length of postoperative hospital stay as the secondary outcomes.

The incidence of intestinal obstruction was evaluated based on five articles (oesophageal, one; gastric, two; colorectal, two). The forest plots are shown in Fig. 5. The RR was 0.60 (95% CI: 0.35 – 1.03), showing no significant difference. Since statistical heterogeneity was low, with $P=0.56$ and $I^2=0\%$, the fixed-effects model was used. In addition,

Fig. 1 PRISMA flow diagram for study selection using EKAT. (1) 38410 articles searched CENTRAL and Ichushi-web, limited to publications from 1986 to 2014. (2) Include 446 articles in EKAT. (3) In the present review, 48 articles in cancer treatment with daikenchuto were selected from the EKAT. (4) Using search formulae of EKAT, limited to publications from 2015 to March 2018.

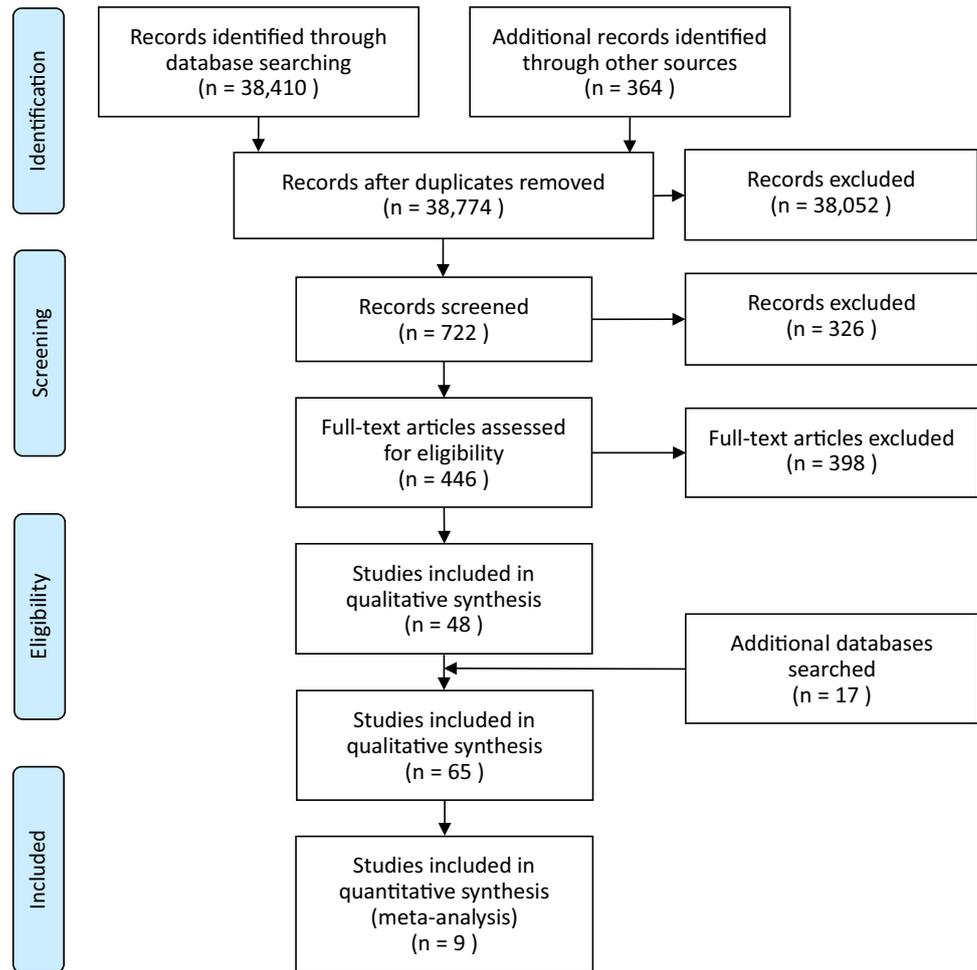


Table 3 Characteristics of included studies (the order of organ)

Author	Year	Language	Design	Cancer	Kampo	Control
Nishino T	2017	English	RCT	Esophageal	19	20
Akamaru Y	2015	English	RCT	Gastric	41	40
Yoshikawa K	2015	English	RCT	Gastric	96	99
Takagi K	2007	Japanese	RCT	Colorectal	86	87
Fujii S	2011	Japanese	Cluster-RCT	Colorectal	57	40
Yoshikawa K	2012	English	Quasi-RCT	Colorectal	15	15
Yaegashi M	2014	English	RCT	Colorectal	26	25
Katsuno H	2015	English	RCT	Colorectal	174	162
Katsuno H	2016	English	RCT	Colorectal	38	33

the funnel plots were symmetric, indicating that the risk for publication bias was low.

The length of postoperative hospital stay was evaluated based on four articles (oesophageal, one; colorectal, three) (Fig. 6). The MD was - 0.95 (95% CI: - 1.70 to - 0.21) days, showing significantly shorter postoperative hospital stay in the daikenchuto group than in the control group ($P=0.01$). Since statistical heterogeneity was moderate, with $P=0.07$ and $I^2=58\%$, the random-effects model was

used. In addition, the funnel plots were asymmetric, indicating that the risk for publication bias was not low.

Subgroup analysis

When colorectal cancer alone was evaluated, the MD in the time to the first postoperative BM was - 0.37 (95% CI: - 0.67 to - 0.07) days, showing a significantly shorter time to first postoperative BM in the daikenchuto group

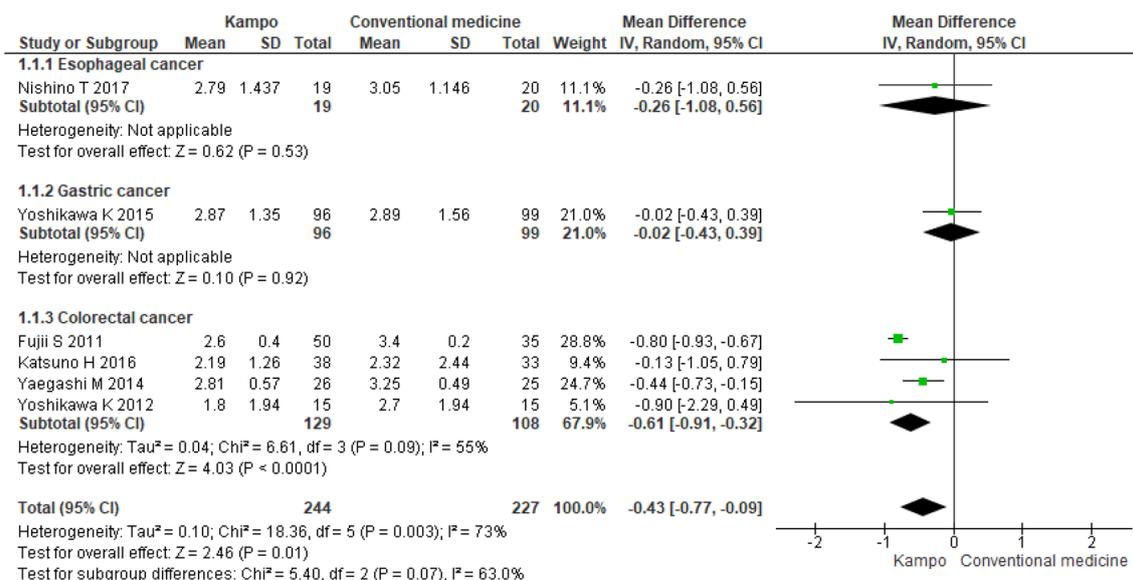


Fig. 2 Forest plot of the first postoperative flatus (days) in patients with gastrointestinal cancers

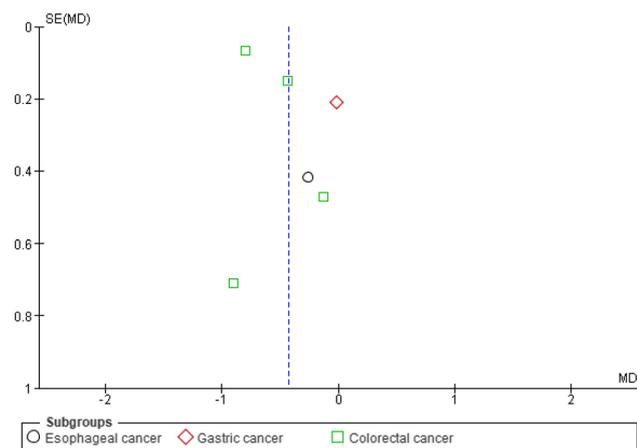


Fig. 3 Funnel plot of the first postoperative flatus (days) in patients with gastrointestinal cancers

than in the control group ($P = 0.01$). Other outcomes were similar to those for the gastrointestinal tract as a whole. Oesophageal cancer and gastric cancer could not be analysed, due to an insufficient number of articles on these topics.

The results were almost the same between each subgroup of language and study design (Figs. 7 and 8). Meanwhile, concerning description of COI, the result combined by studies without description of COI was only significant. The time to first postoperative flatus was evaluated by two articles

without COI description, the MD was -0.64 (95% CI: -0.99 to -0.30) days, and four articles with COI description, the MD was -0.12 (95% CI: -0.45 to 0.21) days (Fig. 9). Concerning description of blindness, the results combined by studies without description were only significant. The time to first postoperative flatus was evaluated by two articles without description of blindness, the MD was -0.80 (95% CI: -0.93 to -0.67) days; two articles by open-labelled studies, the MD was -0.42 (95% CI: -0.69 to -0.15) days; two articles by double-blind studies, the MD was -0.04 (95% CI: -0.41 to 0.34) days (Fig. 10).

Evaluation of the quality of each article

Each article was evaluated for seven bias risk items (Figs. 11 and 12). Particularly high-risk items were performance bias and detection bias. In particular, the risk for detection bias was not low in any of the articles and was unclear or high in all nine articles. Conversely, risk was low for attrition bias and other bias, for which the items' risk was not high in any article.

Of the nine articles, seven (78%), four (44%), and six (67%) described safety, funding source, and COI, respectively.

Evaluation of safety of daikenchuto

Seven articles described that there were no reports of adverse events in patients receiving daikenchuto. The remaining two articles provided no description of adverse events.

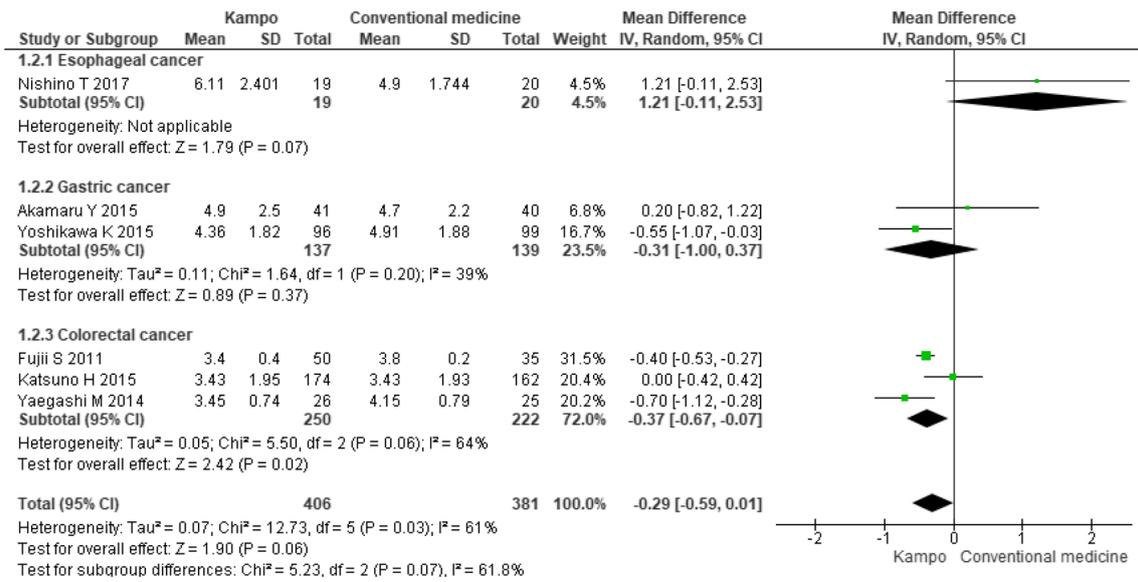


Fig. 4 Forest plot of the first postoperative BM (days) in patients with gastrointestinal cancers

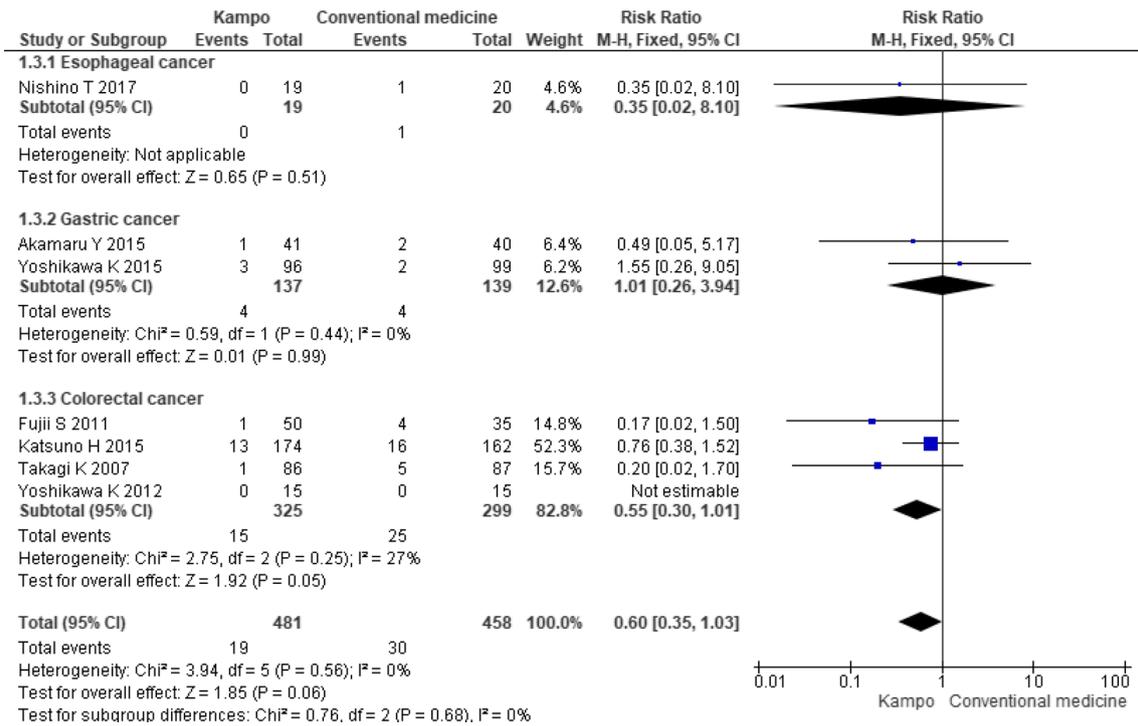


Fig. 5 Forest plot of intestinal obstruction in patients with gastrointestinal cancers

Discussion

The results of RCTs of daikenchuto use for gastrointestinal cancers conducted in Japan demonstrated significantly higher efficacy in terms of the time to first postoperative flatus and the length of postoperative hospital stay, which

were significantly shorter in the daikenchuto group than in the control group ($P=0.01$).

Unlike Western medicine, traditional medicines, such as East Asian medicine, has continued to develop uniquely in each country. Whereas Western drugs are universally evaluated with standardized products, Kampo medicines should

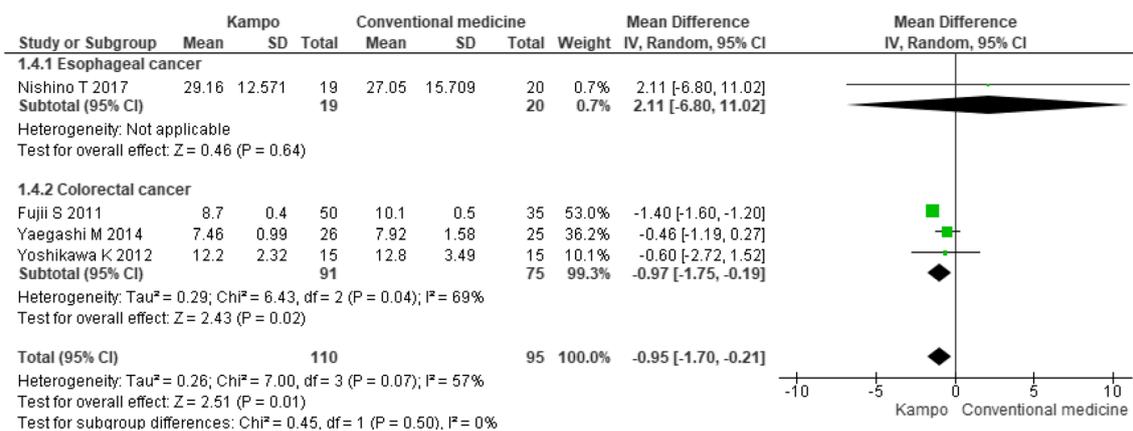


Fig. 6 Forest plot of postoperative hospital stay (days) in patients with gastrointestinal cancers

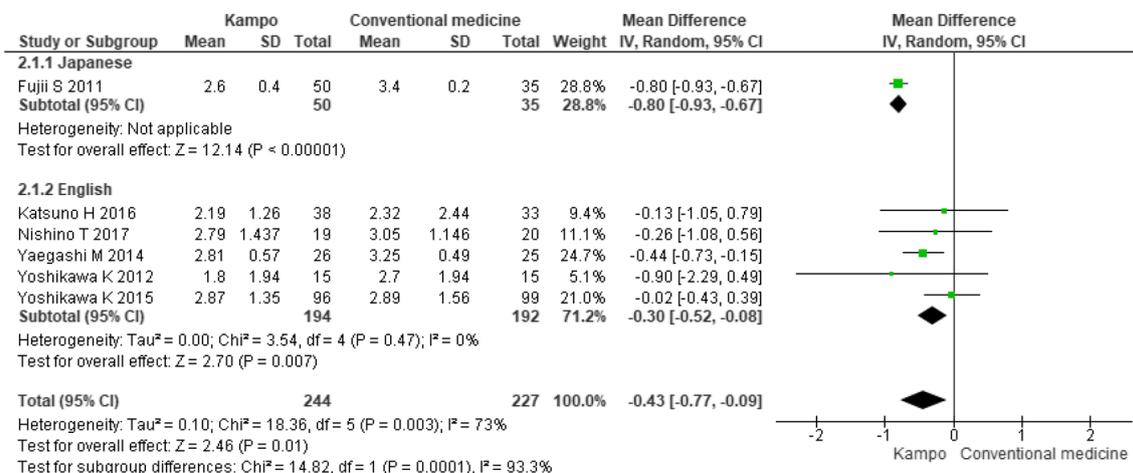


Fig. 7 Forest plot of subgroup analysis of language

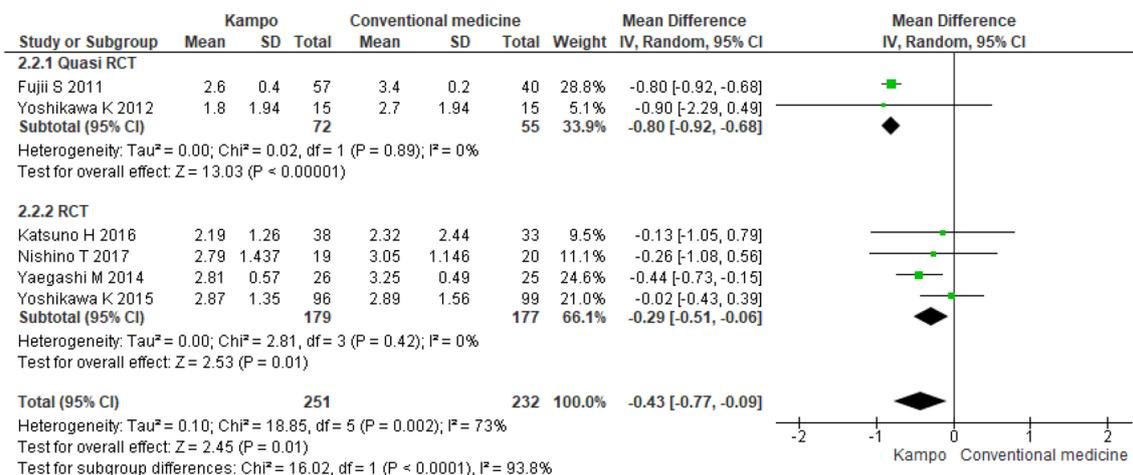


Fig. 8 Forest plot of subgroup analysis of study design

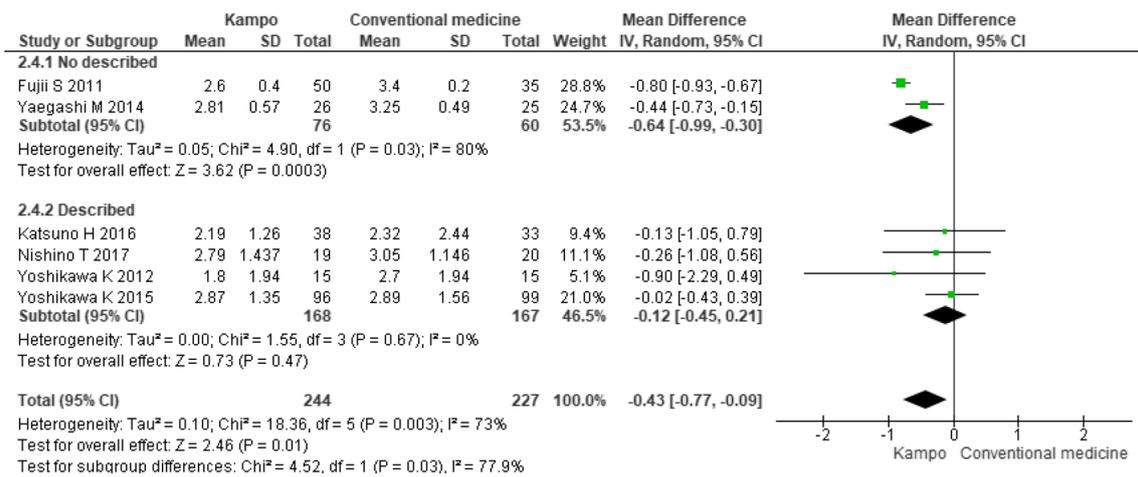


Fig. 9 Forest plot of subgroup analysis of description or not about COI

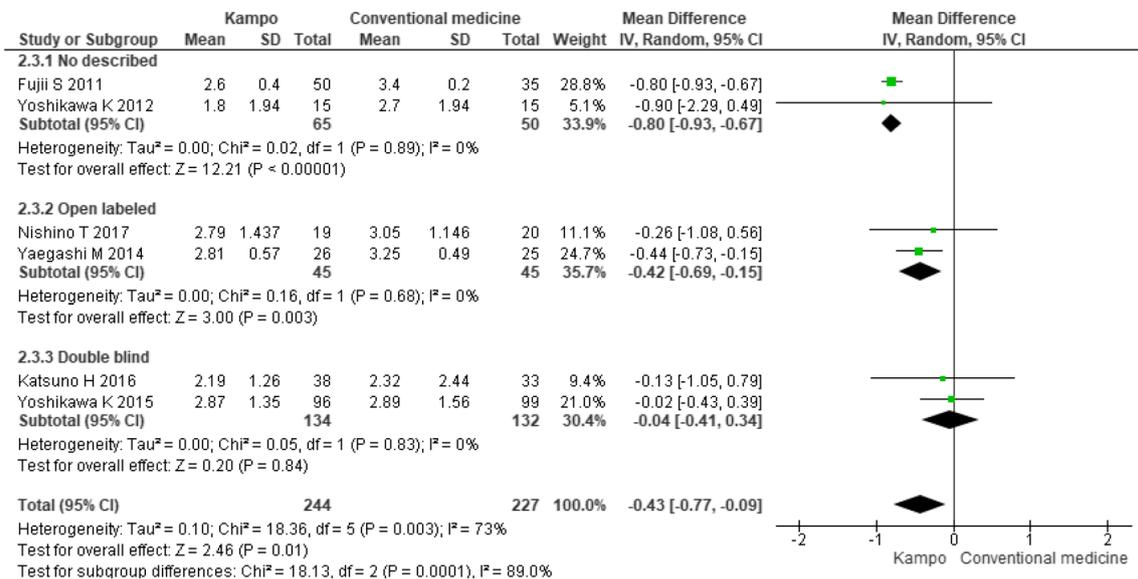
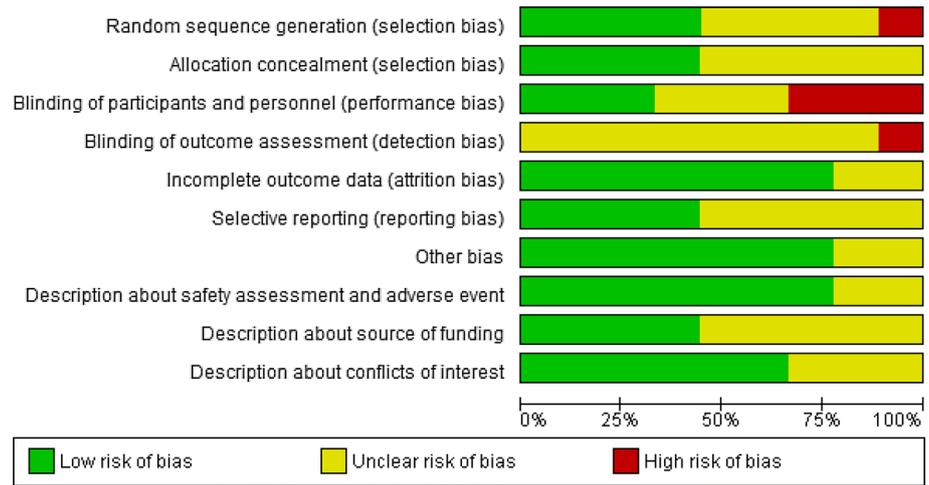


Fig. 10 Forest plot of subgroup analysis of blind or open

be evaluated in consideration of the environment in which they have developed, and, therefore, Kampo medicines used in Japan should be evaluated based on clinical trials conducted in Japan. Although RCTs of Kampo medicines are increasing, searches using a worldwide database, such as MEDLINE or CENTRAL, do not detect sufficient number of articles on Japanese Kampo medicines. EKAT is a list of structured abstracts dedicated to RCTs of Japanese Kampo formulations, developed based on existing databases, as well as unpublished databases of relevant industrial organizations, and by manual searches, and is the only secondary database covering all RCTs of Japanese Kampo formulations published in English and in Japanese.

Next, the efficacy of daikenchuto for functional bowel disorder was described. Bowel dysfunction is an inevitable consequence of abdominal surgery, and is caused by a combination of several factors, such as the use of pharmacological agents (anaesthetics, opioids), neural mechanisms, and intestinal inflammation. The inflammatory response of the intestine after surgical manipulation is the most important pathophysiological mechanism [22]. The mechanism of action by which daikenchuto improves intestinal function reportedly involves motility stimulation, blood flow enhancement, anti-inflammatory action, etc., in the intestine [23]. It is believed that motility stimulation is associated with stimulation of motilin secretion [24] and substance P secretion [25], blood flow enhancement is associated with

Fig. 11 Risk of bias graph in the included studies



calcitonin gene-related peptide (CGRP) secretion [26], and the anti-inflammatory action is associated with inhibition of inflammatory cytokine secretion [27]. Evidence for these premises was provided by basic research using daikenchuto available in Japan.

Yasunaga et al. [28] have reported that the administration of daikenchuto to patients with postoperative intestinal obstruction reduces the period of ileus tube placement and medical expenses, based on the large-scale claim data on insured treatment in Japan, managed by the Ministry of Health, Labour, and Welfare. To have daikenchuto introduced in the clinical practice guidelines for gastrointestinal cancers, the body of evidence should be carefully evaluated. The present systematic review suggests that the certainty of evidence of the efficacy of daikenchuto for improving the subjective symptoms of postoperative cancer patients is moderate or slightly low, given the rate-down factor specified by GRADE/Cochrane. It is caused by the fact that it went down by two phases in total because a bias risk and imprecision have a problem.

The present study had some limitations. First, regardless of the field of disease, RCTs of Kampo medicines tend to involve a high risk for bias and few have been reported, preventing a high certainty of the body of evidence at present. The increased bias risk is attributable to the clinical properties of Kampo medicines. Kampo extract formulations have distinct tastes, odours, and transparency, making it difficult to prepare their placebos, and they have rarely been studied in a double-blind design, as only three such studies were reported from 2016 onward (33%). Furthermore, outcome-raters were not blinded in any of the studies published. When only double-blind studies were evaluated, the results turned to be non-significant. Furthermore, a number of RCTs studied were unbalanced, involving a specialized field; for example, all were concerned with being gastrointestinal surgeons. Therefore, potential COI risk is possible. Additionally, although the forest plots suggested no obvious risk of publication bias, the possibility still remains. We should address these issues by preparing placebos indistinguishable from Kampo extract formulations and using them to conduct double-blind studies actively, and by ensuring

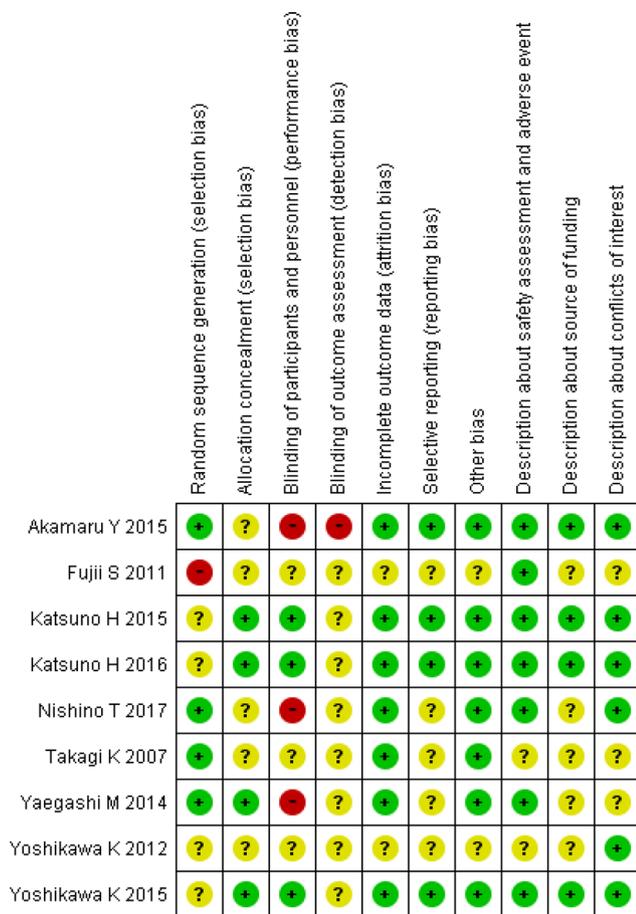


Fig. 12 Risk of bias summary in the included studies

that the number of study collaborators is sufficient, and by attempting blinding of outcome raters, to reduce bias risk. Heterogeneity posed a problem in the present meta-analysis. Each of two primary outcomes (first postoperative flatus and first postoperative BM) had moderate statistical heterogeneity. Methodological heterogeneity was also highly possible because operative methods varied, even for the same cancer. However, no article had described the details of the operation. Therefore, careful considerations are necessary when applying the present results in practice. Furthermore, it is necessary to enhance the quality of clinical studies by adding non-interested statisticians and experts in Kampo medicine as study collaborators to formulate study designs from a broader viewpoint, in consideration of increasing interest in the quality of evidence and bias risk in other fields.

Conclusion

As a result of meta-analysis by all retrieved according to the registered protocol, daikenchuto was efficacious in improving postoperative bowel dysfunction in patients with gastrointestinal cancers. However, limiting to articles with description of COI and blindness, significance disappeared.

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Author contributions All the authors have contributed to this article. MH, IA, TN and YM contributed to the conception and design of this research; MH, YI, TI, YS, TN, YM, TN and YM evaluated articles; MH and TN contributed to statistical analysis and interpretation of data.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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