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Meta-analysis of randomized controlled trials on the efficacy of daikenchuto on improving intestinal dysfunction after abdominal surgery

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Purpose: Intestinal dysfunction is one of the most common complications in patients after abdominal surgery. Daikenchuto (DKT), a traditional herbal medicine, is recently employed to improve postoperative intestinal dysfunction. The aim of this meta-analysis was to assess the efficacy of DKT in improving intestinal dysfunction after abdominal surgery.
Methods: PubMed, Embase, and the Cochrane library were systematically searched to identify randomized controlled trails (RCTs) in adult patients undergoing abdominal surgery, who were randomly distributed to administrate DKT and placebo. The primary outcomes included the time to first postoperative flatus or bowel movement. We used random-effects models to calculate summary mean differences (MDs) with 95% confidence intervals (CIs).
Results: Nine RCTs totaling 1,212 patients (618 in DKT, 594 in control group) were included in our study. Compared with control group, DKT can effectively improve postoperative intestinal dysfunction by shortening the time to first postoperative flatus (MD, -0.41; 95% confidence interval [CI], -0.66 to -0.16; P = 0.001) with significant heterogeneity (I^2 = 71%, P = 0.004), and bowel movement (MD, -0.65; 95% CI, -0.97 to -0.32; P < 0.001) without significant heterogeneity (I^2 = 40%, P = 0.14). Sensitivity analyses by indication of surgery and type of surgery yielded similar results.
Conclusion: These data provide limited evidence that DKT shows efficacy on improving intestinal dysfunction after abdominal surgery. However, the results should be interpreted cautiously, due to the heterogeneity of the studies included. Thus, the efficacy of DKT on improving postoperative intestinal dysfunction warrants further investigation.
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Key Words: Dai-kenchu-to, Abdominal surgery, Intestinal dysfunction, Meta-analysis, Randomized controlled trials

INTRODUCTION

Intestinal dysfunction after abdominal surgery is the leading cause of prolonged hospital stays and additional health-care costs, which has been considered a common and inevitable outcome to some extent [1]. Thus, improving postoperative intestinal dysfunction is of great importance. It is characterized by abdominal distention, nausea, vomiting, delayed passage of

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flatus or bowel movement. In recent decades, many therapeutic strategies have been used to improve postoperative intestinal dysfunction, such as fast track surgery [2]. However, all have limited efficacy and are not free of side effects.

Daikenchuto (DKT) is one of the most widely administered traditional herbal medicines in the Asia-Pacific area with active components containing Japanese pepper, processed ginger, and ginseng [3]. It has been recently employed to improve intestinal dysfunction [4] and very few side effects have been reported. In intestinal ischemia-related diseases, DKT was associated with ameliorating microvascular dysfunction [5]. Several studies demonstrate that DKT significantly increases superior mesenteric artery blood flow resulting in improvement of intestinal dysfunction [6]. However, the studies regarding DKT in improving postoperative intestinal dysfunction have conveyed inconclusive results [7-15]. We therefore conducted a meta-analysis of relevant randomized controlled trials to assess the efficacy of DKT in improving intestinal dysfunction after abdominal surgery.

METHODS

This meta-analysis followed the Cochrane Handbook for Systematic Reviews of Interventions [16] and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary material 1) [17]. Two reviewers separately conducted literature retrieval, data extraction, quality assessment, and statistical analysis, with inconsistency solved by discussion and by the chief reviewer. Specially, a statistician in our group performed and reviewed the statistical section.

Literature search and inclusion criteria

Databases (PubMed, the Cochrane Library, and Embase) were comprehensively searched to identify relevant trials (up to February 10, 2017). The search strategy used the following format terms: "Daikenchuto" or "Dai-kenchu-to" or "Dai-ken-chu-to" or "DKT" or "TJ-100" or "N100" or "TU-100". DKT, TJ-100, N100, and TU-100 are the trade names of Daikenchuto. No language restriction was imposed. Moreover, reference to relevant articles was examined manually for potentially eligible trials. The whole search process was carried out iteratively until no new publications could be found. Detailed search strategies were attached to Supplementary material 2. We present an adapted PRISMA flowchart showing the process of study selection. We only included randomized controlled trails (RCTs) focused on DKT for intestinal dysfunction in patients after abdominal surgery. Detailed inclusion and exclusion criteria are presented in Table 1.

Table 1. Detailed inclusion and exclusion criteria

Criteria	Patients	Intervention	Control	Outcomes	Study design
Inclusion criteria	(1) Patients (≥18 years) undergoing abdominal open or laparoscopic surgery; (2) Patient performance status of 0–2 as determined by the Eastern Cooperative Oncology Group Performances Status Scale, able to tolerate oral administration of DKT; (3) No prior abdominal surgery, chemotherapy or radiotherapy within 4 weeks.	(1) Any administered doses of DKT (2) Whether preparation or postoperation	Placebo or no treatment	(1) Time to first postoperative flatus (2) Time to first postoperative bowel movement;	Randomized controlled trials
Exclusion criteria	(1) Pediatric patients (<18 years); (2) Severe cardiopulmonary disease, liver or kidney disorder and intestinal obstruction; (3) Pregnant, possibly pregnant and lactating; (4) Taking herbal medicine, prokinetic medication or antipsychotic medication within 4 weeks.	Administered other herbal medicine or prokinetic medication	DKT products or other DKT-containing products	Studies which did not report primary outcome	(1) Study protocols; (2) Reviews articles; (3) Cross-over and quasi randomized trials; (4) Conference, abstracts, and letters

Data extraction and risk of bias assessment

The following data would be extracted: first author, year of publication, clinical setting, demographic feature (number of patients, age, and sex), type of interventions for DKT, indication of surgery, type of surgery and outcomes, which would be entered into a normalized data collection Excel form (Microsoft Corp., Redmond, WA, USA). Quality assessment was performed by using the guidelines from the Cochrane tool [18]. All included studies were assigned as 'low,' 'unclear' or 'high' risk, using the following criteria: (1) random, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective reporting, and (6) other bias by 2 independent investigators.

Statistical analysis

We evaluated the efficacy of DKT on improving postoperative intestinal dysfunction based on the data from included RCTs. The time to first postoperative flatus and the time to first postoperative bowel movement were treated as continuous variables and presented as mean difference (MD) with 95% confidence interval (CI). We calculated standard deviations with standard formulae if only medians and ranges were provided. For studies that had not shown the corresponding results, we extracted data from the Kaplan-Meier curves with the Engauge Digitizer version 4.1 (M Mitchell, Engauge Digitizer; http://markummitchell.github.io/engauge-digitizer) [19,20]. Heterogeneity was estimated by using the I^2 statistic, a quantitative measure of inconsistency [21]. I^2 of less than 50% was regarded as accepted heterogeneity. In cases of significant heterogeneity, a random-effects model was used. Whether heterogeneity was present, sensitivity analyses were conducted to evaluate the robustness of our results. Sensitivity analyses were done according to indication of surgery and type of surgery. In addition, the 'leave-one-out' influence analyses were performed to explore the influence of a single study on overall pooled effect estimate by omitting a study each time.

Publication bias was identified through funnel plots and performing Begg and Egger tests [22,23]. Data analyses were conducted using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Trial selection

The initial search identified 435 relevant publications. After excluding duplicate studies (n = 214) and publications not relevant to DKT (n = 133), not RCT (n = 61), only title available (n = 2), only conference abstract available (n = 1), 23 studies were reviewed for full text. Apart from protocols (n = 1), wrong population and/or wrong intervention (n = 11), we also eliminated a quasi-randomized trial and a crossover study. For a detailed description, see Supplementary material 3. Finally, 9 RCTs [7-15] met inclusion criteria and were included in the final analysis. The selection process is shown in Fig. 1.

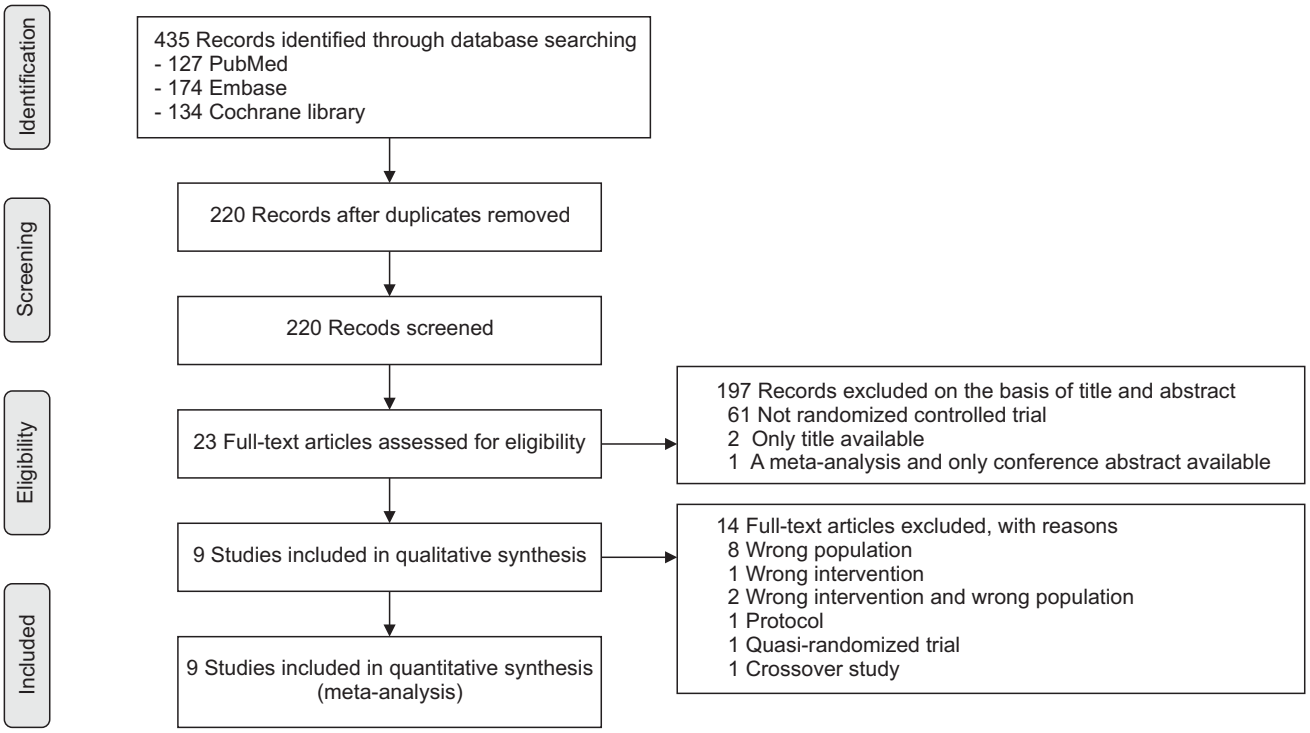

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of literature selection.

Table 2. Baseline characteristics

Reference	Clinical setting	Study period	No. of patients (DKT/control)	Age (yr), mean ± SD/male%		Type of interventions for DKT	Indication of surgery	Type of surgery
				DKT	Control			
Nishi, 2012 [7]	Single center	2007.7–2008.8	32 (16/16)	68.8 ± 8.7/25.0%	64.3 ± 7.3/43.8%	2.5 g, from the morning at POD 1 via nasogastric tube and thereafter orally tid	Hepatectomy	Open
Yoshikawa, 2012 [8]	Single center	2007.7–2008.6	30 (15/15)	62 ± 12/46.7%	70 ± 5/46.7%	2.5 g, tid, from POD 1 to the POD 7	Colectomy	Lapar
Yaegashi, 2014 [9]	Single center	2010.10–2012.3	51 (26/25)	69 ± 8/42.3%	68 ± 11.5/60.0%	2.5 g, tid, orally from PROD 2 until the morning of surgery, and from the morning at POD 1 until discharge	Colectomy	Lapar
Akamaru, 2015 [10]	Multicenter	2007.9–2009.12	81 (41/40)	63.4 ± 8.9/24.4%	63.7 ± 9.2/32.5%	2.5 g, tid, orally from POD 1, when oral intake was allowed. They continued treatment through the third month after surgery	Gastrectomy	Open & Lapar
Katsuno, 2015 [11]	Multicenter	2009.1–2011.6	336 (174/162)	68 ± 10/43.7%	69 ± 9.3/38.9%	15 g/day (5 g, tid) of DKT from POD 2 to POD 8.	Colectomy	Open
Shimada, 2015 [12]	Multicenter	2010.2–2011.5	209 (108/101)	68 ± 8.5/25.9%	69 ± 8.8/26.7%	15 g/day (5 g, tid) of TU-100 from PROD 3 to POD 10, expect on the day of surgery.	Hepatectomy	Open
Yoshikawa, 2015 [13]	Multicenter	2011.1–2012.12	195 (96/99)	68 ± 8.3/24.0%	67 ± 9.3/23.2%	5.0 g, tid, orally or nasogastric tube from POD 1 or 2 to 12	Gastrectomy	Open
Katsuno, 2016 [14]	Multicenter	2009.1–2011.6	71 (38/33)	67.7 ± 8.2/55.3%	68.2 ± 5.7/39.4%	5.0 g, tid, orally from POD 2 to POD 8	Colectomy	Open
Okada, 2016 [15]	Multicenter	2012.8–2013.7	207 (104/103)	68.9 ± 8.4/52.9%	64.9 ± 11.3/63.1%	5.0 g, tid, orally befroe meals from PROD 3 to POD 8, on the operative day, DKT was administered immediately after the operation in 5 g dose via a delivering tube inserted into jejunum; and on POD 1, 15 g were delivered via a delivering tube	Pancreaticoduodenectomy	Open

SD, standard deviation; DKT, Daikenchuto; Lapar, laparoscopic; tid, three times a day; POD, postoperative day; PROD, preoperative day.

Description of eligible studies

Table 2 summarizes the main feature of the nine RCTs, which were published from 2012 to 2016. The individual total sample sizes ranged from 30 to 336 (total of 1,212 participants). Six hundred eighteen participants were randomized to DKT and 594 to control group. Among these nine RCTs, 6 reported the time to first postoperative flatus [7-9,13-15]; 6 reported the time to first postoperative bowel movement [7,9-13]. Two studies [8,9] were about laparoscopic surgery and the others [7,11-15] on open procedures. Akamaru et al. [10] reported on laparoscopic and open surgery. Four trials [8,9,11,14] reported colectomy.

Risk of bias

Risk-of-bias details for individual trials were exhibited in Fig. 2A, and the summary of risk of bias in Fig. 2B. Appropriate randomization was produced to avoid possible selection bias in 2 studies [9,15], which also concealed the allocation sequence using reasonable methods. Two studies [10,12] reported their source of funding. As a whole, 2 studies were low risk of bias [9,15] and others unclear [7,8 ,10-14].

Quantitative synthesis of data

As shown in Figs. 3 and 4, DKT was associated with significantly improving postoperative intestinal dysfunction compared to control group ($P < 0.05$). Six included studies [7-

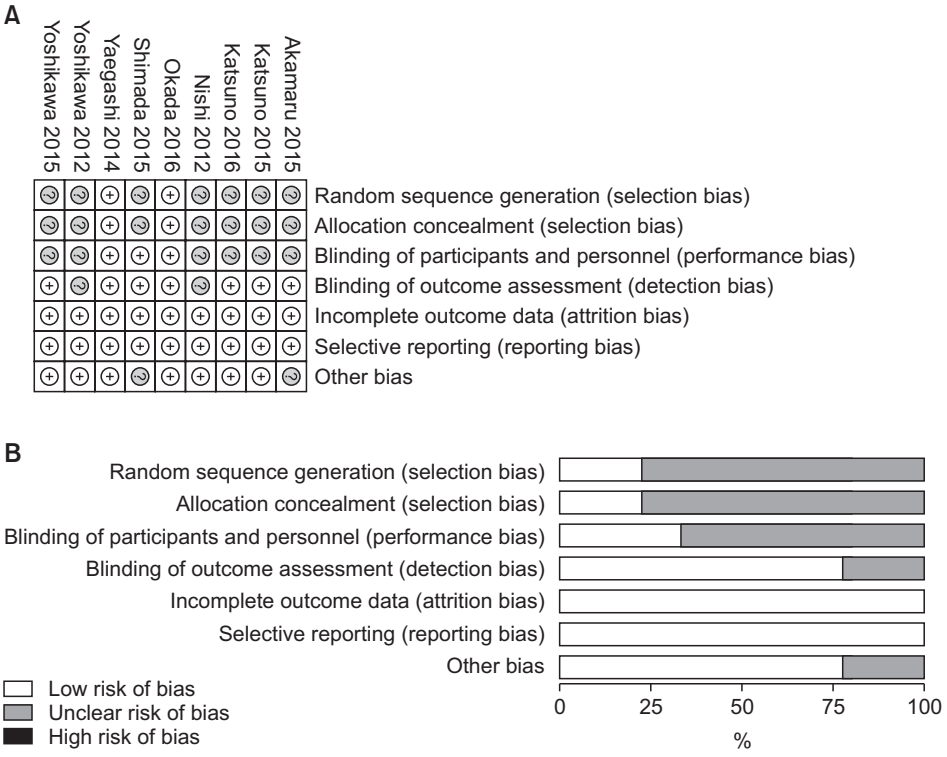

Fig. 2. Risk of bias: risk of bias in individual trials (A) and summary of brisk of bias of included studies (B). The grey and white represent "unclear risk of bias" and "low risk of bias" respectively.

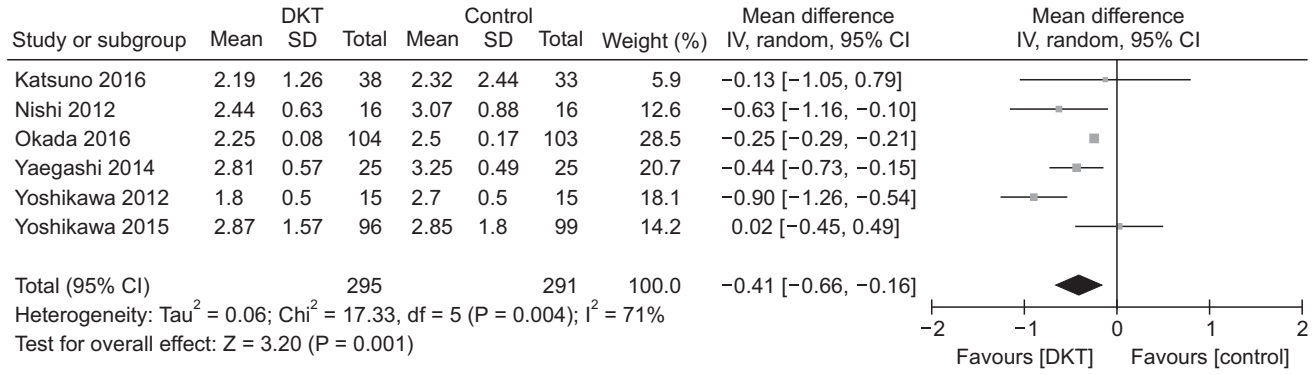

Fig. 3. Meta-analysis comparing Daikenchuto (DKT) versus control group for the time to first postoperative flatus. SD, standard deviation; M-H, Mantel-Haenszel; CI, confidence interval; IV, inverse variance.

9,13-15] totaling 586 patients (295 in DKT group, 291 in control group) reporting the time to first postoperative flatus. The overall effect favored DKT group (MD, -0.41; 95% CI, -0.66 to -0.16; P = 0.001) (Fig. 3), with significant heterogeneity (I^2 = 71%; P = 0.004) (Fig. 3). Moreover, compared with control group, DKT was associated with shortening the time to first postoperative bowel movement (MD, -0.65; 95% CI, -0.97 to -0.32; P < 0.0001) (Fig. 4), without significant heterogeneity (I^2 = 40%, P = 0.14) (Fig. 4).

Sensitivity analyses

Subsequently, sensitivity analyses were performed to explore the underlying source of heterogeneity and examine the influence of various inclusion criteria on the pooled estimates. The sensitivity analysis in Table 3 based on different inclusion criteria also indicated that DKT was associated with significantly improving postoperative intestinal dysfunction. Inclusion studies of open surgery yielded similar results in the time to first postoperative flatus (4 RCTs; MD, -0.25; 95% CI, -0.37 to -0.13; P < 0.001) (Table 3), with no evidence of heterogeneity (I^2 = 9%, P = 0.35), and the time to first postoperative bowel movement (3 RCTs; MD, -0.74; 95% CI, -1.16 to -0.31; P < 0.001) (Table 3), without significant heterogeneity (I^2 = 46%, P = 0.14) (Table 3). After inclusion studies of colectomy, the results were still maintained in the time to first postoperative flatus (4 RCTs; MD, -0.58; 95% CI, -0.98 to -0.19; P < 0.004) (Table 3), yet heterogeneity was still present (I^2 = 59%, P = 0.09) (Table 3). The studies undergoing colectomy were associated with a slightly decreasing trend in the time to first postoperative bowel movement (2 RCTs; MD, -0.48; 95% CI, -0.96 to -0.00; P = 0.05) (Table 3) with heterogeneity (I^2 = 51%; P = 0.15) (Table 3). Furthermore, we performed influence analyses. MD for the time to first postoperative flatus maintained a slight fluctuation from -0.48 (95% CI, -0.77 to -0.20] to -0.28 (95% CI, -0.41 to -0.15), and bowel movement -0.76 (95% CI, -1.07 to -0.45) to -0.57 (95% CI, -0.91 to -0.22) after exclusion of any single trial.

Publication bias

Publication bias was not assessed due to the small number (less than 10) of studies included.

DISCUSSION

To our knowledge, this is the first investigation on the efficacy of DKT on intestinal dysfunction after abdominal surgery using meta-analysis of RCTs methodology. In our meta-analysis, DKT was associated with improving postoperative

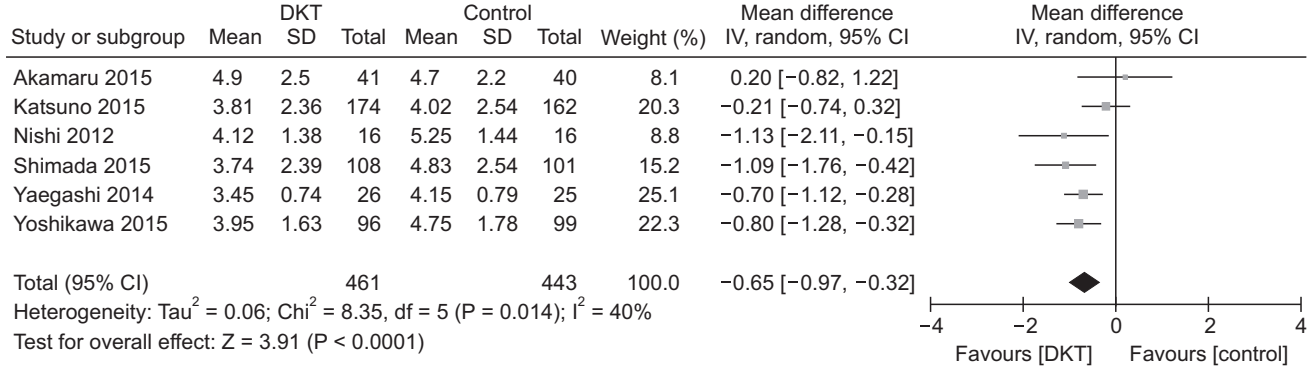

Fig. 4. Meta-analysis comparing Daikenchuto (DKT) versus control group for the time to first postoperative bowel movement. SD, standard deviation; M-H, Mantel-Haenszel; CI, confidence interval; IV, inverse variance.

Table 3. Sensitivity analyses comparing DKT with control group for time to first postoperative flatus and bowel movement

Outcome	No. of patients (DKT/control)	No. of studies	MD (95% CI)	P-value	Heterogeneity	
					I^2 (%)	P-value
Time to first postoperative flatus	295/291	6	-0.41 (-0.66 to -0.16)	0.001	71	0.004
Open	254/251	4	-0.25 (-0.37 to -0.13)	<0.001	9	0.350
Colectomy	79/73	3	-0.58 (-0.98 to -0.19)	0.004	59	0.090
Time to first postoperative bowel movement	461/443	6	-0.65 (-0.97 to -0.32)	<0.001	40	0.140
Open	394/378	4	-0.74 (-1.16 to -0.31)	<0.001	46	0.140
Colectomy	200/187	2	-0.48 (-0.96 to -0.00)	0.05	51	0.150

DKT, Daikenchuto; MD, mean difference; CI, confidence interval.

intestinal dysfunction by shortening the time to first postoperative flatus and bowel movement. This indicates that DKT has benefits and should be available as an approach for patients with postoperative intestinal dysfunction.

The principal finding of our meta-analysis is of clinical value, to some extent. Previous clinical control studies have reported conflicting results, with some showing a decrease in the time to postoperative first flatus and bowel movement [9] and some others demonstrating no effect [14]. What is of note is that the number of participants included in these studies was small, for instance, only 15 per group in Yoshikawa 2012 [8], which makes it difficult to come to a solid conclusion. Obviously, the pooled analysis of RCTs was closer to the true intervention effect, which further reveals the advantage of meta-analysis methodology. Therefore, we used extensive inclusion criteria and included various operations with different characteristics to make the results more clinically useful and generalisable.

The current available evidence of our meta-analysis suggested that DKT can be effectively and safely used to improve intestinal dysfunction in patients after abdominal surgery. Moreover, regardless of difference, sensitivity analyses further confirmed the creditability of the pooled intervention effect in outcome of the time to first postoperative flatus. Laparoscopy surgery has many potential advantages in earlier gastrointestinal recovery and shorter hospital stays over conventional open surgery [24,25]. However, the results of sensitivity analysis for type of surgery showed that studies of open surgery showed significant decreases in the time to first postoperative flatus and the time to first postoperative bowel movement. Inclusion studies of colectomy showed a significant decrease in the time to first postoperative flatus and a decreasing trend in the time to postoperative bowel movement. After carefully checking, we found that the number of studies enrolled was very small (2 RCTs), and the results may have been influenced by potential biases. Therefore, further studies should focus on large, well-designed RCTs that focus on this issue.

There is accumulating evidence of DKT providing an important contribution in improving intestinal dysfunction [7-9,12,15]. Mechanisms underlying this beneficial effect are not fully understood and are most likely multifactorial. The effects of DKT on intestinal transit or motility might be mediated by cholinergic and 5-hydroxytryptamine mechanisms, as demonstrated by experiments finding that DKT was effective against morphine/chlorpromazine-induced intestinal disorders in rodents [26]. It has been demonstrated that DKT has the ability to reduce inflammatory reaction mediated by alpha7 nicotinic acetylcholine receptors activation [27], inhibit cyclooxygenase-2 activity [28], increase the intestinal blood flow through calcitonin gene-related peptide levels [6,29], and reverse bacterial translocation [30]. The current understanding of DKT in patients with intestinal dysfunction remains incomplete and well-designed studies are required further.

DKT is one of the most widely administered herbal medicines in Japan, and is mainly used for patients with postoperative ileus. Apparently, this compound is often used in Asia-Pacific countries but not in the West. However, it has been approved by the U.S. Food and Drug Administration as an investigational drug in the United States [12]. Moreover, several clinical trials have been launched to investigate its efficacy for Crohn disease, irritable bowel syndrome, and constipation [15]. DKT is a pharmaceutical-grade extract, which is under strict quality-control criteria, comparable with western pharmaceutical drugs in terms of therapeutic strength. It is expected that DKT will be more acceptable to patients and doctors in future clinical practice.

Several limitations should be taken into account. First, we confirmed the efficacy of DKT, but we included a variety of surgeries and different surgical approaches with inherent clinical and methodological heterogeneity, which may be restricted in some specific types of surgeries and thereby have an impact on our results. For example, pancreaticoduodenectomy is a multi-organ operative procedure with a high incidence of morbidity. Thus, further individual participant data meta-analysis focusing on more homogeneous clinical situations should be conducted. In our present meta-analysis, we made a pragmatic decision that to combine all kinds of surgeries reporting DKT use would be more generalisable to clinical practice than to group specific types. In addition, to mitigate heterogeneity, we used the random-effects model. Second, the current meta-analysis confirmed the effectiveness of DKT on improvement of postoperative intestinal dysfunction, but the dosage, the method, and the duration of administration varied in the included studies. Actually, the optimum DKT dosage, the method of administration, and the duration associated with DKT products are unclear. Accordingly, further studies are warranted to explore this optimization. Finally, the present meta-analysis is based on limited studies.

In summary, our meta-analysis is of clinical significance. The current available results show that DKT can significantly shorten the time to first postoperative flatus and time to first postoperative bowel movement, and improve intestinal dysfunction after abdominal surgery. However, it should be interpreted with caution, because of the significant heterogeneity of the studies. Thus, the efficacy of DKT on improving postoperative intestinal dysfunction warrants further investigation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

Supplementary materials can be found via https://www.astr.or.kr/src/sm/astr-95-7-001.pdf.

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28. Hayakawa T, Kase Y, Saito K, Hashimoto K, Ishige A, Komatsu Y, et al. Effects of Dai-kenchu-to on intestinal obstruction following laparotomy. J Smooth Muscle Res 1999;35:47-54.
29. Takayama S, Seki T, Watanabe M, Monma Y, Sugita N, Konno S, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. Tohoku J Exp Med 2009;219:319-30.
30. Takasu C, Yismaw WG, Kurita N, Yoshikawa K, Kashihara H, Kono T, et al. TU-100 exerts a protective effect against bacterial translocation by maintaining the tight junction. Surg Today 2017;47:1287-94.

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SUPPLEMENTARY MATERIALS

Supplementary material 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5

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Supplementary material 1

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org.

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Supplementary material 2. Search strategies

Search strategy for Pubmed (from the inception to February 10, 2017)
Search Query

#1. daikenchuto [Title/Abstract]
#2. dai-kenchu-to [Title/Abstract]
#3. dai-ken-chu-to [Title/Abstract]
#4. DKT [Title/Abstract]
#5. TJ-100 [Title/Abstract]
#6. N100 [Title/Abstract]
#7. TU-100 [Title/Abstract]
#8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9. dai-kenchu-to [Supplementary Concept]
#10. #8 OR #9
#11. random*[Title/Abstract]
#12. "Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh]
#13. #11 OR #12
#14. #10 AND #13

Search strategy for CENTRAL, The Cochrane Library (from the inception to February 10, 2017)
ID Search

#1. "daikenchuto":ti,ab,kw
#2. "dai-kenchu-to":ti,ab,kw
#3. "dai-ken-chu-to":ti,ab,kw
#4. "DKT":ti,ab,kw
#5. "TJ-100":ti,ab,kw
#6. "N100":ti,ab,kw
#7. "TU-100":ti,ab,kw
#8. #1 or #2 or #3 or #4 or #5 or #6 or #7

Search strategy for Embase (from the inception to February 10, 2017)

#1. 'daikenchuto':ti,ab
#2. 'dai kenchu to':ti,ab
#3. 'dai ken chu to':ti,ab
#4. dkt:ti,ab
#5. 'tj 100':ti,ab
#6. 'n100':ti,ab
#7. 'tu 100':ti,ab
#8. #1 or #2 or #3 or #4 or #5 or #6 or #7
#9. random*
#10. 'randomized controlled trial'/exp
#11. 'randomized controlled trial (topic)'/exp
#12. #9 or #10 or #11
#13. #8 and #12

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Supplementary material 3

Excluded studies

Forteen studies were excluded after careful evaluation of the full-text article (Itoh 2002; Saida 2005; Endo 2006; Takayama 2009; Manabe 2010; Takayama 2010; Sunagawa 2011; Akiho 2013; Hanazaki 2013; Iturrino 2013; Numata 2014; Kaido 2015; Yuki 2015; Acosta 2016) - **see Figure 1. The reasons for exclusion were: Wrong population** (Itoh 2002; Manabe 2010; Takayama 2010; Akiho 2013; Iturrino 2013; Numata 2014; Yuki 2015; Acosta 2016), **Wrong intervention** (Hanazaki 2013), **Wrong intervention and wrong population** (Saida 2005; Takayama 2009), **Protocol** (Kaido 2015), **Quasi-randomised trials** (Sunagawa 2011), **Crossover study** (Endo 2006). **For further details, see 'Characteristics of excluded studies'.**

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Itoh 2002	Wrong population
Saida 2005	Wrong intervention and wrong population
Endo 2006	Crossover study
Takayama 2009	Wrong intervention and wrong population
Manabe 2010	Wrong population
Takayama 2010	Wrong population
Sunagawa 2011	Quasi-randomised trials
Akiho 2013	Wrong population
Hanazaki 2013	Wrong intervention
Iturrino 2013	Wrong population
Numata 2014	Wrong population
Kaido 2015	Protocol
Yuki 2015	Wrong population
Acosta 2016	Wrong population

References to studies excluded from this review

Itoh 2002
Itoh T, Yamakawa J, Mai M, et al. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. J Int Med Res 2002;30(4):428-32.

Saida 2005
Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, a herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: Results of a prospective ramdomized controlled trial. In: Digestive endoscopy; 2005. p. 50-3.

Endo 2006
Endo S, Nishida T, Nishikawa K, et al. Dai-kenchu-to, a Chinese herbal medicine, improves stasis of patients with total gastrectomy and jejunal pouch interposition. Am J Surg 2006;192(1):9-13.

Takayama 2009
Takayama S, Seki T, Watanabe M, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. Tohoku J Exp Med 2009;219(4):319-30.

Manabe 2010
Manabe N, Camilleri M, Rao A, et al. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol 2010;298(6):G970-5.

Takayama 2010
Takayama S, Seki T, Watanabe M, et al. The effect of warming of the abdomen and of herbal medicine on superior mesenteric artery blood flow - a pilot study. Forsch Komplementmed 2010;17(4):195-201.

Sunagawa 2011
Sunagawa H, Oshiro N. Influence of daikenchuto on patient's portal blood flow after pancreatoduodenectomy. HPB 2011;13:209.

Akiho 2013
Akiho H. Effects of herbal medicines in patients with irritable bowel syndrome. Journal of Gastroenterology and Hepatology Research 2013;2(2):387-390.

Hanazaki 2013
Hanazaki K, Ichikawa K, Munekage M, et al. Effect of Daikenchuto (TJ-100) on abdominal bloating in hepatectomized patients. World J Gastrointest Surg 2013;5(4):115-22.

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Iturrino 2013
Iturrino J, Camilleri M, Wong BS, et al. Randomised clinical trial: the effects of daikenchuto, TU-100, on gastrointestinal and colonic transit, anorectal and bowel function in female patients with functional constipation. Aliment Pharmacol Ther 2013;37(8):776-85.
Numata 2014
Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. Evid Based Complement Alternat Med 2014;2014:231258.
Kaido 2015
Kaido T, Shimamura T, Sugawara Y, et al. Multicentre, randomised, placebo-controlled trial of extract of Japanese herbal medicine Daikenchuto to prevent bowel dysfunction after adult liver transplantation (DKB 14 Study). BMJ Open 2015;5(9):e008356.
Yuki 2015
Yuki M, Komazawa Y, Kobayashi Y, et al. Effects of Daikenchuto on Abdominal Bloating Accompanied by Chronic Constipation: A Prospective, Single-Center Randomized Open Trial. Curr Ther Res Clin Exp 2015;77:58-62.
Acosta 2016
Acosta A, Camilleri M, Linker-Nord S, et al. A Pilot Study of the Effect of Daikenchuto on Rectal Sensation in Patients with Irritable Bowel Syndrome. J Neurogastroenterol Motil 2016;22(1):69-77.