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Rikkunshito for upper gastrointestinal symptoms: A systematic review and meta-analysis

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ABSTRACT

Background: Upper gastrointestinal symptoms are major issues in various diseases such as postgastrectomy syndrome and functional dyspepsia. These symptoms cannot be fully controlled in such conditions and result in poorer quality of life. Rikkunshito has been traditionally used in Japan to relieve these symptoms. This systematic review assessed the efficacy and safety of rikkunshito for relieving upper gastrointestinal symptoms.

Methods: A systematic literature search was conducted using Ovid MEDLINE, Scopus, the Cochrane Central Register of Controlled Trials, and ICHUSHI. Randomized controlled trials comparing rikkunshito to alternative drugs for the treatment of upper gastrointestinal symptoms were searched without language restriction. Two review authors independently assessed the literature and extracted data from identified studies. The risk of bias in each study was assessed.

Results: Twenty-four studies with a combined total of 2175 participants were included in this review. Rikkunshito did not significantly relieve upper gastrointestinal symptoms when compared with other treatments via the Gastrointestinal Symptom Rating Scale (standardized mean difference, −0.07; 95% confidence interval [CI], −0.31 to 0.17; $P = 0.59$), while it significantly relieved the symptoms on a 5-point scale (mean difference, −0.38; 95% CI, −0.55 to −0.21; $P < 0.001$). No drug-related severe adverse events were reported. Most of the included studies had high or unclear overall risk of bias.

Conclusions: It remains still unclear whether rikkunshito is effective for the relief of upper gastrointestinal symptoms. Further high-quality studies are needed.

1. Introduction

Upper gastrointestinal symptoms are common problems in various digestive diseases, such as gastritis and functional dyspepsia, and are also common adverse events caused by drugs and surgical interventions.[1–4] Many patients experience these symptoms because the standard therapies are not fully effective for some conditions.[1–4]

Rikkunshito is a Japanese herbal medicine (Kampo) that is widely used in Japan to treat upper gastrointestinal dysfunction regardless of the causative disorder.[5] Rikkunshito is a powdered medicine and is composed of 8 crude drug extracts including Atractylodis lanceae rhizoma, radix ginseng, pinelliae tuber, hoelen, zizyphi fructus, aurantii nobilis pericarpium, radix glycyrrhizae, and rhizoma zingiberis. This combination of extracts in fixed proportions is considered effective for the relief of gastrointestinal motility disorder.[5] Rikkunshito was reported to stimulate gastrointestinal contractions through cholinergic neurons and 5-HT type 3 receptors in the animal study.[6] Also, recent studies have suggested that rikkunshito accelerates bowel movements by increasing the secretion of ghrelin.,[5,7] In this systematic review, we examined the efficacy and safety of rikkunshito for upper gastrointestinal symptoms, and its impact on ghrelin secretion.

2. Methods

2.1. Registration and protocol

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) at the National Institute for Health Research and Centre for Reviews and Dissemination, University of York (registration number: CRD42016052661).[8] The protocol was prospectively created in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines.[9]

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2.2. Inclusion criteria

All randomized controlled trials were eligible for this systematic review except for cluster-randomized and quasi-randomized trials. All adult patients (aged ≥ 18 years) who had gastrointestinal symptoms were eligible for inclusion, regardless of the causative diseases.

Rikkunshito was included as an experimental intervention, and a placebo, any other drug that might relieve upper gastrointestinal symptoms, and no treatment at all were included as comparator interventions. All drug interventions regularly taken by study participants were eligible for inclusion, regardless of dose, frequency, or duration of administration.

2.3. Outcome measures

The primary outcomes were upper gastrointestinal symptoms measured by the Gastrointestinal Symptom Rating Scale (GSRS), incidence of adverse events associated with rikkunshito via the Common Terminology Criteria for Adverse Events (CTCAE), and quality of life (QOL) measured by any scale. Secondary outcomes were upper gastrointestinal symptoms measured on any other scale, appetite on any scale, and serum ghrelin level (fmol/mL).

2.4. Study search and selection

A systematic literature search was conducted on August 30, 2018, using Ovid MEDLINE, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL), and ICHUSHI.

Titles and abstracts of the identified studies were independently screened by two review authors (N.H. and D.N.). After screening, the full texts of the potential eligible articles were assessed. Disagreement between the authors was resolved by discussion. Duplicate publications were identified and eliminated by checking study author names, study design and period, setting, characteristics of the participants, and so on. After the selection, reference lists of included studies were checked to identify further relevant studies.

2.5. Data extraction

Data were independently extracted by the same review authors (N.H. and D.N.) and checked for accuracy. Extracted data included study design and period, setting, characteristics of the participants, interventions, and the primary and secondary outcomes of this review. The data were entered into Review Manager 5.3 (Cochrane Collaboration software). If the included studies were registered anywhere, details of the registration were also checked.

2.6. Risk of bias assessment

Risk of bias in the included studies was independently assessed by the same review authors (N.H. and D.N.) in each of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Risk of bias was classified as high, low, or unclear according to the Cochrane Handbook for Systematic Review of Interventions.[10] The overall risk of bias for each study was assessed based on judgment of the 7 domains. Publication bias was planned to be assessed by funnel plots when 10 or more studies were included in each meta-analysis.

2.7. Statistical analysis

Data synthesis was performed using Review Manager 5.3 (Cochrane Collaboration software). A random-effects model was used for all analyses because this review included various disorders that cause upper gastrointestinal symptoms. The effects of each study and the overall effect of the meta-analysis were reported as mean difference (MD) with a 95% confidence interval (CI) in a forest plot for continuous variables when a single outcome measure was used. The overall effect was reported as standardized mean difference (SMD) with a 95% CI when multiple outcome measures were used. Standard deviation (SD) was calculated using the calculator function of Review Manager when a mean with a standard error was reported. When a result of a study was reported as a figure, the SD was estimated from that figure. All *P*-values were two-sided, and *P*-values less than 0.05 were considered statistically significant. Heterogeneity was assessed based on a visual inspection of the forest plot, followed by chi-square testing, in which a *P*-value less than 0.10 was considered statistically significant because the power of the chi-square test was low to detect heterogeneity. Heterogeneity was quantified by the I^2 statistics and interpreted as follows: 0–40%, low heterogeneity; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity.

3. Results

3.1. Characteristics of included studies

The primary literature search of the four electronic databases identified 1096 articles. After checking for duplications, 828 articles were screened by the two review authors for potential inclusion via titles and abstracts, and 31 full-text articles were examined by the same authors to determine whether they met the inclusion criteria (Fig. 1). Twenty-three articles were identified, and one of them included 2 studies. Thus, 24 two-arm studies with a combined total of 2175 participants were finally included.[11–33] Among the studies, 13 were single-centric and 11 were multi-centric. Rikkunshito was compared with a placebo in 4 studies, with other comparator drugs in 9 studies, and with no other treatment in 11 studies (Table 1).

A parallel design was used in 21 studies and a cross-over design in 3. We had planned to include only the first treatment phase of cross-over studies to avoid cross-over effects. However, 2 of the cross-over studies reported only the final data by combining the first and second treatment phases, and no data about the first treatment phase was available. Therefore, the final data were included in the meta-analyses because no comparator drugs were used in the studies and there were few, if any, cross-over effects. Rikkunshito was used for dysfunctional diseases in 8, drug-related adverse events in 7, inflammatory diseases in 4 studies, postoperative care in 3, neurological diseases in 1, and the management of mechanical ventilated patients in 1 (Table 2).

3.2. Risk of bias assessment

A summary of the assessment of risk of bias assessment for the following domains is shown in Fig. 2.

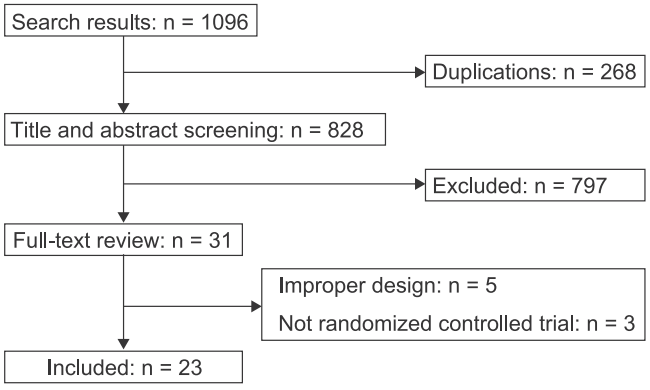

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of included studies.

Study	Year	Setting	Language	Centers	Design	Arms	Overall risk of bias
Arai [10]	2012	Japan	English	Single	parallel	2	Unclear
Fushiki [11]	2003	Japan	Japanese	Single	parallel	2	High
Harada_1 [12]	2018	Japan	English	Multi	parallel	2	Unclear
Harada_2 [12]	2018	Japan	English	Multi	parallel	2	Unclear
Harasawa [13]	1998	Japan	Japanese	Multi	parallel	2	Low
Hayakawa [14]	2014	Japan	English	Single	parallel	2	Low
Kawamura [15]	1992	Japan	Japanese	Single	parallel	2	Unclear
Komatsuzaki [16]	1993	Japan	Japanese	Single	parallel	2	Unclear
Miyoshi_1 [17]	1991	Japan	Japanese	Multi	parallel	2	High
Miyoshi_2 [18]	1991	Japan	Japanese	Multi	parallel	2	Unclear
Mizuno [19]	2001	Japan	Japanese	Single	parallel	2	High
Ohnishi [20]	2017	Japan	English	Multi	parallel	2	Unclear
Ohno [21]	2011	Japan	English	Single	cross-over	2	High
Oka [22]	2007	Japan	English	Single	parallel	2	High
Seike [23]	2011	Japan	English	Single	parallel	2	High
Suzuki [24]	2014	Japan	English	Multi	parallel	2	Low
Takahashi [25]	2009	Japan	English	Single	cross-over	2	High
Takemoto [26]	1990	Japan	Japanese	Multi	parallel	2	High
Tatsuta [27]	1993	Japan	English	Single	parallel	2	High
Tominaga_1 [28]	2012	Japan	English	Multi	parallel	2	High
Tominaga_2 [29]	2014	Japan	English	Multi	parallel	2	Low
Tominaga_3 [30]	2018	Japan	English	Multi	parallel	2	Low
Uehara [31]	2013	Japan	English	Single	parallel	2	High
Yakabi [32]	2017	Japan	English	Single	cross-over	2	Unclear

3.2.1. Random sequence generation

Fourteen studies used a computer random number generator, a random number table, minimization, or envelopes, and were judged to have low risk of bias in this domain. The remaining 10 studies did not refer to a method of random sequence generation and were judged to have unclear risk of bias in this domain.

3.2.2. Allocation concealment

Eight studies were considered to protect allocation concealment. These studies were judged to have low risk of bias in this domain. The remaining 16 studies did not refer to allocation concealment and were judged to have unclear risk of bias.

3.2.3. Blinding of participants and personnel

Four studies used a placebo as a comparator and the participants and personnel were blinded, and thus they were judged to have low risk of bias in this domain. Nine studies used another drug as a comparator. Among them, risk of bias in this domain was judged to be at low in 1 study, high in 2, and unclear in 6. Eleven studies used no comparator drug and the participants and personnel were not blinded, and thus

Table 2
Treatment data for study participants.

Study	Participants (n)	Disease/Status	Interventions			Comparators		
			Drug	Amount (/day)	Duration (weeks)	Drug	Amount (/day)	Duration (weeks)
Arai [10]	27	Dyspepsia	Rikkunshito	7.5 g	4	Domperidone	30 mg	4
Fushiki [11]	120	Iron pills for pregnancy	Rikkunshito	7.5 g	2	No treatment	–	–
Harada_1 [12]	58	HEC for LC	Rikkunshito	7.5 g	1	No treatment	–	–
Harada_2 [12]	62	MEC for LC	Rikkunshito	7.5 g	1	No treatment	–	–
Harasawa [13]	296	Dyspepsia	Rikkunshito	7.5 g	2	Placebo	7.5 g	2
Hayakawa [14]	23	Tube feeding	Rikkunshito	7.5 g	(a)	Metoclopramide	30 mg	(a)
Kawamura [15]	28	Gastiritis	Rikkunshito	7.5 g	4	Sulpiride	150 mg	4
Komatsuzaki [16]	35	Gastiritis	Rikkunshito	7.5 g	4	Azuren-Glutamine	2g	4
Miyoshi_1 [17]	248	Dyspepsia	Rikkunshito	7.5 g	4	Cisapride	7.5 mg	4
Miyoshi_2 [18]	236	Gastiritis	Rikkunshito	7.5 g	4	Azuren-Glutamine	2 g	4
Mizuno [19]	46	Gastrectomy for GC	Rikkunshito	7.5 g	NR	No treatment	–	–
Ohnishi [20]	40	Chemotherapy for UC	Rikkunshito	7.5 g	2	No treatment	–	–
Ohno [21]	10	Chemotherapy for GC	Rikkunshito	7.5 g	3	No treatment	–	–
Oka [22]	50	Fluvoxamine for DD	Rikkunshito	7.5 g	8	No treatment	–	–
Seike [23]	19	Chemotherapy for EC	Rikkunshito	7.5 g	2	No treatment	–	–
Suzuki [24]	247	Dyspepsia	Rikkunshito	7.5 g	8	Placebo	7.5 g	8
Takahashi [25]	11	Gastrectomy for GC	Rikkunshito	7.5 g	4	No treatment	–	–
Takemoto [26]	74	Gastiritis	Rikkunshito	7.5 g	4	Cetraxate hydrocloride	800 g	4
Tatsuta [27]	42	Dyspepsia	Rikkunshito	7.5 g	1	Combizym	NR	NR
Tominaga_1 [28]	104	GERD	Rikkunshito	7.5 g	4	Rabeprazole	10 mg	4
Tominaga_2 [29]	242	NERD	Rikkunshito	7.5 g	8	Placebo	7.5 g	8
Tominaga_3 [30]	128	Dyspepsia	Rikkunshito	7.5 g	8	Placebo	7.5 g	8
Uehara [31]	13	ESD for GC	Rikkunshito	7.5 g	8	No treatment	–	–
Yakabi [32]	16	Parkinson disease	Rikkunshito	7.5 g	4	No treatment	–	–

a: during gastric tube feeding or 10 days DD: depressive disorder, ESD: endoscopic submucosal dissection, GC: gastric cancer, GERD: gastro-esophagus reflux disease, HEC: highly emetogenic chemothrapy, LC: lung cancer, MEC: moderately emetogenic chemothrapy, NERD: non-errosive reflux disease, NR: not reported, UC: uterine cancer.

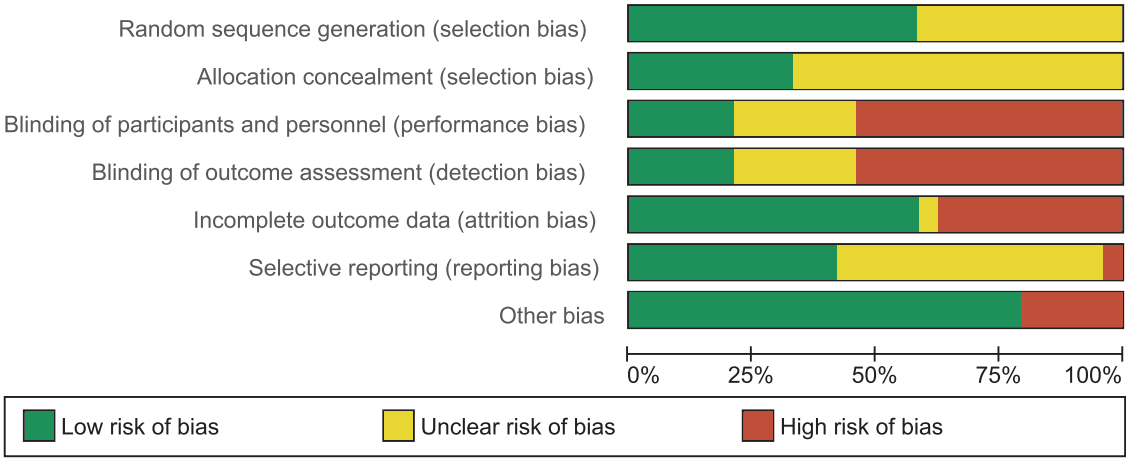

Fig. 2. Summary of the assessment of risk of bias among the included studies.

they were judged to have high risk of bias in this domain.

3.2.4. Blinding of outcome assessment

Four studies used a placebo as a comparator and blinded the outcome assessment, and thus these were judged to have low risk of bias in this domain. Nine studies used another drug as a comparator. Among them, risk of bias in this domain was judged to be at low in 1 study, high in 2, and unclear in 6. Eleven studies used no comparator drug and did not blind the outcome assessment, and thus they were judged to have high risk of bias in this domain.

3.2.5. Incomplete outcome data

The number of missing participants was not small and/or not well-balanced between 2 groups in 8 studies, and the result of per protocol analysis was reported in 1 study. These 9 studies were judged to have high risk of bias in this domain. There were no missing participants in another 8 studies while a few were missing in 6 studies. These 14 studies were judged to have low risk of bias in this domain. The remaining 1 study did not refer to missing participants and was judged to have unclear risk of bias in this domain.

3.2.6. Selective reporting

Ten studies were registered in UMIN Clinical trial registry or ClinicalTrials.gov, and the registered outcomes were reported in the articles. These studies were judged to have low risk of bias in this domain. Thirteen studies were not registered anywhere and were judged to have unclear risk of bias in this domain. One study did not report on the results of adverse events, which was mentioned in the method section of the study, and thus the study was judged to have high risk of bias.

3.2.7. Other bias

The treatment periods were potentially different between two groups in 2 studies, banned drugs were different between the groups in 1 study, and cross-over design was employed in 2 studies. These 5 studies were judged to have high risk of bias in this domain. Nineteen studies had no other apparent biases and were judged to have low risk of bias in this domain.

3.2.8. Overall risk of bias

Eleven studies were judged to have high overall risk of bias because most domains had a high or unclear (potentially high) risk of bias that included the lack of blinding of participants, personnel, and outcome assessors. Five studies were judged to have low overall risk of bias because most of the domains were judged to have low risk of bias. The remaining 8 studies were judged to have an unclear overall risk of bias (Table 1).

3.3. Primary outcomes

3.3.1. Upper gastrointestinal symptoms (GSRS)

Six studies reported on upper gastrointestinal symptoms using GSRS. Among the studies, 4 reported symptoms using means and SD, 1 study reported symptoms as a figure, and the remaining 1 study reported the percentage of reduction in GSRS. These 6 studies, with a combined total of 481 participants, were included in the meta-analysis. Rikkunshito did not significantly relieve upper gastrointestinal symptoms compared with comparator drugs (SMD, −0.07; 95% CI, −0.31 to 0.17; $P = 0.59$) and heterogeneity was low ($I^2 = 25\%$) (Fig. 3).

Rikkunshito was used for dysfunctional diseases in 3 studies, drug-related adverse events in 1, postoperative care in 1, and neurological diseases in 1. The overall risk of bias in included studies was high in 2 studies, low in 2, unclear in 2. Therefore, the quality of this evidence was considered to be low.

3.3.2. Adverse effects (CTCAE)

Twenty studies investigated the adverse events of rikkunshito, and 19 of these reported the results. Only 1 study reported using CTCAE, 6 studies reported using a subjective scale, and the remaining 12 studies did not refer to what they used to measure adverse events. We did not perform a meta-analysis of the adverse events. However, there were no adverse events in 11 studies and no significant differences between two groups in the remaining 8 studies.

3.3.3. QOL (self-rating depressive scale [SDS])

Nine studies reported on the QOL using one or two of the following scales: the SDS, the Self-rating Questionnaire for Depression (SRQ-D), the Gastrointestinal Quality-Of-Life Index (GIQLI), a 5-point scale based on the Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs (QOL-ACD), the Short-Form Health Survey-8 questionnaires (SF-8), the Hospital Anxiety and Depression Scale (HAD), or the Quality of Life Questionnaire (QLQ-30). Of these studies, 3 reported using SDS, of which 2 reported the results as means plus SD and the other reported them as a figure. These 3 studies, which included a total of 73 participants, were included in the meta-analysis. Rikkunshito did not improve QOL compared with comparator drugs (MD, −0.73; 95% CI, −4.52 to 3.06; $P = 0.70$). Heterogeneity was low ($I^2 = 0\%$) (Fig. 3).

Rikkunshito was used for dysfunctional diseases in 1 study, drug-related adverse events in 1, and neurological diseases in 1. The overall risk of bias in included studies was high in 1 study, unclear in 2. Therefore, the quality of this evidence was considered to be low.

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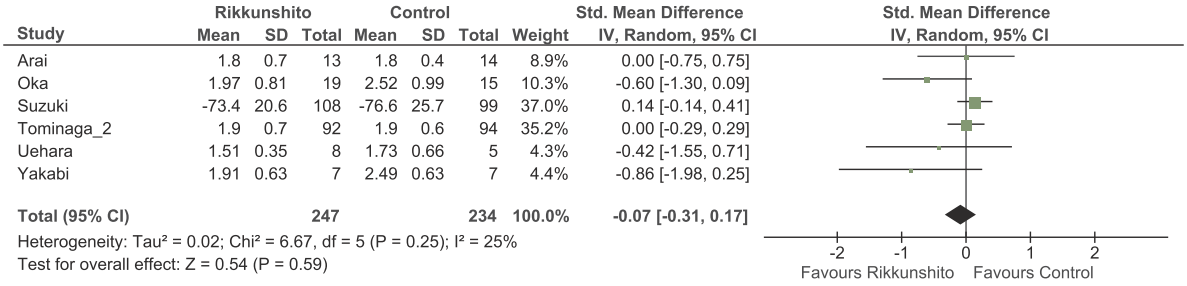

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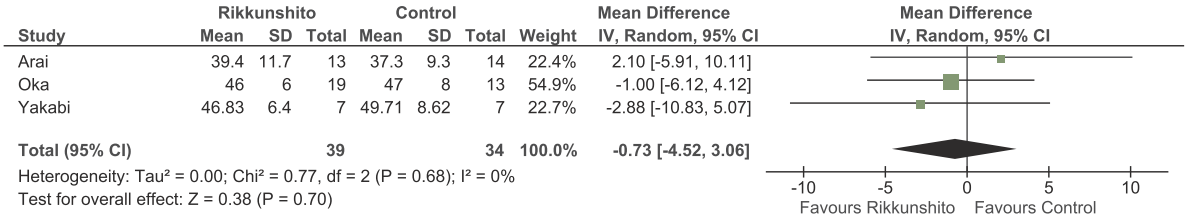

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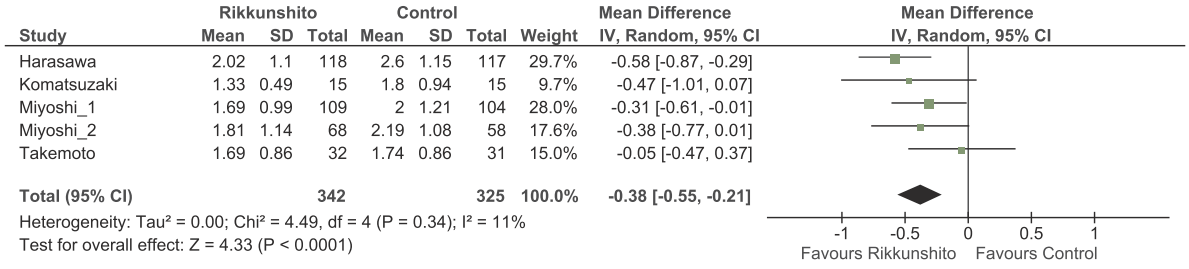

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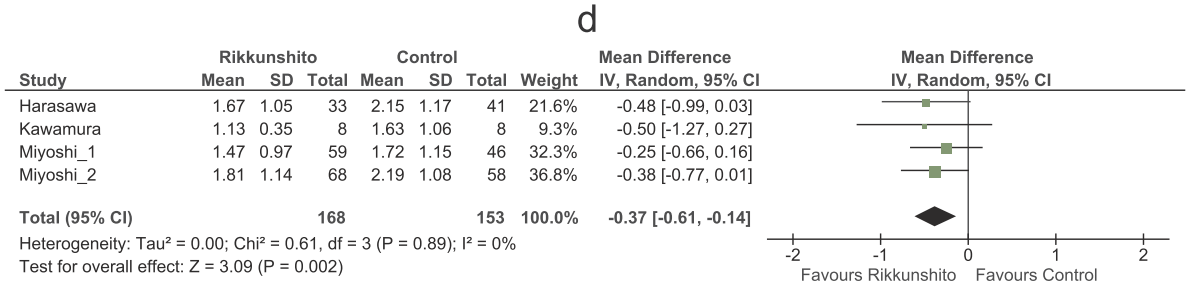

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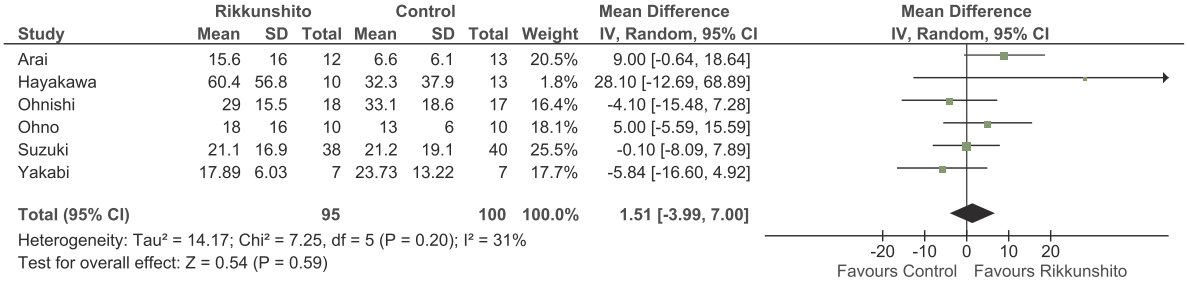

Fig. 3. Meta-analysis of rikkunshito for upper gastrointestinal symptoms.
a: upper gastrointestinal symptoms (gastrointestinal symptom rating scale), b: quality of life, c: upper gastrointestinal symptoms (5-point scale), d: appetite (5-point scale), e: serum acylated ghrelin (fmol/mL).

3.4. Secondary outcomes

3.4.1. Upper gastrointestinal symptoms (5-point scale)

Ten studies reported upper gastrointestinal symptoms using a scale other than GSRS. Among them, 5 studies used a 5-point scale, 2 used the Frequency Scale for the Symptom of GERD (FSSG), 1 used the modified FSSG, the Overall Treatment Efficacy (OTE), the Patient Assessment of Upper Gastrointestinal Disorder-Symptom scale (PAGI-SYM) and the Global Overall Symptom scale (GOS), 1 used stasis-related symptom score and Sigstad scoring, and 1 used the global patient assessment (GPA) score. We performed a meta-analysis using the 5-point scale, the details of which are as follows: much improved = 1, moderately improved = 2, mildly improved = 3, not changed = 4, and worsening = 5. Five studies, including 667 participants total, were included in the analysis. Rikkunshito significantly relieved upper gastrointestinal symptoms compared with the comparators (MD, −0.38; 95% CI, −0.55 to −0.21; $P < 0.001$) and heterogeneity was low ($I^2 = 11\%$) (Fig. 3).

Rikkunshito was used for inflammatory diseases in 3 studies, and dysfunctional diseases in 2. The overall risk of bias in included studies was high in 2 studies, low in 1, unclear in 2. Therefore, the quality of this evidence was considered to be low.

3.4.2. Appetite (5-point scale)

Eleven studies reported data on appetite. Among them, 4 studies reported on the degree of anorexia using a 5-point scale, 2 used CTCAE, 1 used a 4-point scale, 1 used a visual analogue scale (VAS), and 1 study used the anorexia–cachexia score. The remaining 2 studies reported the proportion of participants with anorexia. We performed a meta-analysis using a 5-point scale, the details of which are as follows: 1 = disappeared; 2 = much improved; 3 = mildly improved; 4 = not changed; or 5 = worsening. Four studies with a combined total of 321 participants were included in the meta-analysis. Rikkunshito significantly improved appetite compared with comparator drugs (MD, -0.37; 95% CI, −0.61 to −0.14; $P = 0.002$) and heterogeneity was low ($I^2 = 0\%$) (Fig. 3).

Rikkunshito was used for inflammatory diseases in 2 studies, and dysfunctional diseases in 2. The overall risk of bias in included studies was high in 1 study, low in 1, unclear in 2. Therefore, the quality of this evidence was considered to be low.

3.4.3. Ghrelin (f/moL)

Six studies reported data on serum acylated ghrelin. Among them, 5 reported the data as the mean with SD and 1 reported the data as a figure. The 6 studies with a combined total of 195 participants were included in the meta-analysis. One study mentioned that 2 participants dropped out of the study but did not mention the groups that they had been allocated to. We supposed that 1 participant was dropped out from each group. Rikkunshito did not significantly increase serum acylated ghrelin compared with comparator drugs (MD, 1.51; 95% CI, -3.99 to 7.00; $P = 0.59$) and heterogeneity was low ($I^2 = 31\%$) (Fig. 3).

Rikkunshito was used for dysfunctional diseases in 2 studies, drug-related adverse events in 2, neurological diseases in 1, and the management of mechanical ventilated patients in 1. The overall risk of bias in included studies was high in 1 study, low in 2, unclear in 3. Therefore, the quality of this evidence was considered to be low.

3.5. Assessment of publication bias

Funnel plots are shown in Fig.4. The funnel plots seemed to be asymmetrical by visual inspection in all meta-analyses. However, it was not possible to conduct a test for publication bias because there were fewer than 10 studies included in each meta-analysis[10].

3.6. Sensitivity analysis

Sensitivity analysis was performed restricting to the studies of low risk of bias.

3.6.1. Upper gastrointestinal symptoms (GSRS)

Two studies of low risk of bias were identified in the main analysis of this outcome. These studies were included in the sensitivity analysis. Rikkunshito did not significantly relieve upper gastrointestinal symptoms compared with comparator drugs (SMD, 0.07; 95% CI, −0.13 to 0.27; $P = 0.47$) and heterogeneity was low ($I^2 = 0\%$) (Fig. 5). The result of sensitivity analysis corresponded to that of main analysis in this outcome.

3.6.2. QOL (SDS)

No studies of low risk of bias were identified in the main analysis of this outcome.

3.6.3. Upper gastrointestinal symptoms (5-point scale)

Only 1 study of low risk of bias was identified in the main analysis of this outcome. This study reported that rikkunshito significantly relieved upper gastrointestinal symptoms compared with the comparators (MD, −0.58; 95% CI, −0.87 to −0.29; $P < 0.001$) (Fig. 5). The result of sensitivity analysis corresponded to that of main analysis in this outcome.

3.6.4. Appetite (5-point scale)

Only 1 study of low risk of bias was identified in the main analysis of this outcome. This study reported that rikkunshito tended to improve appetite compared with comparator drugs (MD, −0.48; 95% CI, −0.99 to 0.03; $P = 0.06$) (Fig. 5). The result of sensitivity analysis almost corresponded to that of main analysis in this outcome.

3.6.5. Ghrelin (f/moL)

Two studies of low risk of bias were identified in the main analysis of this outcome. These studies were included in the sensitivity analysis. Rikkunshito did not significantly increase serum acylated ghrelin compared with comparator drugs (MD, 6.62; 95% CI, −16.93 to 7.89; $P = 0.58$) and heterogeneity was moderate ($I^2 = 43\%$) (Fig. 5). The result of sensitivity analysis was not much different from that of main analysis in this outcome other than the degree of heterogeneity.

4. Discussion

In this systematic review, rikkunshito did not significantly relieve upper gastrointestinal symptoms based on GSRS, QOL, and ghrelin secretion. However, it significantly relieved the symptoms based on the 5-point scale and improved appetite. The quality of evidence was considered to be low in all outcomes other than adverse events because the overall risk of bias in included studies was high or unclear in most of the included studies in each meta-analysis. Also, the efficacy of rikkunshito was investigated for various conditions and the intervention period ranged widely from 1 to 8 weeks. The results of meta-analyses should be interpreted cautiously. Adverse effects were rare across the included studies regardless of the risk of bias in included studies.

Rikkunshito has been frequently used to treat upper gastrointestinal symptoms in Japan and has had no severe adverse events reported[5]. Older studies support the efficacy of rikkunshito in relieving the symptoms and improving appetite.[14, 17–19] The 5-point scale was frequently used in those studies, which might have led to high statistical power showing the efficacy of rikkunshito (Fig. 3). However, most of these studies were at high or unclear risk of bias mainly because there was lack of blinding and/or many drop-out participants. On the contrary, various scales have been used to evaluate the efficacy of rikkunshito in recent studies. In this meta-analysis, GSRS was set as the primary outcome because it was the most common scale used among

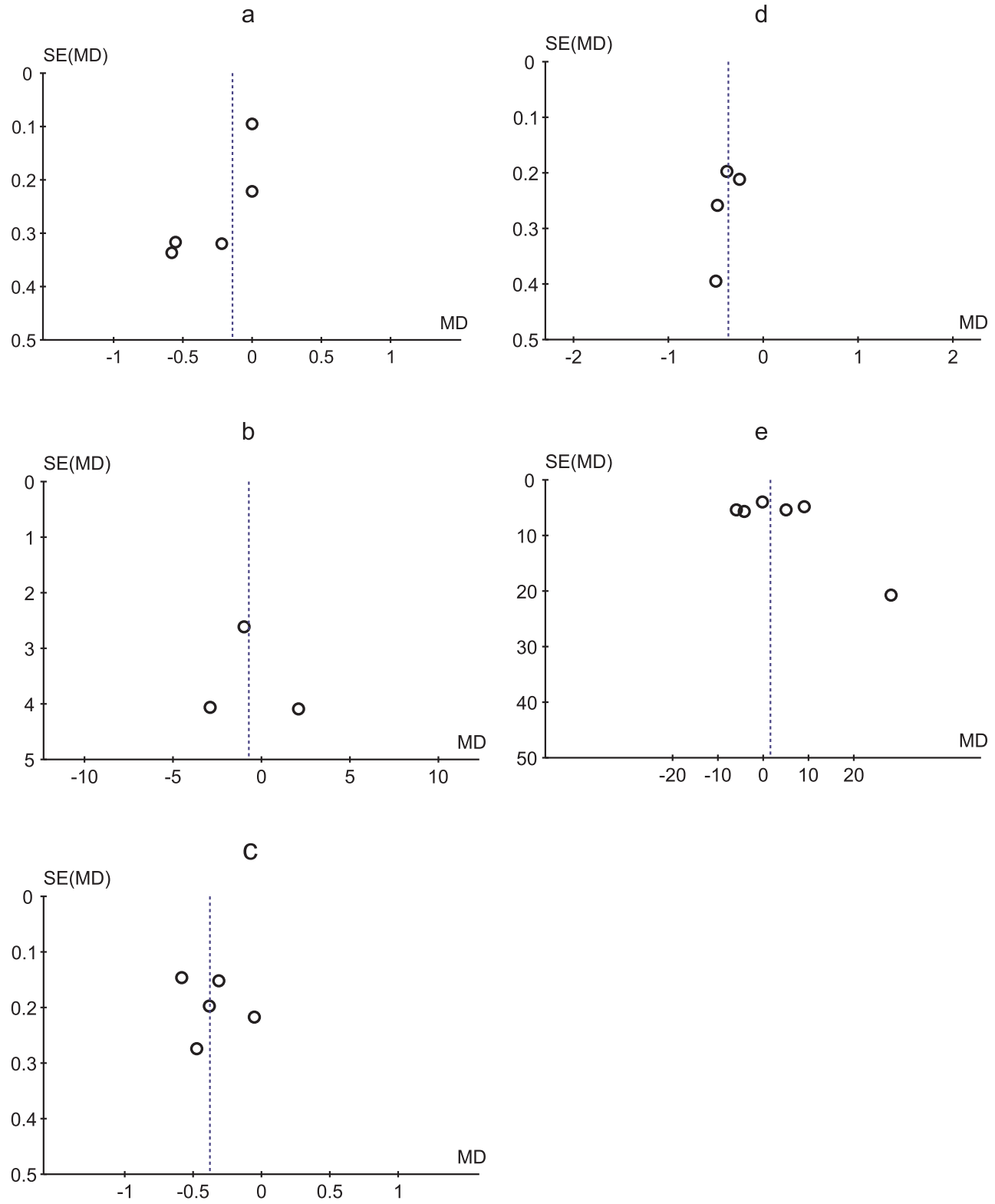

Fig. 4. Funnel plots.
a: upper gastrointestinal symptoms (gastrointestinal symptom rating scale), b: quality of life, c: upper gastrointestinal symptoms (5-point scale), d: appetite (5-point scale), e: serum acylated ghrelin (fmol/mL).

recent studies, but only 5 studies with a combined total of 274 participants were included in the meta-analysis (Fig. 3). Rikkunshito might have shown a tendency to improve the symptoms, but the efficacy remains unclear because of the small number of studies included. There is currently no standard scale to assess gastrointestinal symptoms, and thus it would be advantageous to use several scales in each study to evaluate upper gastrointestinal symptoms because subjective symptoms are difficult to score accurately. Moreover, it may be helpful to use a common scale across studies for a future meta-analysis to enable an accurate investigation into the effects of rikkunshito. Also, adverse

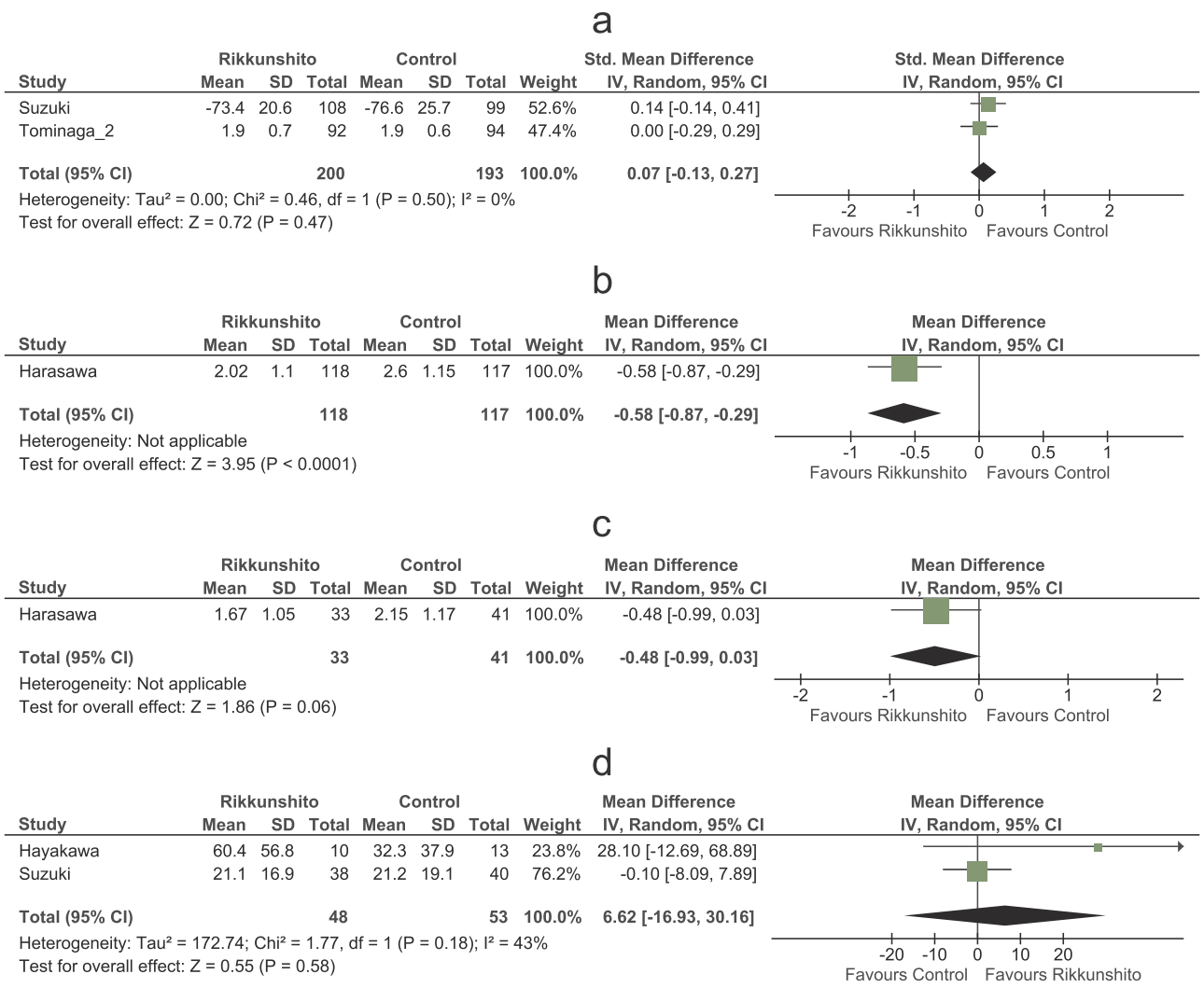

Fig. 5. Sensitivity analysis.
a: upper gastrointestinal symptoms (gastrointestinal symptom rating scale), b: upper gastrointestinal symptoms (5-point scale), c: appetite (5-point scale), d: serum acylated ghrelin (fmol/mL).

events were reported using various scales but there were few events in each study, so we considered that these events are rare.

Recent reports suggested that rikkunshito could relieve upper gastrointestinal symptoms by stimulating the secretion of ghrelin.[5,7] However, in this meta-analysis, it was unclear whether rikkunshito could enhance the secretion of acylated ghrelin (Fig. 3).

Many diseases are accompanied by persistent upper gastrointestinal symptoms including postgastrectomy syndrome, persistent GERD, and functional dyspepsia.[1,2] Moreover, various drugs can cause upper gastrointestinal discomfort.[3,4] Persistent upper gastrointestinal symptoms can reduce the QOL in chronic conditions and might cause treatment cessation in chemotherapy, which could lead to cancer progression. In this meta-analysis, rikkunshito tended to relieve the symptoms. However, there is room for further analysis because of the insufficient number or low quality of the studies included.

5. Strengths and limitations

The strengths of this review include a search of the literature without language restriction, which could reduce publication bias.[10] However, this review has some limitations. Various conditions that result in upper gastrointestinal symptoms were included in the meta-analysis and there may be clinical heterogeneity among the studies. Several types of comparator drugs were included in the meta-analysis, which may also lead to heterogeneity. In addition, it was impossible to combine the data of several studies because the mean with SD were not obtained or estimated. Also, publication bias was not fully assessed because of the small number of included studies.

This systematic review included many studies of high risk of bias. This might weaken the robustness of the result of meta-analysis. The main reasons for high risk of bias in the included studies were lack of blinding of participants and personnel (performance bias), lack of blinding of outcome assessment (detection bias), and incomplete outcome data (attrition bias) (Fig. 2). For future trials, researchers should protect blinding and avoid missing participants to improve the study quality.

6. Conclusion

Low-quality evidence suggests that the efficacy of rikkunshito on gastrointestinal symptoms remains uncertain. Further high-quality studies are needed for a more accurate evaluation.

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Declarations of interest

None.

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