

## Daikenchuto for postoperative adhesive small bowel obstruction: A systematic review and meta-analysis

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### Abstract

#### AIM

To assess the effectiveness of Daikenchuto for patients with postoperative adhesive small bowel obstruction (ASBO).

#### METHODS

A systematic search of PubMed (MEDLINE), CINAHL, the Cochrane Library and Ichushi Web was conducted, and the reference lists of review articles were hand-searched. The outcomes of interest were the incidence rate of surgery, the length of hospital days and mortality. The quality of the included studies, publication bias and between-study heterogeneity were also assessed.

#### RESULTS

Three randomized controlled trials (RCTs) and three retrospective cohort studies were selected for analysis. In the three RCTs, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.13; 95%CI: 0.03-0.50). Similarly, Daikenchuto significantly reduced the incidence of surgery (pOR = 0.53; 95%CI: 0.32-0.87) in the three cohort studies. The length of hospital stay and mortality were not measured or described consistently.

#### CONCLUSION

The present meta-analysis demonstrates that administering Daikenchuto is associated with a lower incidence of surgery for patients with postoperative ASBO in the Japanese population. In order to better generalize these results, additional studies will be needed.

**Key words:** Herbal medicine; Kampo medicine; Post-operative adhesive small bowel obstruction; Systematic

review; Meta-analysis

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**Core tip:** Daikenchuto, a traditional herbal medicine, is commonly used by gastroenterologists for postoperative adhesive small bowel obstruction in Japan. However, the effectiveness of Daikenchuto has not been systemically investigated. The systematic review and meta-analysis demonstrated that Daikenchuto is associated with a lower incidence of surgery for patients with postoperative adhesive bowel obstruction in the Japanese population.

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## INTRODUCTION

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery. ASBO accounts for up to 6% of all surgical admissions and 60% to 70% of small bowel obstruction<sup>[1,2]</sup>. Conservative management is chosen for patients with no strangulation or peritonitis, patients who underwent surgery more than six weeks before ASBO, patients with partial ASBO and patients with signs of resolution on admission<sup>[3]</sup>. Conservative management is successful in 73% to 90% of patients<sup>[4,5]</sup>, but approximately one-fifth of patients later require surgery.

Essential conservative management includes decompression using a long tube or nasogastric tube intubation and intravenous fluid supplementation. According to guidelines for ASBO<sup>[3]</sup>, other supplementary non-operative management options include water-soluble contrast agent administration<sup>[6]</sup>, oral therapy with magnesium oxide, *Lactobacillus acidophilus* and simethicone<sup>[7]</sup>, and hyperbaric oxygen therapy<sup>[8]</sup>. Water-soluble contrast agent administration, in particular, has the diagnostic value of predicting the need for surgery while the procedure itself also has therapeutic value<sup>[9]</sup>.

Daikenchuto, a traditional herbal medicine, is frequently used by gastroenterologists in Japan for patients with ASBO<sup>[10]</sup> as well as chronic constipation, irritable bowel syndrome, Crohn's disease and paralytic ileus<sup>[11-14]</sup>. It comprises extract granules of processed ginger (kankyo), ginseng (ninjin) and zanthoxylum fruit (sansho). Basic research has shown several pharmacological mechanisms of Daikenchuto, including an increase in the blood flow of the intestinal tract, activation of intestinal motility, and prevention of bacterial translocation<sup>[15-17]</sup>. Recently, increasing evidence from clinical research has been accumulated<sup>[10]</sup>. However, while it is already widely used, no systematic analysis of

the research has been conducted. The objective of this study was to examine the effectiveness of Daikenchuto in patients who developed postoperative ASBO.

## MATERIALS AND METHODS

A systematic review was conducted, and the results were described according to the preferred reporting items for systematic reviews and meta-analyses statement<sup>[18]</sup>.

### Literature search

We systematically searched MEDLINE (PubMed), CINAHL, the Cochrane library and Ichushi Web, which is the largest medical article database in Japan, in November 2014. The MEDLINE search was conducted using the free-text words "Daikenchuto", "Dai-kenchuto", "DKT" and "TJ-100". A similar literature search was conducted in the other three databases. References of review articles were also hand-searched.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the studies were randomized controlled trials (RCTs) or observational studies with exposure and control groups; (2) the participants were patients who developed postoperative ASBO; (3) daikenchuto was administered enterally; and (4) the study was performed in humans. No restriction was placed on the language. The exclusion criteria were as follows: (1) observational studies without controls; (2) Daikenchuto was administered to prevent postoperative adhesive small bowel obstruction; and (3) experimental animal research studies.

### Outcome measures

The outcomes of interest were the incidence rate of surgery, the length of hospital stay, and mortality.

### Quality assessment and data extraction

Two researchers (Ukai T and Shikata S) independently assessed the quality of each trial using the Critical Appraisal Skills Programme (CASP)<sup>[19]</sup> for RCTs and the Newcastle Ottawa Quality Assessment Scale (NOQAS)<sup>[20]</sup> for observational studies. The CASP asks six questions regarding the quality of RCTs. The NOQAS consists of three domains: Selection, comparability and outcome; the quality is assessed by the number of stars, with each domain having a maximum of four stars, two stars and three stars, respectively. The extracted data included the first author, year of publication, country, number of participants allocated to each group, and dosage of Daikenchuto.

### Statistical analysis

The meta-analysis was conducted using the software Cochrane Collaboration Review Manager (version 5.3). All statistical analyses were performed using the Mantel-Haenszel method<sup>[21]</sup>, and the summary statistics were described with odds ratios (ORs). An OR

**Table 1** Characteristics of included studies

Ref.	Year	Country	Study design	Dose (g)	No. of patients with Daikenchuto (surgery: No surgery)	No. of patients without Daikenchuto (surgery: No surgery)	OR (95%CI)
Oyabu <i>et al</i> <sup>[23]</sup>	1995	Japan	RCT	15	1:27	5:20	0.15 (0.02-1.37)
Kubo <i>et al</i> <sup>[24]</sup>	1995	Japan	RCT	15	1:17	2:10	0.29 (0.02-3.67)
Itohet <i>et al</i> <sup>[25]</sup>	2002	Japan	RCT	15	5:8	10:1	0.06 (0.01-0.65)
Moriwaki <i>et al</i> <sup>[26]</sup>	1992	Japan	Retrospective cohort	15	1:23	49:154	0.14 (0.02-1.04)
Furukawa <i>et al</i> <sup>[27]</sup>	1995	Japan	Retrospective cohort	7.5-15.0	6:20	26:49	0.57 (0.20-1.58)
Yasunaga <i>et al</i> <sup>[28]</sup>	2011	Japan	Retrospective cohort	Not mentioned	20:124	28:116	0.67 (0.36-1.25)

RCT: Randomized controlled trial.

**Table 2** Critical appraisal for randomized controlled trials using critical appraisal skills program

	Oyabu <i>et al</i> <sup>[23]</sup>	Kubo <i>et al</i> <sup>[24]</sup>	Itohet <i>et al</i> <sup>[25]</sup>
1 Was the assignment of patients to treatments randomized?	Y	Y	Y
2 And if so, was the randomization list concealed (blinded or masked) to those deciding on patient eligibility for the study?	Y	Y	-
3 Were all patients analysed in the groups to which they were randomized (was an "intention to treat" analysis used)?	Y	N	Y
4 Were patients in the treatment and control groups similar with respect to known prognostic factors?	Y	Y	Y
5 Were patients, clinicians and outcome assessors kept "blind" to which treatment was being received?	-	-	-
6 Was follow-up complete?	Y	Y	Y

Y: Yes; N: No.

less than one favored the intervention group, and the point estimate of the OR was considered statistically significant at the 0.05 level if the 95%CI did not include the value of one. A fixed-effects model was initially adapted for all outcome measures. We tested for homogeneity among the studies by calculating the  $I^2$  value.  $I^2$  can be calculated as  $I^2 = 100\% \times (Q - df)/Q$ , where  $Q$  is Cochran's heterogeneity statistic and  $df$  the degrees of freedom<sup>[22]</sup>. We defined  $I^2$  values of less than 25% as low heterogeneity, 25% to 50% as moderate heterogeneity and more than 50% as high heterogeneity<sup>[22]</sup>. If the hypothesis of homogeneity was rejected, a random-effects model was employed.

## RESULTS

The search strategy yielded 1507 articles (Figure 1). After duplications were removed, we checked the title and abstract of the articles according to the inclusion and exclusion criteria. Full texts of the remaining articles were read, and three RCTs<sup>[23-25]</sup> and three cohort studies<sup>[26-28]</sup> were chosen based on the inclusion and exclusion criteria. Finally, the data were extracted from the studies (Table 1).

The publication year ranged from 1992 to 2011, and all research was conducted in Japan. All studies compared patients who were administered Daikenchuto with patients who were not administered Daikenchuto. The dosage of Daikenchuto was 15.0 g in four studies<sup>[23-26]</sup>, 7.5-15.0 g in one study<sup>[27]</sup>, and unreported in one study<sup>[28]</sup>. Daikenchuto was administered orally in one study<sup>[25]</sup>, through a tube in three studies<sup>[23,24,28]</sup>, or both in one study<sup>[26]</sup>. Participants were chosen regardless of

the kind of abdominal surgical history in five studies<sup>[23-27]</sup>, whereas only patients with a history of colorectal cancer were chosen in one study<sup>[28]</sup>. None of the included studies described the criteria of diagnosis of ASBO or pre-defined decision process for proceeding to surgery. The funnel plot of publication bias is shown in Figure 2.

### Quality assessment for selected articles

Among the three RCTs, one was conducted at multiple hospitals<sup>[24]</sup>, and the other two were conducted at one hospital<sup>[23,25]</sup>. In two RCTs<sup>[23,24]</sup>, patients were randomly assigned using a concealed envelope, and in a third study<sup>[25]</sup>, the method of assignment was not described. None of these articles mentioned the method of blinding. Patient follow-up continued until the obstruction was released and symptoms were relieved or until the patient underwent a surgery to remove the obstruction. In one trial<sup>[23]</sup>, the reasons for the surgical intervention were retrospectively explained, but no explanation was provided in the other two studies<sup>[24,25]</sup>. An intention-to-treat analysis was not used in one study<sup>[24]</sup> (Table 2).

Of the three retrospective cohort studies, one was conducted using a national inpatient database using propensity score analysis<sup>[28]</sup>, and both the exposure and control groups were recruited at one or several hospitals in a community<sup>[26,27]</sup>. Regarding outcome domains, the criteria for the decisions to proceed to surgery for the ASBO were not described in any of the three studies (Table 3).

### Incidence of surgery in the RCTs

A total of 107 patients were included in the three

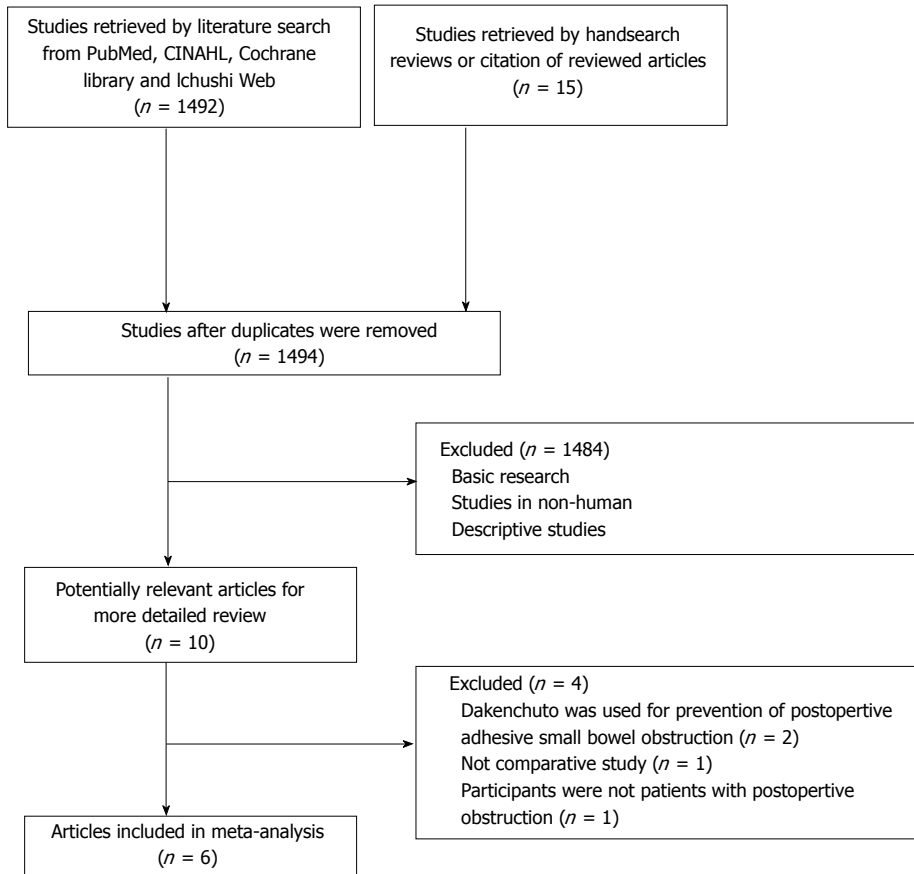


Figure 1 Search strategy according to the preferred reporting items for systematic review and meta-analyses.

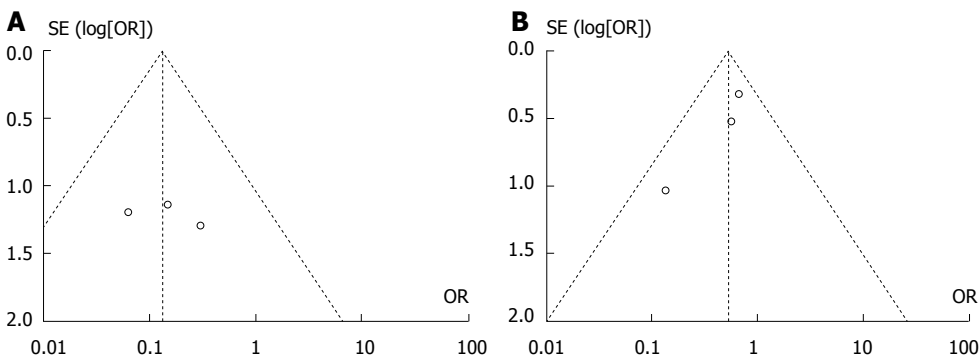


Figure 2 Funnel plot of randomized controlled trials (A) and cohort studies (B) reporting the risk of surgery in patients with postoperative adhesive small bowel obstruction given Daikenchuto. OR: Odds ratio; SE: Standard error.

RCTs (Figure 3). In the Daikenchuto group, seven of 59 (11.9%) patients eventually underwent surgery for the ASBO, whereas 17 of 48 (35.4%) patients underwent surgery in the control group. The overall OR was 0.13 (95%CI: 0.03-0.50), demonstrating statistical significance. There was no heterogeneity among the trials ( $I^2 = 0\%$ ).

#### Incidence of surgery in the cohort studies

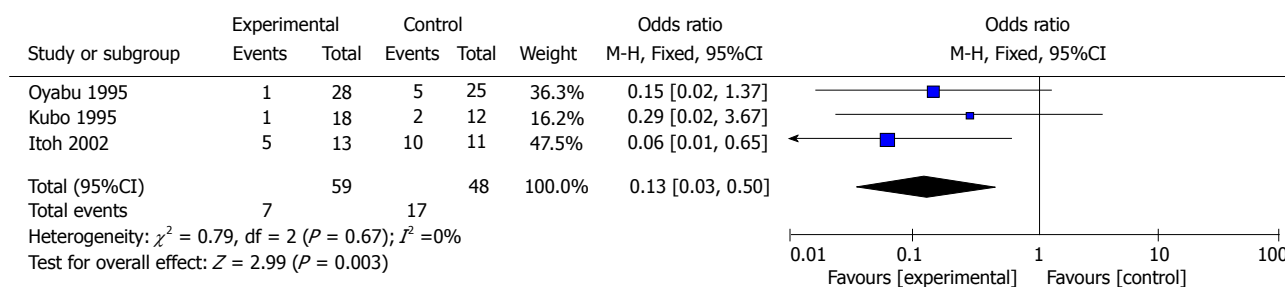
A total of 616 patients were included in the three cohort studies (Figure 4). The incidences of surgical intervention were 27 of 194 (13.9%) in the Daikenchuto group and 103 of 422 (24.4%) in the control group.

The overall OR was 0.53 (95%CI: 0.32-0.87), also demonstrating statistical significance. There was low heterogeneity among the trials ( $I^2 = 12\%$ ).

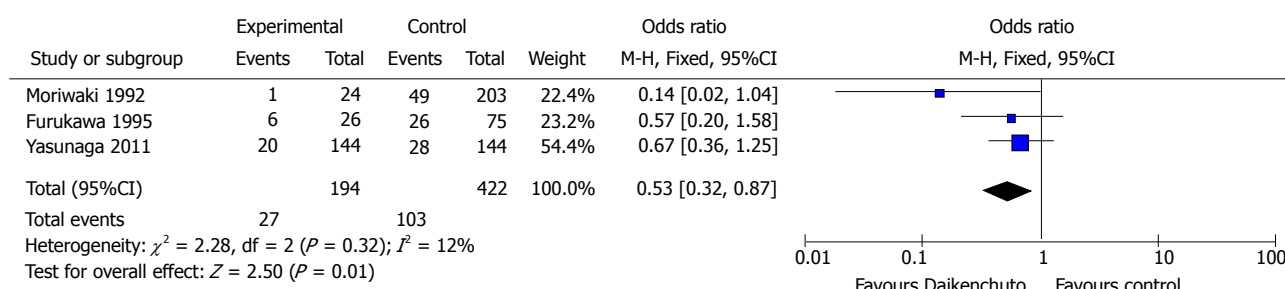
#### Other outcomes

Mortality was described in the one cohort study with a total of 288 patients<sup>[28]</sup>. The number of deaths identified was four (2.8%) in the Daikenchuto group and two (1.4%) in the control group, and this difference was not found to be significant.

Length of hospital stay was described in two studies. One RCT<sup>[27]</sup> showed that the length of the hospital stay was 5.90 d shorter (95%CI: 4.77-7.03) in the



**Figure 3** Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from randomized controlled trials. Boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CI. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.



**Figure 4** Effect of Daikenchuto on need for surgery for postoperative adhesive small bowel obstruction from cohort studies boxes indicate estimated odds ratio; Diamond, summary statistic; limit lines, 95%CI. Size of the data marker corresponds to the relative weight assigned to the pooled analysis using fixed-effects model. The X-axis uses a log scale.

**Table 3** Critical appraisal for cohort studies using newcastle ottawa quality assessment scale

	Moriwaki <i>et al</i> <sup>[26]</sup>	Furukawa <i>et al</i> <sup>[27]</sup>	Yasunaga <i>et al</i> <sup>[28]</sup>
Selection			
Representativeness of the exposed cohort			Y
Selection of non-exposed cohort	Y	Y	Y
Ascertainment of exposure	Y	Y	Y
Demonstration that outcome of interest was not present at start of study	Y	Y	Y
Comparability			
Comparability of cohorts on the basis of the design or analysis	Y	Y	Y
Outcome			
Assessment of outcome			
Was follow-up long enough to occur	Y	Y	Y
Adequacy of follow up of cohorts	Y	Y	Y

Y: Yes.

Daikenchuto group. Also, one cohort study<sup>[28]</sup> showed statistical significance in favor of the Daikenchuto group using Kaplan-Meier methods and log-rank test ( $P = 0.018$ ).

## DISCUSSION

This systematic review provides evidence from three RCTs and three cohort studies conducted in Japan concerning the effectiveness of the traditional herbal medicine Daikenchuto in reducing the risk of surgery for patients with postoperative ASBO. From the synthesized results, ASBO patients who received Daikenchuto had a significantly lower risk of surgery. The study assessed RCTs and cohort studies individually, and they provided consistent results.

### Potential benefit of daikenchuto

There are several treatment options recommended in guidelines for ASBO<sup>[3]</sup>. Among the options, water-soluble contrast agent administration is highly recommended because there is robust evidence for its efficacy both in predicting a need for surgery and for preventing surgery<sup>[9]</sup>. However, despite its established efficacy, 20.8% of ASBO patients treated this way proceed to surgery<sup>[9]</sup>. Daikenchuto has widely been used in Japan and has a low risk of side effects<sup>[29]</sup>, and the cost is only 145.5 JPY (US\$1.25) per day. From these perspectives, Daikenchuto could be used as part of initial non-operative management adjunct to water-soluble contrast

administration. It is potentially useful for patients who have a high risk of anaphylactoid reaction to water-soluble contrast agent or patients who cannot tolerate surgery.

### Traditional herbal medicine in Japan

Traditional Japanese herbal medicine is known as Kampo medicine. Kampo medicine has its roots in traditional Chinese medicine and was introduced to Japan in the middle of the sixth century. The Japanese Ministry of Health, Labour and Welfare has officially approved 212 types of Kampo medicines, and these medicines are covered by the National Health Insurance programme<sup>[30]</sup>. All certified medical doctors can prescribe both Western and Kampo medicines, and they choose the optimal one depending on the condition of the patients. Kampo medicine is referred to as an alternative medicine, but in practice, Japanese physicians use both Western medicine and Kampo medicine; in particular, Kampo medicine is commonly used for patients with medically unexplained symptoms that Western medicine often fails to solve<sup>[10]</sup>. The mechanism of the pharmacological effect is becoming clear, but more clinical research is needed before Kampo medicine will be widely adopted in other countries.

### Limitations

This study has several limitations. First, the included studies have methodological problems. None of included three RCTs described the blinding of clinicians and assessors. Also, none of the included studies described the criteria of decisions of proceeding to surgery. Since the decision to proceed to surgery can be subjective, there may be bias in this outcome statistic, especially when clinicians were not blinded.

Second, the reviewed studies were conducted in Japan using Japanese populations. In three studies<sup>[23,25,26]</sup>, participants were recruited at one hospital. These facts pose the question of generalizability. Thus, additional evidence is needed from patients in other countries.

Finally, all studies included compared those patients who were administered Daikenchuto and who were not. We could not find studies that compared Daikenchuto and water-soluble contrast agent. Since administering water-soluble contrast agent is the standard of care, Daikenchuto and water-soluble contrast agent should be directly compared before it is applied to clinical practice.

The traditional herbal medicine Daikenchuto significantly reduces the risk of surgery for patients with postoperative ASBO in a Japanese population. In order to better generalize these results, additional studies incorporating a broader set of outcomes and an expanded population base will be needed.

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## COMMENTS

### Background

Adhesive small bowel obstruction (ASBO) is a common complication for patients with a history of abdominal surgery, and one fifth of them later require surgery. Daikenchuto, a traditional herbal medicine, is commonly used for postoperative adhesive small bowel obstruction, but the effectiveness of Daikenchuto in preventing surgery for patients with postoperative ASBO is not systemically assessed.

### Research frontiers

Evidence in traditional herbal medicine from clinical research, as well as basic research has increasingly been accumulated. However, the evidence is not systemically collected and integrated.

### Innovations and breakthroughs

In the present study, the authors demonstrated the effectiveness of Daikenchuto for preventing patients by pooling results from randomized controlled trials and cohort studies. This is the first report of meta-analysis to assess the traditional herbal medicine, Daikenchuto.

### Applications

The present study allows understanding the role of Daikenchuto for patients with postoperative ASBO to prevent surgery.

### Peer-review

It is a very interesting paper and a new approach to manage the adhesive small bowel obstruction.

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