Evidence Reports of Kampo Treatment (EKAT)

Appendix 2018

漢方治療エビデンスレポート(EKAT) Appendix 2018

1 June 2020

Task Force for Evidence Report (ER -TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

ver.1.0 1 June 2020

History of version upgrades

1 Jun. 2020: Kampo Chiryo Ebidensu Repoto Appendix 2018 (Evidence Reports of Kampo Treatment Appendix 2018)
18 May 2020: Kampo Chiryo Ebidensu Repoto Appendix 2017 (Evidence Reports of Kampo Treatment Appendix 2017)
1 Nov. 2018: Kampo Chiryo Ebidensu Repoto 2016 (Evidence Reports of Kampo Treatment 2016)
31 Mar. 2017: Kampo Chiryo Ebidensu Repoto Appendix 2015 (Evidence Reports of Kampo Treatment Appendix 2015)
6 Jun. 2015: Kampo Chiryo Ebidensu Repoto Appendix 2014 (Evidence Reports of Kampo Treatment Appendix 2014)
31 Dec. 2013: Kampo Chiryo Ebidensu Repoto 2013 - 402 no RCT (Evidence Reports of Kampo Treatment 2013: 402 Randomized Controlled Trials)
31 Dec. 2012: Kampo Chiryo Ebidensu Repoto Appendix 2012 (Evidence Reports of Kampo Treatment Appendix 2012)
1 Oct. 2011: Kampo Chiryo Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)
1 Jun. 2010: Kampo Chiryo Ebidensu Repoto 2010 - 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)
1 Jun. 2009: Kampo Chiryo Ebidensu Repoto 2009 - 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)
1 Apr. 2008: Kampo Chiryo Ebidensu Repoto Dai 2-han - RCT wo Shu ni Shite- Chukan Hokoku 2007 ver 1.1 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007 ver.1.1)
15 Jun. 2007: Kampo Chiryo Ebidensu Repoto Dai 2-han - RCT wo Shu ni Shite- Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007)
20 Jul. 2005: Kampo Chiryo niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (Nihon Toyo Igaku Zasshi [Kampo Medicine] 2005: 56, EBM supplementary issue)
20 Sept. 2002: Kampo Chiryo niokeru EBM - 2002 nen Chukan Hokoku (EBM in Kampo 2002, Interim Report) (Nihon Toyo Igaku Zasshi [Japanese Journal of Oriental Medicine] 2002: 53 [5], supplementary issue)

version/date	Title	Year of publication of target references	No. of references	No. of structured abstracts (SAs)	No. of excluded references
2020.6.1	Evidence Reports of Kampo Treatment Appendix 2018 (EKAT Appendix 2018)	From EKAT 2017 2017	594 [2]	493 [1), 2)]	203 [2]
2020.5.18	Evidence Reports of Kampo Treatment Appendix 2017 (EKAT Appendix 2017)	From EKAT 2016 2016	578 [3]	478 [1), 3)]	188 [3]
2018.11.1	Evidence Reports of Kampo Treatment 2016:467 Randomized Controlled Trials (EKAT 2016)	1986-2015	567	467 [1]	181
2017.3.31	Evidence Reports of Kampo Treatment Appendix 2015(EKAT Appendix 2015)	From EKAT 2014 2014	545 [4]	447 [1), 4)]	177 [4]
2015.6.6	Evidence Reports of Kampo Treatment Appendix 2014 (EKAT Appendix 2014)	From EKAT 2013 2013 (First half)	513 [5]	418 [1), 5)]	167 [5]
2013.12.31	Evidence Reports of Kampo Treatment 2013:402 Randomized Controlled Trials (EKAT 2013)	1986-2012 (First half)	494	403 [1),	159
2012.12.31	Evidence Reports of Kampo Treatment Appendix 2012 (EKAT Appendix 2012)	From EKAT 2011 2011 (First half)	457 [6]	379 [1), 6)]	150 [6]
2011.10.1	Evidence Reports of Kampo Treatment Appendix 2011 (EKAT Appendix 2011)	From EKAT 2010 2010 (First half)	432 [7]	360 [1), 7)]	-
2010.6.1	Evidence Reports of Kampo Treatment 2010:345 Randomized Controlled Trials (EKAT 2010)	1986-2009 (First half)	416	346 [1]	132
2009.6.1	Evidence Reports of Kampo Treatment 2009:320 Randomized Controlled Trials (EKAT 2009)	1986-2008 (First half)	385	321 [1]	111
2008.4.1	Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007 ver.1.1	1999-2005	116	98	32

2007.6.15	Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007	1999-2005	104	102	42

[1)] Including 1 meta-analysis
[2)] Total of all references added or removed in EKAT 2016, EKAT Appendix 2017 and EKAT Appendix 2018
[3)] Total of all references added or removed in EKAT 2016, EKAT Appendix 2017
[4)] Total of all references added or removed in EKAT 2013, EKAT Appendix 2014 and EKAT Appendix 2015
[5)] Total of all references added or removed in EKAT 2013, EKAT Appendix 2014.
[6)] Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012.
[7)] Total of all references added in EKAT 2010 and EKAT Appendix 2011.

Notes on the current version

The Task Force for Evidence Reports (ER-TF) of the Committee for Evidence-based Medicine (EBM), Japan Society for Oriental Medicine (JSOM), comprehensively gathers data obtained in randomized controlled trials (RCTs) of Kampo formulations in Japan, compiles structured abstracts (SAs), and then publishes them on the website of the Committee for Evidence-based Medicine as Evidence Reports of Kampo Treatment (EKAT). It has been doing this since 2007.

As indicated in the "History of version upgrades" on the previous page, the “Evidence Reports of Kampo Treatment 2016 - 467 RCTs” (EKAT 2016) was published on November 1, 2018. The EKAT 2016 presented the results of 465 RCTs and 2 meta-analyses performed between 1986, when the current quality specifications for Kampo formulations for medical use were established, and 2015. On May 18, 2020, EKAT Appendix 2017 was published and additionally contained only SAs of RCT reports published approximately one year after the publication of EKAT 2016.

EKAT Appendix 2018 contains SAs (12 RCTs and 2 meta-analyses) of 14 of the RCT reports published within approximately one year after the publication of EKAT Appendix 2018. Even though the ER-TF website has not been updated since the publication of the EKAT 2016, the Google search engine available on the website allows users to access all SAs in EKAT 2016, EKAT Appendix 2017, and EKAT Appendix 2018.

And, in the conventional EKAT SA, one International Classification of Diseases (ICD-10) code was assigned to each RCT report. However, the classification did not always match the imagined codes of the users, and multiple ICD-10 subcodes were provided in order to make it easier for the users to find RCT reports dealing with the disease area they wanted. At the time of full EKAT revision, it is expected that RCT reports will be reproduced in multiple disease areas.

The ER-TF carried out a search for RCT reports for the present EKAT in April 2018, to prepare SAs of RCT reports published in most medical journals in 2017. Although publication of EKAT 2018 was planned in 2018, it was actually published in 2020 due to a delay in the publication of EKAT 2016. However, it is expected that the ER-TF will carry out its search for RCT reports in April of each year and publish the EKAT within the fiscal year going forward.

In the next revision, the ER-TF will carry out a full revision of the EKAT, including the website.

The Japan Society for Oriental Medicine (JSOM)

Fifth Phase (September 2015 – June 2018)
Committee for Evidence-based Medicine (EBM)
Task Force for Evidence Reports (ER-TF)

(Affiliations of the EBM Committee members of fiscal year of 2018 may be different from those of the current members.)

Chair and chairperson of Committee for EBM:

Yoshiharu MOTOO Department of Medical Oncology, Kanazawa Medical University

Members (10 persons, order of the Japanese syllabary):

Ichiro ARAI Department of Pharmaceutical Sciences, Nihon Pharmaceutical University Field of herbal pharmacology

Yasuhito KATO, Department of Obstetrics and Gynecology, Asahikawa Medical University

Masamichi KITAGAWA, Academic Information Center, The Jikei University School of Medicine.

Hiroshi KOIKE Department of General Internal Medicine, Tokyo Saiseikai Central Hospital

Toshiaki KOGURE Department of Japanese Oriental Medicine, Gunma Central Hospital

Hirozo GOTO Department of Kampo Medicine, Hokusei Hospital

Hiroki TAKUMA Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba

Hideyuki NAKATA Kampo Internal Medicine/ Health Medical Center, Nerima General Hospital

Etsuo HOSHINO General Incorporated Foundation Kukai Memorial Integrated Medicine Foundation Kukai Memorial Integrated Medicine Clinic

Miyuki MINARI Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association

Observer of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (trustee in charge of Committee for EBM, JSOM)

Lists of Structured Abstracts
(structured abstract and included references list)

Abbreviations: C, The Cochrane Library (CENTRAL); I, Igaku Chuo Zasshi (Japana Centra Revuo Medicana, Ichushi); N, Hand searching Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
A49.3 J20.0	To evaluate the efficacy of bakumondoto (麦門冬湯) for coughing associated with mycoplasma bronchitis	bakumondoto (麦門冬湯)	Watanabe N, Makino S, Nakagawa T, et al. A study on the efficacy of bakumondoto for coughing associated with mycoplasma infections. *Science of Kampo Medicine* 2017; 41:116-8 (in Japanese).	RCT-envelope	I	9
C15.9	To evaluate the efficacy of daikenchuto (大建中湯) for postoperative recovery in patients with esophageal carcinoma	daikenchuto (大建中湯)	Nishino T, Yoshida T, Goto M, et al. The effects of the herbal medicine daikenchuto (TJ-100) after esophageal cancer resection, open-label, randomized controlled trial. *Esophagus* 2018; 15: 75-82.	RCT	C	10
C57.7 R11.0	To evaluate the efficacy and safety of rikkunshito (六君子湯) added to antiemetics for nausea, vomiting, and anorexia in patients treated with cisplatin and paclitaxel for cervical and endometrial cancers	rikkunshito (六君子湯)	Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02) . *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28. e44	RCT	C	11
C61 N42.8	To evaluate the efficacy and safety of Kampo medicines (hochuekkito [補中益気湯] and keishibukuryogan [桂枝茯苓丸]) for enhancing the immune response to tailor-made cancer peptide vaccine therapy (PPV) in men with castration-resistant prostate cancer (CRPC)	hochuekkito (補中益気湯) + keishibukuryogan (桂枝茯苓丸)	Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32.	RCT	N	12
C80.0 F05.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for postoperative delirium in patients with gastrointestinal and lung cancers	yokukansan (抑肝散)	Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncology* 2017; 7: 569-73.	RCT	C&N	13
G20.0	To evaluate the efficacy and safety of rikkunshito (六君子湯) for anorexia and indigestion in patients with Parkinson's disease	rikkunshito (六君子湯)	Yakabi K, Yamaguchi N, Ono S, et al. Open label trial of the efficacy and safety profile of rikkunshito used for the treatment of gastrointestinal symptoms in patients with Parkinson's disease: a pilot study. *Current Therapeutic Research* 2017; 87: 1-8.	RCT-cross over	N	14

G30.1	To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia due to Alzheimer's disease	yokukansan (抑肝散)	Furukawa, K, Tomita N, Une K, et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. *Geriatrics and Gerontology International* 2017; 17: 211-8.	DB-RCT	C	15
G81.9	To evaluate the efficacy and safety of hochuekkito (補中益気湯) for decreased ADL, nutrition, and immune state in patients with hemiplegia due to sequelae of cerebrovascular disorders who are undergoing rehabilitation	hochuekkito (補中益気湯)	Fukumura N, Yamamoto H, Kitahara M, et al. Hochuekkito suppresses the incidence of inflammatory complications in patients with sequelae of cerebrovascular disorders in the convalescent rehabilitation ward – Study in a multicenter randomized controlled trial. *Japanese Journal of Rehabilitation Medicine* 2017; 54: 303-14 (in Japanese).	RCT	I	16
K30	To evaluate the efficacy and safety of rikkunshito (六君子湯) in patients with functional dyspepsia	rikkunshito (六君子湯)	Tominaga K, Sakata Y, Kusunoki H, et al. Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study). *Neurogastroenterology and Motility* 2018; 1-12. doi: 10.1111/nmo.13319	DB-RCT	N	17
K76.9 Z94.4	To evaluate the efficacy and safety of daikenchuto (大建中湯) on the reinforcing effect of oral/tubal caloric intake in patients undergoing liver transplantation	daikenchuto (大建中湯)	Kaido T, Shinoda M, Inomata Y, et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: a multicenter, randomized controlled trial. *Nutrition* 2018; 54: 68-75.	DB-RCT	N	18
K91.0	To evaluate the efficacy and safety of goreisan (五苓散) for nausea and vomiting after gynecological surgery under general anesthesia	goreisan (五苓散)	Kume K, Kasuya Y, Ozaki M. Effect of Goreisan, a traditional Japanese Kampo medicine, on postoperative nausea and vomiting in gynecological patients. *JA Clinical Reports* 2017; 3: 52: 1-6. doi: 10.1186/s40981-017-0122-5	DB-RCT	N	19
L50.8	To evaluate the efficacy of jumihaidokuto (十味敗毒湯) in urticaria	jumihaidokuto (十味敗毒湯)	Murota H, Azukizawa H, Katayama I. Impact of jumihaidokuto (shi-wei-bai-du-tang) on treatment of chronic spontaneous urticaria: a randomized controlled study. *Chinese Journal of Integrative Medicine* 2017; 1-5. doi: 10.1007/s11655-017-2950-6 (2019; 11: 820-4.)	RCT	C	20
Z03.8	To evaluate the efficacy of intraduodenal administration of shakuyakukanzoto (芍薬甘草湯) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography (ERCP)	shakuyakukanzoto (芍薬甘草湯)	Fujinami H, Kajiura S, Nishikawa J, et al. The influence of duodenally-delivered Shakuyakukanzoto (Shao Yao Gan Cao Tang) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography: a randomised controlled trial. *Chinese Medicine* 2017; 12: 3: 1-6. doi: 10.1186/s13020-016-0125-6	RCT	N	21

[Meta-analyses]

C78.8 K91.3	A meta-analysis of to evaluate the efficacy of perioperative daikenchuto (DKT)(大建中湯) treatment for postoperative bowel obstruction (postoperative ileus) in gastrointestinal cancer	daikenchuto (大建中湯)	Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74.	meta-analysis	N	22
C80.0	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in peripheral neuropathy during chemotherapy	goshajinkigan (牛車腎気丸)	Hoshino N, Ganeko R, Hida K, et al. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *International Journal of Clinical Oncology* 2018; 23: 434–42.	meta-analysis	N	23

[Revisions of Already Included References]

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
H66.9	To evaluate the efficacy and safety of juzentaihoto (十全大補湯) in children with recurrent otitis media	juzentaihoto (十全大補湯)	Yoshizaki T. A multicenter, double-blind, randomized controlled trial on the usefulness of juzentaihoto in children with recurrent otitis media* (2009—clinical study—general—007) *Chozai to Joho (Dispensing and Information) Health Labour Sciences Research Grant, General Research Program for Practical Application of Medical Technology*, fiscal year of 2009, General Research Report in fiscal year of 2011. 2012: 1-23 (in Japanese)	RCT	N	24
			Ito M, Maruyama Y, Kitamura K, et al. Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media *Auris Nasus Larynx* 2017; 44: 390-7.		I	

1. Infections (including Viral Hepatitis)
10. Respiratory Diseases (including Influenza and Rhinitis)

References

Watanabe N, Makino S, Nakagawa T, et al. Efficacy of bakumondoto on cough in mycoplasma infection. *Science of Kampo Medicine* 2017; 41: 116-8. Ichushi Web ID: 2017285714

1. Objectives

To evaluate the efficacy of bakumondoto（麦門冬湯）on cough in mycoplasma bronchitis

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

Study sites not stated (authors' institutions: a research center and clinics), Japan.

4. Participants

Twenty-four patients who presented with persistent cough, who underwent chest X-ray that excluded pneumonia findings such as ground-glass opacity, and who had an increased mycoplasma antibody titer (PA method) of 1:80 or above and thus were clinically considered as having mycoplasma bronchitis, and were started on treatment with azithromycin hydrate 500 mg once daily for 3 days.

5. Intervention

Arm 1: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g t.i.d. for 2 weeks (n=7)
Arm 2: oral administration of tipepidine hibenzate 20 mg t.i.d. for 2 weeks (n=9)
Arm 3: oral administration of TSUMURA Bakumondoto（麦門冬湯）Extract Granules 3 g plus tipepidine hibenzate 20 mg, t.i.d. for 2 weeks (n=8)

6. Main outcome measures

Change in the cough score

7. Main results

The cough score significantly decreased on day 4 in the bakumondoto group, on day 7 in the tipepidine hibenzate group, and on day 4 in the bakumondoto + tipepidine hibenzate group (P<0.05 for all).

8. Conclusion

Add-on use of bakumondoto to a macrolide antimicrobial agent is effective for cough in mycoplasma bronchitis. In particular, combination use of bakumondoto plus a central antitussive agent more promptly alleviates cough in mycoplasma infection.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

This is a meaningful article on evaluation of the effect of bakumondoto on persistent cough as a common complaint in the context of mycoplasma infection. Drawbacks include lack of statement about the specific scale used for the cough scoring, which makes the symptomatic course assessments difficult. In addition, because of lack of intergroup comparison, assessment of the effect of the intervention with bakumondoto is also difficult. A question also remains whether mycoplasma infection can be diagnosed only from a mycoplasma PA antibody titer in single serum of 1:80 or above (rather than 1:320 or above) without a paired serum and without chest X-ray opacity. The authors concluded that combination use of bakumondoto plus a central antitussive agent is useful, but did not specify how the results led to this conclusion. Efficacy of bakumondoto on cough is generally discussed, but has rarely been investigated by RCTs, and such studies are meaningful. Future studies designed to compare symptomatic changes between treatment arms are awaited. Also, while determination of causative bacteria is often difficult in clinical practice, further studies with determination of causative organisms or evolutionary studies without determination of causative organisms would be warranted.

12. Abstractor and date

Koike H, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Nishino T, Yoshida T, Goto M, et al. The effects of the herbal medicine Daikenchuto (TJ-100) after esophageal cancer resection, open-label, randomized controlled trial. *Esophagus* 2018; 15: 75-82. CENTRAL ID: CN-01440554, Pubmed ID: 29892933

1. Objectives

To evaluate the efficacy of daikenchuto（大建中湯）for postoperative recovery of patients with esophageal cancer

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

One university hospital (department of surgery), Japan

4. Participants

Forty patients with esophageal cancer undergoing transthoracoabdominal subtotal esophagectomy with stomach tube reconstruction

5. Intervention

Arm 1: TSUMURA Daikenchuto（大建中湯）Extract Granules 15.0 g/day (5.0 g t.i.d.) via a tube from the day of surgery (postoperatively) to the 21st day (n=20)

Arm 2: no administration of daikenchuto (n=20)

6. Main outcome measures

Primary endpoints: nutritional condition (body weight and serum albumin), postoperative recovery of gastrointestinal function (number of days until the first flatus/defecation, number of days until becoming able to eat meals of 800 kcal/day).

Secondary endpoints: C-reactive protein (CRP), plasma adrenomedullin (ADM), incidence of postoperative complications, length of hospital stay after surgery

7. Main results

One patient in Arm 1 was found to have unresectable cancer, and thus was excluded. Thus, the analysis was conducted on 19 patients in Arm 1 and 20 patients in Arm 2. Change in body weight showed intergroup differences from postoperative day 3, with significantly greater body weight in Arm 1 than in Arm 2 at postoperative day 21 (P=0.014). No significant intergroup differences were shown for serum albumin, serum CRP, plasma ADM, incidence of postoperative complications, parameters of the postoperative recovery of gastrointestinal function, or length of hospital stay after surgery.

8. Conclusion

Postoperative tubal administration of daikenchuto suppresses body weight decrease after subtotal esophagectomy in patients with esophageal cancer.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

The Methods section of the article states that adverse events were evaluated using the CTCAE ver. 3.0. However, the Results section does not include safety data.

11. Abstractor's comments

While daikenchuto has been used for ileus prevention or recovery of gastrointestinal function after surgery for colorectal cancer, gastric cancer, hepatocellular carcinoma, etc., this is the first report to evaluate the efficacy of daikenchuto after highly invasive surgery for esophageal cancer. A groundbreaking finding of this study is that the postoperative body weight change showed an intergroup difference from postoperative day 3, and body weight at postoperative day 21 was significantly greater in the daikenchuto arm than in the control arm. However, other endpoints showed no significant differences. CRP tended to be lower and ADM tended to be higher in the daikenchuto arm compared with the control group, suggesting the anti-inflammatory effect of daikenchuto. Further studies with increased sample sizes may yield significant differences. While daikenchuto can promote movement of the contents of the large intestine or a duodenal pouch, in the setting of post-subtotal esophagectomy, as reported in this article, our concern is the effect of daikenchuto on the residual esophagus and reconstructed stomach tube. Although the authors focused mainly on anti-inflammatory effect, further studies are awaited to characterize involvement of other factors such as gastrointestinal transit or increase in gastrointestinal blood flow.

12. Abstractor and date

Motoo Y, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
18. Symptoms and Signs

References

Ohnishi S, Watari H, Sakuragi N, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02). *Journal of Gynecologic Oncology* 2017; 28: 1-10. doi: 10.3802/jgo.2017.28. e44
CENTRAL ID: CN-01403248, Pubmed ID: 28657216

1. Objectives

To evaluate the efficacy and safety of add-on rikkunshito（六君子湯）to antiemetics for nausea, vomiting, and anorexia in patients receiving cisplatin plus paclitaxel for uterine cervical or corpus cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Four institutions, Japan

4. Participants

Forty patients aged 20 years or older, with histologically diagnosed uterine cervical or corpus cancer, and with an ECOG Performance Status score of 0 to 2.

Patients were excluded if they had brain metastasis, seizure, unconsciousness, gastrointestinal obstruction, vomiting, or nausea of CTCAE (version 4.0) grade ≥3, or had received treatment within one month with steroids, androgens, progesterones, other herbal medicines, other medicines with the potential to increase appetite, or opioids.

Efficacy was analyzed in 19 patients in the rikkunshito group and 17 patients in the control group. Safety was analyzed in 20 patients in the rikkunshito group and 19 patients in the control group.

5. Intervention

Arm 1: oral administration of rikkunshito（六君子湯）(manufacturer unknown) 7.5 g (on days 0-13) plus antiemetics (n=20)
Arm 2: administration of antiemetics alone (n=20)

6. Main outcome measures

Nausea using a 100-mm visual analog scale (VAS) with 0–5 mm indicating “no nausea” and 5–25 mm indicating “no significant nausea”, the rate of complete control (CC) (i.e., no emesis, no rescue medication, and no significant nausea), and the rate of complete response (CR) (i.e., no emesis and no rescue medication) were assessed.

7. Main results

Two-tailed $P<0.20$ was considered significant. For the overall phase (0–120 hours), both the CC rate and the CR rate were significantly higher in the rikkunshito group ($P=0.175$ and $P=0.042$, respectively). When the overall phase was divided into acute (0–24 hours) and delayed (24–120 hours) phases, the CC and CR rates were similar between the two groups during the acute phase and significantly higher in the rikkunshito group during the delayed phase ($P=0.095$ for the CC rate, $P= 0.042$ for the CR rate). In terms of anorexia and nausea VAS scores, rikkunshito appeared to be effective from day 2 through day 6 (without significant difference), but no differences were shown between the groups from day 7 through day 13.

8. Conclusion

Rikkunshito provides an additive effect to antiemetic therapy for vomiting and anorexia.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

In the rikkunshito group, there was increased ALT in 2 patients (10.0%), increased AST in 1 patient (5.0%), and increased GGT in 1 patient (5.0%).

11. Abstractor’s comments

Severe gastrointestinal symptoms during chemotherapy may make chemotherapy completion difficult. In cancer therapy, whether chemotherapy is completed or not is important because it changes the prognosis. This study showed significant reductions of nausea and vomiting by add-on rikkunshito to antiemetics. Add-on use of rikkunshito is considered to be particularly effective in highly emetogenic anticancer drug therapy.

12. Abstractor and date

Nakata H, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
14. Genitourinary Tract Disorders (including Climacteric Disorders)

References
Koga N, Moriya F, Waki K, et al. Immunological efficacy of herbal medicines in prostate cancer patients treated by personalized peptide vaccine. *Cancer Science* 2017; 108: 2326-32. Pubmed ID: 28898532

1. Objectives
To evaluate the immune-enhancing efficacy and safety of Kampo medicines using hochuekkito（補中益気湯）and keishibukuryogan（桂枝茯苓丸)in combination with personalized cancer peptide vaccination (PPV) in patients with castration-resistant prostate cancer (CRPC)

2. Design
Randomized controlled trial (RCT)

3. Setting
One university hospital, Japan

4. Participants
Seventy patients with CRPC aged 20 years or older with a Performance Status score of 0 or 1 (ECOG).
Inclusion criteria: life expectancy of 12 weeks or more, HLA haplotype of A2, A24, A26, A3, A11, A31, or A33, and normal hepatorenal functions.
Exclusion criteria: acute infection, history of severe allergic reactions, cardiac or pulmonary insufficiency

5. Intervention
Arm 1: PPV (weekly 8 times) plus TSUMURA Hochuekkito（補中益気湯）Extract Granules 7.5 g/day and TSUMURA Keishibukuryogan（桂枝茯苓丸）Extract Granules 7.5 g/day (2.5 g t.i.d. administered orally before meals for 50 days) (n=31)
Arm 2: PPV alone (weekly 8 times) (n=35)

6. Main outcome measures
Primary endpoint: immune response to PPV.
Secondary endpoints: overall survival (OS), progression-free survival (PFS), and safety.

7. Main results
Four patients withdrew consent prior to treatment in Arm 1. Treatment was discontinued because of disease progression or death in 3 patients in Arm 1 and 4 patients in Arm 2. At the end of follow-up, 19 patients in Arm 1 (63%; median duration of follow-up 14.9 months) and 26 patients in Arm 2 (74%; 13.6 months) had disease progression or died. The OS and PFS did not differ significantly between the arms. The baseline and Week 8 cancer peptide-specific IgG, CTL, and regulatory T cells (Treg) did not significantly differ between the arms. Comparing before to after the treatment, the frequency of monocytic myeloid-derived suppressor cells (Mo-MDSC) (before-after: 1.91%–1.92%) and the IL-6 level (19.2 pg/mL–16.1 pg/mL) were stable in Arm 1 but significantly increased in Arm 2 (0.91%–1.49% for Mo-MDSC [P=0.012] and 9.2 pg/mL–19.4 pg/mL for IL-6[P=0.043]).

8. Conclusion
In CRPC patients, the use of herbal medicines of hochuekkito and keishibukuryogan during PPV treatment had no impact on clinical outcome but has the potential to modify the immune response to PPV.

9. From Kampo medicine perspective
None

10. Safety assessment in the article
No treatment-related deaths occurred in either arm. Adverse events such as injection site reactions did not differ between the two treatment arms. Appetite loss was less frequent in the PPV + herbal medicines arm than in the PPV alone arm.

11. Abstractor's comments
While cancer immunotherapies are entering a new phase, this pioneering study applied a novel immunotherapy with personalized cancer peptide vaccination (PPV) to patients with CRPC, and analyzed whether herbal medicines could modify the immune response to PPV. Since the RCT design was employed, the study yielded objective results, and was meaningful both basically and clinically. In Arm 1, the frequency of Mo-MDSC (%) and the IL-6 level were stable, suggesting the possibility that these herbal medications may prevent a decrease in the immune response to PPV, although clinical endpoints unfortunately failed to show significant differences. The results of this study are clinically interesting, considering that the authors previously reported significantly lower IL-6 levels in long-term survivors of prostate cancer. As the authors state that more research is needed, new results are awaited in the future.

12. Abstractor and date
Kogure T, 1 June 2020.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
5. Psychiatric/Behavioral Disorders

References

Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Molecular and Clinical Oncology*. 2017; 7: 569-73. CENTRAL ID: CN-01421749, Pubmed ID: 28855990

1. Objectives

To evaluate the efficacy and safety of yokukansan（抑肝散）for postoperative delirium in patients with gastrointestinal or lung cancer

2. Design

Randomized controlled trial (RCT)

3. Setting

Nine hospitals, including one university hospital, Japan

4. Participants

A total of 186 patients aged 70 years or older who underwent surgery for gastrointestinal or lung cancer with an Eastern Cooperative Oncology Group Performance Status score of 2 or less, who underwent a mini-mental state examination (MMSE), and who had normal hepatic, renal, and bone marrow functions. Patients were excluded if they had a history of severe hypersensitivity to drugs, had serious constipation, were pregnant, or were lactating.

5. Intervention

Arm 1: TSUMURA Yokukansan（抑肝散）Extract Granules 7.5 g/day (2.5 g t.i.d.) administered orally for 7 days preoperatively and 4 days postoperatively, excluding the operation day (n=93)

Arm 2: Control group (n=93)

6. Main outcome measures

Primary endpoints were the incidence of postoperative delirium and safety. Secondary endpoint was the length of hospital stay. Delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, independently by two physicians.

7. Main results

The incidence of delirium was 6.5% in Arm 1 (n=6) and 9.7% in Arm 2 (n=9), showing no significant difference between the two arms. A subgroup analysis showed that, among patients with MMSE scores of ≤26, the incidence of postoperative delirium was 9.1% in Arm 1 and 26.9% in Arm 2 (risk ratio, 0.338; 95% CI, 0.078–1.462, *P*=0.115). Among patients with MMSE scores of ≥27, the incidence of postoperative delirium was 6.8% in Arm 1 and 3.6% in Arm 2 (risk ratio, 1.864; 95% CI, 0.356–9.778, *P*=0.453). The length of hospital stay was 16 days in Arm 1 and 15 days in Arm 2, showing no difference between the arms.

8. Conclusion

In patients with MMSE scores of ≤26, yokukansan reduces the risk of delirium after surgery for gastrointestinal or lung cancer.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Occurrence of adverse reactions did not differ between the two arms. No adverse reactions appeared to be related to yokukansan.

11. Abstractor's comments

Postoperative delirium is an important postoperative management issue. With a focus on this, and using yokukansan, which has been widely used recently for delirium in patients with other behavioral and psychological symptoms of dementia (BPSD), the authors conducted this interesting clinical study evaluating the effects of yokukansan on postoperative delirium in patients with gastrointestinal or lung cancer. Analysis of the primary endpoint failed to show an intergroup difference, partly because the incidence of delirium in the control group was lower than expected, as stated by the authors in the Discussion section, for which further studies in larger samples would be needed. The subgroup analysis showed reduction in the risk of delirium after yokukansan administration in those with MMSE scores of ≤26. This indicates that yokukansan may be effective in suppressing delirium in patients with lower cognitive function. However, regarding those with MMSE scores ≥26, the article does not provide details such as the number of the patients. Furthermore, the article does not provide any basis for the MMSE cutoff score of 26, and therefore the efficacy may not be convincing. Given that this was a phase 2 study, a phase 3 clinical study based on these data is awaited to further clarify the disease conditions for which yokukansan is indicated.

12. Abstractor and date

Goto H, 1 June 2020.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Yakabi K, Yamaguchi N, Ono S, et al. Open label trial of the efficacy and safety profile of rikkunshito used for the treatment of gastrointestinal symptoms in patients with Parkinson's disease: a pilot study. *Current Therapeutic Research* 2017; 87: 1-8. Pubmed ID: 28912900

1. Objectives

To evaluate the efficacy and safety of rikkunshito（六君子湯）for anorexia and dyspepsia in patients with Parkinson’s disease

2. Design

Randomized controlled trial (cross over) (RCT- cross over)

3. Setting

One university hospital, Japan

4. Participants

Fourteen patients with Parkinson’s disease aged between ≥20 and ≤85 years, with Hoehn-Yahr stage I to III, and symptoms of anorexia or dyspepsia

Exclusion criteria were intolerance to oral administration of medication, use of drugs that could not be used concomitantly with rikkunshito, current presence of cardiac, hepatic, renal, or hematological disease or malignancy, and history of allergy to Kampo medicines.

5. Intervention

Arm 1: TSUMURA Rikkunshito（六君子湯）Extract Granules 7.5 g/day administered orally (2.5 g t.i.d. 4-week treatment, followed by 4-week off treatment) (n=7)

Arm 2: TSUMURA Rikkunshito（六君子湯）Extract Granules 7.5 g/day administered orally (2.5 g t.i.d. 4-week off treatment, followed by 4-week treatment) (n=7)

6. Main outcome measures

Primary endpoint was the change in appetite score on a 100-mm visual analog scale (VAS). Secondary endpoints were the changes in gastric emptying, plasma acylated ghrelin level, depression as assessed using the self-rating depression scale (SDS), and gastrointestinal quality of life (QOL) as assessed using the Gastrointestinal Symptom Rating Scale (GSRS).

7. Main results

Rikkunshito treatment produced a significant increase in the appetite VAS score (1.84 [2.34]), compared to a decrease in the score over the off-treatment period (−1.36 [2.94]) (P=0.041). The SDS score significantly decreased with rikkunshito treatment (P=0.026). No effects of rikkunshito were determined on the GSRS score, plasma acylated ghrelin level, or gastric emptying.

8. Conclusion

Rikkunshito may improve anorexia in patients with Parkinson’s disease.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Throughout the study period, no adverse events or abnormal changes were identified with rikkunshito treatment.

11. Abstractor’s comments

Rikkunshito is known to be effective for gastrointestinal symptoms (anorexia and dyspepsia). Since gastroparesis and constipation commonly occur in patients with Parkinson’s disease, this report indicating improvement of anorexia by rikkunshito in Parkinson’s disease patients is important. In addition, the study suggested that the positive effects of rikkunshito on depression and anorexia in Parkinson’s disease patients may improve their QOL. However, as stated by the authors, the sample size in each arm was limited and did not permit multiple comparisons. Validation of the results using a randomized, double-blind, controlled trial in a larger sample size is awaited.

12. Abstractor and date

Kato Y, 1 June 2020.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Furukawa, K, Tomita N, Une K, et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. *Geriatrics and Gerontology International* 2017; 17: 211-8. CENTRAL ID: CN-01337019, Pubmed ID: 26711658, J-STAGE

1. Objectives

To evaluate the efficacy and safety of yokukansan（抑肝散） for behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Twenty-two sites (clinics, hospitals, and nursing homes), Japan

4. Participants

A total of 145 patients with probable Alzheimer's disease, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Main inclusion criteria were age 55–84 years, total score of greater than 4 on the Neuropsychiatric Inventory Brief Questionnaire (NPI-Q), the sum of the NPI-Q subcategory scores for "agitation/aggression" and "irritability/lability" greater than 2, and the Mini-Mental State Examination (MMSE) score within the range of 10–26. Patients were excluded if they had cerebral infarction possibly affecting cognitive function, or they had depression, bipolar disorder, malignant tumor, or other life-threatening disease within the previous 2 years. Patients were also excluded if they had received typical or atypical neuroleptics, tricyclic or tetracyclic antidepressants, or Kampo medicines other than yokukansan.

5. Intervention

Arm 1: TSUMURA Yokukansan（抑肝散）Extract Granules 7.5 g/day (2.5 g t.i.d.) administered orally for 12 weeks (n=75)

Arm 2: Matching placebo (3 times daily) administered orally for 12 weeks (n=70)

The first 4 weeks of the treatment were double-blinded for comparison of the effects, and the following 8 weeks were non-double-blinded for safety assessment.

6. Main outcome measures

The primary outcome measure was the 4-week change in the NPI-Q total score. The secondary outcome measures were 12-week changes in NPI-Q total score, NPI-Q subcategory scores, MMSE total score, rescue drug dose, and safety.

7. Main results

The 4-week change in NPI-Q total score, which was the primary outcome measure, and the changes in NPI-Q subcategory scores did not differ significantly between the two arms. The NPI-Q total score significantly decreased from baseline at Week 4 in both arms (P <0.001 for both). Among the secondary outcome measures, the 12-week changes in NPI-Q total score and MMSE total score did not differ between the arms. However, a subgroup analysis showed that the agitation/aggression score significantly decreased after 4 weeks of treatment in Arm 1 compared with Arm 2 among patients with baseline MMSE <20 and patients aged ≤74 years (P =0.007 and P =0.049, respectively). Also, among patients with hallucinations at baseline, NPI-Q total score significantly decreased in Arm 1 compared with Arm 2 (P =0.019).

8. Conclusion

Yokukansan improves symptoms including agitation/aggression and hallucinations with low frequencies of adverse reactions.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Hypokalemia was observed in 4 of the 72 patients in the yokukansan group. However, there were no significant differences between the two arms.

11. Abstractor's comments

This is a valuable clinical study that evaluated the efficacy and safety of yokukansan for BPSD in Alzheimer's disease, conducted as a multicenter, double-blind, randomized, controlled trial. Although primary and secondary outcome measures did not demonstrate efficacy of yokukansan, the subgroup analysis revealed some significant findings. Further clinical studies based on these findings are awaited, to further clarify the disease conditions for which yokukansan is indicated.

12. Abstractor and date

Goto H, 1 June 2020.

6. Nervous System Diseases (including Alzheimer's Disease)

References

Fukumura N, Yamamoto H, Kitahara M, et al. Hochuekkito reduced the incidence of inflammatory complications in patients with sequelae of cerebrovascular disease in convalescent rehabilitation wards: a randomized multicenter study. *Japanese Journal of Rehabilitation Medicine* 2017; 54: 303-14. Ichushi Web ID: 2017298884

1. Objectives

To evaluate the efficacy and safety of hochuekkito（補中益気湯）to address reduced activities of daily living (ADL), nutritional status, and immunity in patients undergoing rehabilitation for hemiplegia as a sequela of cerebrovascular disease

2. Design

Randomized controlled trial (RCT)

3. Setting

Four hospitals (departments of rehabilitation)

4. Participants

Thirty-one patients with hemiplegia as a sequela of cerebrovascular disease who were treated between April 2013 and March 2015. Participants had to be 50 years of age, have started their recovery period in a rehabilitation setting within the past 1 week, have a Functional Independence Measure (FIM) total score of ≤40, and be able to orally take medication. Patients were excluded if they had insufficient nutritional intake (<1200 kcal/day), blood C-reactive protein (CRP) ≥10 mg/dL, Physical Disability Certificate Grade ≥2 or Long-term Care Requirement Level ≥3 since before the onset of cerebrovascular disease, taken any Kampo medicine within 4 weeks before participation in this study, had any hepatic, renal, cardiac, hematologic, or metabolic disease that was considered serious, or other conditions not suitable for this study in the opinion of the investigator.

5. Intervention

Arm 1: oral administration of TSUMURA Hochuekkito（補中益気湯）Extract Granules 7.5 g/day (in 2 or 3 divided doses) for 24 weeks, starting at the initiation of rehabilitation (n=11)

Arm 2: no administration of hochuekkito (n=17)

6. Main outcome measures

Primary endpoints were FIM total score, FIM motor subscale score, and FIM cognitive subscale score, and these scores upon admission were compared with those at discharge. Secondary endpoints were albumin, body weight, Body Mass Index (BMI), % ideal body weight, total lymphocyte count, hemoglobin, CRP, and incidence of inflammatory complications.

7. Main results

The analysis excluded 3 patients who did not fulfill the inclusion criteria. The FIM total score significantly improved in both arms (P<0.001), without significant difference between the arms. Albumin significantly increased in both arms (P<0.001 for Arm 1, P=0.01 for Arm 2). CRP significantly decreased after the treatment only in Arm 1 (P=0.04). Other endpoints showed no significant differences. Among the patients with an FIM motor subscale score of ≤20, the total lymphocyte count tended to increase in Arm 1 compared with Arm 2. The incidence of inflammatory complications was 9.1% in Arm 1 and 41.2% in Arm 2, and significantly lower in Arm 1 (P=0.049).

8. Conclusion

Oral administration of hochuekkito was not shown to improve ADL in patients with hemiplegia as a sequela of cerebrovascular disease. Oral administration of hochuekkito significantly reduces occurrence of inflammatory complications.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Adverse events occurred in 5 patients (8 events) in Arm 1 and 10 patients (14 events) in Arm 2. No adverse reactions to hochuekkito were noted.

11. Abstractor's comments

This article reports an interesting clinical study that evaluated the efficacy and safety of hochuekkito in patients with severe sequelae of cerebral infarction who started their recovery period in a rehabilitation setting. No ADL-improving effects were shown, possibly because of the limited sample size. However, an exploratory analysis showed a significantly reduced incidence of inflammatory complications in the hochuekkito group. Future clinical studies are awaited that have larger sample sizes to re-evaluate the presence or absence of the ADL-improving effect of hochuekkito in the setting of rehabilitation, or that are designed to test new hypotheses, for example using prevention of inflammatory diseases as a primary endpoint.

12. Abstractor and date

Koike H, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Tominaga K, Sakata Y, Kusunoki H, et al. Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study). *Neurogastroenterology and Motility* 2018; 1-12. doi: 10.1111/nmo.13319 Pubmed ID: 29498457

1. Objectives

To evaluate the efficacy and safety of rikkunshito（六君子湯）in patients with functional dyspepsia

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Fifty-six hospitals, Japan

4. Participants

A total of 128 patients aged >20 years who had functional dyspepsia diagnosed according to the ROME III criteria, who were *Helicobacter pylori*-negative, and who had continuous symptoms after 2 weeks of placebo administration.

5. Intervention

Arm 1: oral administration of Rikkunshito（六君子湯）Extract Granules (manufacturer unknown) 2.5 g t.i.d. for 8 weeks (n=63)

Arm 2: oral administration of placebo 2.5 g t.i.d. for 8 weeks (n=65)

6. Main outcome measures

The primary endpoint was overall treatment efficacy (OTE). The secondary endpoints were the scores from the patient assessment of upper gastrointestinal disorders-symptom severity index (PAGI-SYM), Global overall symptom (GOS), Modified frequency scale for the symptoms of GERD (m-FSSG), Hospital anxiety and depression scale (HADS), and Short-form health survey-8 (SF-8).

7. Main results

During the study period, 2 patients in the rikkunshito group and 1 patient in the placebo group dropped out of the study. The OTE after 8 weeks of treatment in the rikkunshito group was “extremely improved” in 8.2% and “improved” in 29.5%, which were significantly higher compared with 1.8% and 21.1%, respectively, in the placebo group (P=0.019). After 8 weeks of treatment, the PAGI-SYM, GOS, m-FSSG, and HADS total scores were significantly decreased in the rikkunshito group compared with the placebo group (P=0.018, P =0.009, P =0.036, and P =0.027, respectively). The SF-8 did not show significant difference.

8. Conclusion

Rikkunshito alleviates gastrointestinal and psychological symptoms in *Helicobacter pylori*-negative patients with functional dyspepsia.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Adverse events and adverse drug reactions occurred in 10.8% and 4.6%, respectively, of the patients in the rikkunshito group and 11.1% and 1.6%, respectively, of the patients in the placebo group.

11. Abstractor’s comments

This article describes an important clinical study that evaluated the efficacy of rikkunshito for functional dyspepsia. Knowing that assessment of subjective symptoms is relatively unlikely to show significant differences in RCTs, this study is particularly meaningful because it showed that a significantly higher percentage of patients in the rikkunshito group experienced relief of subjective symptoms. In addition, this study used existing scales to assess gastrointestinal and psychological symptoms, and demonstrated improvements in the rikkunshito group with significant differences, and so is a good reference for other physicians. Furthermore, since this study used Western medicine rather than Oriental medicine in diagnosing functional dyspepsia and evaluating the effect of rikkunshito on functional dyspepsia, the results from this study are usable by clinicians in Japan where Western medicine is predominant. Although clinical questions remain, such as whether rikkunshito should be continued or switched to another formula in patients with poor improvement after 8 weeks of treatment with rikkunshito, this article appears to be of great significance in that it provides a foundation for future clinical practices and studies.

12. Abstractor and date

Koike H, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases
21. Others

References

Kaido T, Shinoda M, Inomata Y, et al. Effect of herbal medicine daikenchuto on oral and enteral caloric intake after liver transplantation: A multicenter, randomized controlled trial. *Nutrition.* 2018 54: 68-75. Pubmed ID: 29747091

1. Objectives

To evaluate the efficacy and safety of daikenchuto（大建中湯）to enhance oral and enteral caloric intake after liver transplantation

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

Fourteen institutions including university hospitals, Japan

4. Participants

A total of 112 patients with end-stage liver disease.

Inclusion criteria: Patients aged ≥20 years who met the indication criteria for liver transplantation at each study center.

Exclusion criteria: Uncontrollable acute infection other than in the liver, uncontrollable malignant disease other than hepatocellular carcinoma, severe postoperative adhesions, use of psychotropic, gastrointestinal prokinetic, or other Kampo medicines, current pregnancy or lactation.

5. Intervention

Arm 1: administration of TSUMURA Daikenchuto（大建中湯）Extract Granules 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=57)

Arm 2: administration of placebo 15.0 g/day (5 g three times daily orally immediately before meals or enterally via tube every 8 hours) (n=55)

In both Arms 1 and 2, the treatment was given from postoperative day (POD) 1 to POD 14.

6. Main outcome measures

Primary endpoints: total oral/enteral caloric intake at POD 7, abdominal distension, abdominal pain (numeric rating scale [NRS]).

Secondary endpoints: 1) chronological changes in total oral or enteral caloric intake, 2) chronological changes in abdominal distension and abdominal pain, 3) elapsed time from extubation to first postoperative defecation, 4) quality of life (QOL) assessment using the Gastrointestinal Symptom Rating Scale (GSRS) score, 5) liver regeneration rate between POD 14 and POD 21, 6) incidence of sepsis, 7) incidence of acute cellular rejection, 8) rate of discharge from the hospital within 2 months after liver transplantation, 9) portal vein flow volume and velocity.

7. Main results

Since 2 patients in Arm 1 and 6 patients in Arm 2 dropped out of the study, the analysis was conducted in 55 patients in Arm 1 and 49 patients in Arm 2. Arm 1 and Arm 2 did not significantly differ in total caloric intake (972.6±595.3 kcal in Arm 1 and 966.0±615.7 kcal in Arm 2; P=0.957), abdominal distension (3.5±2.9, 3.2±2.8; P=0.609), and abdominal pain (3.4±2.5, 3.0±2.3; P=0.530). As for chronological changes, the total caloric intake at PODs 3, 5, 7, 10, and 14 did not significantly differ between the two arms. However, between POD 3 and POD 10, the rate of increase in the caloric intake was significantly higher in Arm 1 (P=0.023). No significant intergroup differences were shown in the chronological changes in abdominal distension or abdominal pain, elapsed time from extubation to first postoperative defecation, QOL, liver regeneration rate, incidence of sepsis, incidence of acute cellular rejection, discharge rate within 2 months after liver transplantation. On the other hand, the portal vein flow volume was significantly higher in Arm 1 than in Arm 2 at POD 10 and POD 14 (P=0.047, P=0.025). The portal vein flow velocity at POD 14 was significantly higher in Arm 1 than in Arm 2 (P=0.014). In a subgroup analysis conducted on 70 patients (i.e., 37 in Arm 1 and 33 in Arm 2) in whom oral or enteral nutrition was started within 3 days postoperatively, the total caloric intake between POD 3 and POD 7 was significantly higher in Arm 1 than in Arm 2 (P=0.014). The portal vein flow volume was significantly higher in Arm 1 between POD 0 and POD 14 (P=0.010), and the portal vein flow velocity and volume were significantly higher in Arm 1 at POD 14 (P=0.032 and P=0.030, respectively).

8. Conclusion

Administration of daikenchuto after liver transplantation may enhance total oral and enteral caloric intake in the early postoperative period, in which involvement of increased portal vein flow volume and velocity is suggested.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

There was no significant difference in the frequency of grade ≥3 major complications between the daikenchuto group and the placebo group.

11. Abstractor's comments

This is a highly objective article describing an analysis from a DB-RCT (14 study centers) on the effect of daikenchuto in enhancing oral/enteral caloric intake in patients who underwent liver transplantation. As the authors described, unfortunately no significant intergroup difference was shown in total caloric intake as a primary endpoint. However, a subgroup analysis among the patients with early resumption of oral/enteral caloric intake showed significantly higher caloric intake in the daikenchuto group. Follow-up of this finding is awaited.

12. Abstractor and date

Kogure T, 1 June 2020.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Kume K, Kasuya Y, Ozaki M. Effect of Goreisan, a traditional Japanese Kampo medicine, on postoperative nausea and vomiting in gynecological patients. *JA Clinical Reports* 2017; 3: 552: 1-6. doi: 10.1186/s40981-017-0122-5 Pubmed ID: 29457096

1. Objectives

To evaluate the efficacy and safety of goreisan（五苓散）on postoperative nausea and vomiting (PONV) after gynecological surgery under general anesthesia

2. Design

Double-blind, randomized, controlled trial (DB-RCT)

3. Setting

One university hospital, Japan

4. Participants

Eighty-three patients aged 20 to 50 years who underwent gynecological surgery.

Exclusion criteria: American Society of Anesthesiologists Physical Status (ASA-PS) 3 or more, Body Mass Index (BMI) ≥35, pregnancy or lactation, use of other Kampo medicines, steroids, immunosuppressants, or chemotherapy agents, insufficient follow-up

5. Intervention

The following solution or water was administered through a nasogastric tube one hour before completion of the surgery:

Arm 1: Goreisan（五苓散）Extract Granules 7.5 g (manufacturer unknown) dissolved in 20 mL of water at 40°C (n=40)

Arm 2: placebo: 20 mL of water at 40°C (n=43)

6. Main outcome measures

The primary outcome measure was the incidence of PONV and the requirement of antiemetic use.

The secondary outcome measures were the incidence and severity of postoperative pain and the requirement of analgesic use.

7. Main results

The incidence of PONV during the first 2 hours after extubation was 45% in Arm 1 and 46.5% in Arm 2 ($P = 0.89$), showing no significant difference. The incidence and severity of PONV up to 24 hours after extubation showed no significant differences. Since the interim analysis showed no significant differences, the study was terminated with a sample size of 83 patients, although more patients were to be recruited.

8. Conclusion

Goreisan does not prevent PONV.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Postoperative pain, clinical course, etc. were assessed in the goreisan and placebo groups, and showed no significant differences. The study was conducted safely.

11. Abstractor's comments

There is evidence that drugs such as 5-HT_3 receptor antagonists reduce PONV. This clinical study investigated whether goreisan has such an effect, but unfortunately found none. However, this study appears to be meaningful in that it provided a foundation for other studies (to investigate other Kampo medicines, etc.).

12. Abstractor and date

Kato Y, 1 June 2020.

12. Skin Diseases

References

Murota H, Azukizawa H, Katayama I. Impact of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) on treatment of chronic spontaneous urticaria: a randomized controlled study. *Chinese Journal of Integrative Medicine* 2017; 1-5. doi: 10.1007/s11655-017-2950-6 CENTRAL ID: CN-01404751, Pubmed ID: 28819778

1. Objectives

To evaluate the efficacy of jumihaidokuto（十味敗毒湯）on urticaria

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital, Japan

4. Participants

Twenty-one patients who met the diagnostic criteria for urticaria in the guideline set by the Japanese Dermatological Association

5. Intervention

Arm 1: administration of Kracie Jumihaidokuto（十味敗毒湯） 6.0 g/day (3.0 g b.i.d.) plus an antihistamine for 8 weeks (n=11)

Arm 2: administration of an antihistamine alone for 8 weeks (n=10)

6. Main outcome measures

Primary endpoint: Urticaria severity score proposed by the Japanese Dermatological Association

Secondary endpoints: Comparison of itch VAS score, scores from a brief questionnaire about itch and skin condition, and QOL (Skindex-16 score)

7. Main results

The urticaria severity score at 8 weeks of the treatment was significantly lower in Arm 1 than in Arm 2 ($P<0.01$). The itch VAS score did not significantly differ between the two arms. The brief questionnaire results showed significant improvement of itch and skin condition in Arm 2 ($P<0.05$). The Skindex-16 results showed no significant differences between the two arms for all symptoms.

8. Conclusion

In patients with refractory chronic urticaria, jumihaidokuto may be effective treatment.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

No adverse events were noted.

11. Abstractor's comments

Refractory chronic urticaria impairs the quality of life of the patients. For urticaria that does not improve with antihistamines, concomitant use of jumihaidokuto is considered to be an effective approach. The itch VAS score analysis in this study did not show a significant difference, but graphically, tended to favor jumihaidokuto use. Thus, further studies with larger sample sizes are desired.

From the viewpoint of Oriental medicine, spleen deficiency may play a role in the background of chronic urticaria. Thus, dietary advice and prescription of medicine that can promote gastrointestinal function may warrant investigations.

12. Abstractor and date

Nakata H, 1 June 2020.

21. Others

References

Fujinami H, Kajiura S, Nishikawa J, et al. The influence of duodenally-delivered Shakuyakukanzoto (Shao Yao Gan Cao Tang) on duodenal peristalsis during endoscopic retrograde cholangiopancreatography: a randomised controlled trial. *Chinese Medicine* 2017; 12: 3: 1-6. doi: 10.1186/s13020-016-0125-6. Pubmed ID: 28077962

1. Objectives

To evaluate the inhibitory effect of intraduodenal administration of shakuyakukanzoto（芍薬甘草湯）on duodenal peristalsis during endoscopic retrograde cholangiopancreatography (ERCP)

2. Design

Randomized controlled trial (RCT)

3. Setting

One university hospital (department of internal medicine), Japan

4. Participants

Twenty-eight patients undergoing ERCP

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto（芍薬甘草湯）Extract Granules 5.0 g dissolved in 50 mL of warm water (concentration, 100 mg/mL), endoscopically sprayed once towards the major papilla of the duodenum (n=15)

Arm 2: Warm water as placebo sprayed in a similar manner (n=13)

6. Main outcome measures

Duodenal peristalsis was assessed using a 4-grade scoring system: +0 = no peristalsis and easy cannulation; +1 = slight peristalsis and easy cannulation; +2 = moderate peristalsis and difficult cannulation; +3 = severe peristalsis and impossible cannulation.

Primary endpoint: Duodenal peristalsis inhibition rate (i.e., proportion of patients with inhibition of grade +0 or +1 peristalsis).

Secondary endpoints: Required time (RT [seconds]) from dosing to inhibition of peristalsis, and stop duration time (DT [minutes]) of peristalsis

7. Main results

The analysis was conducted on 10 patients in Arm 1 and 9 patients in Arm 2, after exclusion of 5 patients in Arm 1 and 4 patients in Arm 2 who had no evident duodenal peristalsis at duodenoscopy. In Arm 1, duodenal peristalsis was inhibited in 8 (80%) of the 10 patients, and the RT was 76.0 ± 23.9 seconds and the DT was 11.3 ± 23.9 minutes. In Arm 2, inhibition of duodenal peristalsis occurred in no patients (0%), with RT and DT not measurable.

8. Conclusion

Endoscopic spraying of shakuyakukanzoto as premedication for ERCP inhibits duodenal peristalsis and allows easy cannulation.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Serum potassium was measured for detection of pseudoaldosteronism, but showed no significant difference between the two groups. No safety issues were noted.

11. Abstractor's comments

This is the first report of an RCT demonstrating that endoscopically sprayed shakuyakukanzoto solution in ERCP can inhibit duodenal peristalsis and permits easy cannulation. Typically, premedication before ERCP uses intravenous anticholinergic agents or glucagon, but adverse reactions to these agents can be problematic especially in elderly patients. If endoscopically sprayed shakuyakukanzoto is effective, the approach is of great significance. The reported mean time to the onset of action was 1+ minutes and mean duration of action was 11 minutes, which seem quite acceptable in clinical practice. However, since the sample size was small in this study, confirmation in a larger sample is warranted. In addition, since the warm water described as the placebo must be obviously different in appearance from shakuyakukanzoto solution, in a strict sense the warm water should probably be described as the "control" rather than the "placebo". It may also worth conducting an RCT using an intravenous anticholinergic agent as a control.

12. Abstractor and date

Motoo Y, 1 June 2020.

Meta-Analysis
2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References
Ishizuka M, Shibuya N, Nagata H, et al. Perioperative administration of traditional Japanese medicine daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: a systemic review and meta-analysis. *Anticancer Research* 2017; 37: 5967-74. Pubmed ID: 29061775

1. Objectives
To conduct a meta-analysis to determine the efficacy of perioperative daikenchuto (大建中湯) (DKT) administration for relief of postoperative ileus (PI) in patients undergoing surgery for gastrointestinal (GI) cancer

2. Data source
Cochrane Library, PubMed, the Web of Science, and ICHUSHI (literature published up to December 2016) were searched to collect relevant articles, using the search terms of daikenchuto, TJ-100, and TU-100.

3. Selection of study
Inclusion criteria: 1) RCTs or other comparative studies except for those with a retrospective design; 2) description of the evaluation of PI in GI cancer; 3) description of the data on the risk ratio (RR) or standardized incidence ratios (with 95% confidence interval); 4) description of sample size; 5) written in Japanese or English; 6) any types of PI (including paralytic ileus).
Exclusion criteria: 1) non-reporting of a control group, or inability to extract the number of outcome events; 2) surgery for urological, gynecological, or pediatric malignancies or non-malignancies, surgery on animal models; 3) letters, comments, correspondences, editorials, or reviews; 4) studies for which published articles had considerable overlap between authors, centers, and participants.

4. Data extraction
Full text reviews were performed independently by two authors on the basis of the inclusion and exclusion criteria and PICO criteria. Any disagreements were resolved by discussion. The same two authors also independently extracted the following information from each eligible article: first author's name, year of publication, country of the study, study design, number of PI occurrences, and sample size. If required data could not be obtained, the original authors were contacted.

5. Main results
The search yielded 661 articles, of which 165 were regarded as duplicate articles and thus excluded. Additional 468 articles were also excluded by title/abstract review and PICO. The remaining 28 articles were reviewed in full-text, of which 7 articles (6 RCTs and 1 prospective study; n=1134) were applicable to this study and thus included in this meta-analysis.
Arm 1: administration of DKT (n=588); Dose 15 g/day in 5 studies, 7.5 g/day in 1 study, and 27 g/day in 1 study
Arm 2: no administration of DKT (n=546)
PI occurred in 67 patients (11.4%) in Arm 1 and 87 patients (15.9%) in Arm 2, showing significant reduction of PI occurrence in Arm 1 compared with Arm 2 (RR=0.58; 95% CI, 0.35–0.97; P=0.04; I^2=48%).

6. Conclusion
Daikenchuto significantly reduces postoperative ileus in GI cancer patients.

7. From Kampo medicine perspective
None

8. Safety assessment in the article
Not mentioned.

9. Abstractor's comments
Daikenchuto is the Kampo medicine most commonly studied regarding its efficacy as an inhibitor of GI motility and for the prevention of ileus. This is a clinically meaningful and valuable article describing a meta-analysis showing the efficacy of daikenchuto for postoperative ileus in GI cancer patients. Evidence-based Kampo medicine has long been advocated, but evidence from meta-analyses has been limited. With increases in RCTs, further systematic reviews are desired.

10. Abstractor and date
Kogure T, 1 June 2020.

Meta-Analysis

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

References

Hoshino N, Ganeko R, Hida K, et al. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *International Journal of Clinical Oncology* 2018; 23: 434-42. Pubmed ID: 29270698

1. Objectives

To assess the efficacy and safety of goshajinkigan（牛車腎気丸）for chemotherapy-induced peripheral neuropathy (CIPN)

2. Data source

Scopus, Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, ICHUSHI

3. Selection of study

RCTs (other than cross-over or quasi-RCTs) that compared goshajinkigan with a control for CIPN

4. Data extraction

Titles and abstracts of the studies identified by the literature search were independently screened by two researchers (other than those who performed the literature search). Data were then extracted and entered into the Review Manager software, version 5.3.

5. Main results

Five RCTs were included in the analysis, consisting of 1 study of docetaxel for breast cancer, 1 study of paclitaxel for breast cancer, and 3 studies of FOLFOX (oxaliplatin-based) for colorectal cancer. As a primary endpoint, the efficacy of goshajinkigan was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) in 4 RCTs, which did not show preventive effect of goshajinkigan against grade ≥2 and ≥3 CIPN compared with the controls (no administration of goshajinkigan). The efficacy was evaluated using the Neurotoxicity Criteria of Debiopharm (DEB-NTC) in 3 RCTs (including 2 RCTs that also used CTCAE), where goshajinkigan showed a tendency to reduce the risk of grade ≥2 and ≥3 CIPN compared with the controls (no administration of goshajinkigan). As a secondary endpoint, 1 RCT evaluated CIPN subjectively on a visual analogue scale (VAS) and reported significant improvement with goshajinkigan. Goshajinkigan had no influence on hematotoxicity in 3 RCTs and tumor response in 2 RCTs. The risk of bias was assessed in the 5 studies. Three RCTs used a computer random number generator. Two RCTs used central registration. Two RCTs included a placebo arm and were reported to be double-blinded. Two RCTs followed all enrolled patients. Of the remaining 3 studies, 2 studies excluded only a few patients. Four studies were registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR).

6. Conclusion

Goshajinkigan tended to prevent persistence but not severity of CIPN.

7. From Kampo medicine perspective

None

8. Safety assessment in the article

In five RCTs that reported on adverse events, there were no serious adverse events.

9. Abstractor's comments

This is the first meta-analysis of the efficacy and safety of goshajinkigan for CIPN for which currently no effective treatment exists. CTCAE or DEB-NTC can be used to assess CIPN severity and persistence, with the former being superior for severity assessment and the latter for persistence assessment. This meta-analysis revealed that goshajinkigan tended to reduce the risk of CIPN compared with the controls when the DEB-NTC was used for assessment, but had no significant effect when the CTCAE was used for assessment. However, since the pathogenesis of CIPN can primarily involve either axonopathy (caused by taxanes) or neuronopathy (caused by platinum-based drugs), and since the severity and the time to resolution can differ depending on the pathogenesis, the analysis of CIPN irrespective of pathogenesis may be somewhat impractical. Also, since CIPN can only be measured subjectively, RCTs using objective parameters such as serum biomarkers are desired. Further, these published RCTs had high risk of bias, which should be addressed in the future.

10. Abstractor and date

Motoo Y, 1 June 2020.

8. Ear Diseases

Reference

Yoshizaki T. A multicenter, double-blind, randomized controlled trial on the usefulness of juzentaihoto in children with recurrent otitis media* (2009−clinical study−general—007) *Chozai to Joho* (*Dispensing and Information*) Health Labour Sciences Research Grant, General Research Program for Practical Application of Medical Technology, 2009, General Research Report in 2011. 2012: 1-23 (in Japanese).

Ito M, Maruyama Y, Kitamura K, et al. Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media *Auris Nasus Larynx* 2017; 44: 390-7. Ichushi Web ID: 2018007858, Pubmed ID: 278101268

1. Objectives

To evaluate the efficacy and safety of juzentaihoto (十全大補湯) in children with recurrent otitis media.

2. Design

Randomized controlled trial (RCT).

3. Setting

Seven university hospitals, 8 hospitals, and 11 otorhinolaryngological clinics, Japan.

4. Participants

Eighty-seven children aged ≥six months and <4 years with otitis media, recurrences of otitis media that were difficult to treat with standard therapy, a diagnosis of recurrent otitis media "acute otitis media occurring three times or more within the past 6 months, or four times or more within the past 12 months," and any of the following symptoms: a decrease in physical strength, fatigue and malaise, anorexia, night sweat, cold extremities, or anemia.

5. Intervention

Arm 1: Juzentaihoto (十全大補湯) (manufacturer unknown) administered orally at 0.05 to 0.125 g/kg b.i.d and standard therapy for 3 months (n=39).

Arm 2: Standard therapy alone (n=48).

6. Main outcome measures

Primary outcome: The mean number of recurrences with acute otitis media per month during the study.

Secondary outcome: The mean number of recurrences with coryza per month, mean frequency of antibiotic use per month, number of subjects treated by eardrum ventilation tube insertion during the study and the period of treatment.

7. Main results

A total of 70 subjects were included in the analysis: 31 subjects in the juzentaihoto arm and 39 subjects in the standard therapy alone arm. For the primary outcome, a significant decrease in the mean number of acute otitis media recurrences was observed in Arm 1 (0.61±0.54 recurrences/month) compared to Arm 2 (1.07±0.72 recurrences/month) (P=0.005). For the secondary outcomes, significant improvements were observed for both the mean number of coryza recurrences per month and the mean frequency of antibiotic use per month (P=0.015, P=0.024) in Arm 1 compared to Arm 2.

8. Conclusions

Juzentaihoto decreases the incidence of recurrent otitis media in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject in the juzentaihoto arm experienced skin rash, leading to suspension of treatment. No significant inter-arm difference in blood chemistry was found throughout the study.

11. Abstractor's comments

This clinical study, which evaluated the efficacy of juzentaihoto in pediatric patients with recurrent otitis media, a widely prevalent and refractory disease, is highly valuable with regard to clinical significance, setting, and study methods. Initially the study was presented in the form of a report, but in 2017 the details were clearly described and was published as a research paper. The report issued in 2012 mentioned that juzentaihoto showed efficacy in the subjects showing indications of "decreased physical strength after illness, fatigue, loss of appetite, night sweats, coldness in the extremities, and anemia". Furthermore, the authors also investigated overall physical condition, including nutritional status and whether or not there was any improvement in anemia, and reported that there was no difference between the Arms. As the authors mentioned, this clinical research is fully expected to generate evidence for the efficacy of juzentaihoto in the treatment of childhood recurrent otitis media in the future.

12. Abstractor and date

Goto H, 31 March 2017, 1 June 2020.

List of Excluded References (Appendix 2018)

Abbreviations: C, The Cochrane Library (CENTRAL); I, Igaku Chuo Zasshi (Japana Centra Revuo Medicana, Ichushi); N, Hand searching Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

Reasons for exclusion were classified as follows:

1) Clinical studies that were not RCTs or meta-analyses.

2) Studies using medicines that were not approved as Kampo preparations in Japan (Kampo tozai [decoctions], Chinese preparations, and others).

3) Studies using Kampo preparations manufactured before 1985 (their quality being different from that currently available).

4) Studies citing existing RCT papers.

5) Studies with unclear content.

6) Others (reasons are described in the list).

ICD-10	Research Question	Kampo Formula	References	Reason for exclusion	Source
C18.9 K91.9	Evaluation of the efficacy of daikenchuto (大建中湯) for gastrointestinal symptoms after laparoscopic colon cancer resection	daikenchuto (大建中湯)	Hoshino N, Kawada K, Hida K, et al. Effect of Daikenchuto (TJ-100) on gastrointestinal symptoms following laparoscopic colectomy in patients with colon cancer: study protocol for a randomized controlled trial. *Trials* 18: 1-6.	5) Reference had only a protocol	C
C26.9 K91.3	Meta-analysis evaluation of the efficacy of daikenchuto (大建中湯) for prolonged ileus after open surgery	daikenchuto (大建中湯)	Kono T, Shimada M, Nishi M, et al. Daikenchuto administration for intestinal hypomotility after open abdominal surgery: a pooled analysis of three randomized controlled trials. *Annals of Cancer Research and Therapy* 2017; 25: 41-3.	5) Reference had only a protocol	C
C34.9 R63.0	Effect of rikkunshito (六君子湯) on loss of appetite due to cancer chemotherapy	rikkunshito (六君子湯)	Inoue T, Takagi H, Owada Y, et al. The efficacy of the Kampo medicine rikkunshito for chemotherapy-induced anorexia (RICH trial) : study protocol for a randomized controlled trial. *Trials* 2017; 18 :1-8.	5) Reference had only a protocol	C
E78.5	Effect of seiryu (青流) on dyslipidemia and alcoholic liver disease	herbal products (seiryu [青流])	Sou S, Shu G. A study of dyslipidemia and alcoholic liver disease diagnosed based on the Chinese medicine concept. *The Journal of Comparative Integrative Medicine/Japan* 2017; 25:21-6.	2), 6) Basic study	I
F03	Meta-analysis evaluation of the efficacy of herbal medications on the management of behavioral and psychological symptoms (BPSD) associated with dementia	yokukansan (抑肝散) ninjinyoeito (人参養栄湯)	Hyde A, May B, Lin Dong L, et al. Herbal medicine for management of the behavioural and psychological symptoms of dementia (BPSD): a systematic review and meta-analysis. *Journal of Psychopharmacology* 2017; 31: 169-83.	2) Meta-analysis included non-Japanese medicines	N

ICD-10	Research Question	Kampo Formula	References	Reason for exclusion	Source
J45.9	Meta-analysis evaluation of the efficacy and safety of adjunctive Chinese therapy for the treatment of pediatric cough variant asthma	Chinese medicines	Song P, Zeng L, Liang Z, et al. Clinical efficacy and safety of Chinese herbal medicine auxiliary therapy for childhood cough variant asthma: a systematic review and meta-analysis of 20 randomized controlled trials. *Internal Medicine* 2017; 55: 2135-43.	2)	I
M62.81	Effect of the thumb kneading method and thumb compression method on shoulder stiffness	acupressure	Okina Y, Yano T. A comparison study of effect of the thumb kneading method and thumb compression method on shoulder stiffness. *Journal of Japanese of Oriental Physiotherapy,* 2016; 41:57-64	2)	I
N94.6	Evaluation of the efficacy of herbal treatments for dysmenorrhea	herbal medicines	Horiba Y, Yoshino T, Watanabe K, et al. Effectiveness of Japanese kampo treatment in dysmenorrhea: single-center observational study. *Traditional and kampo medicine* 2018; 5: 51-5.	1) Observational study	C
R05	Meta-analysis evaluation of the efficacy and safety of bakumondoto (麦門冬湯) for cough	bakumondoto (麦門冬湯)	Kim KI, Shin S, Lee N, et al. A traditional herbal medication, Maekmoondong-tang, for cough: a systematic review and meta-analysis. *Journal of Ethnopharmacology*. 2016; 3: 144-54.	2) Meta-analysis included non-Japanese medicines	N
R20.8	Effect of acupuncture stimulation on depth perception	acupuncture	Tezuka C, Nakamura M. Effect of acupuncture on depth perception. *Journal of the Society for Integrative Medicine Japan* 2017; 10:196-200.	2)	I
R68.8	Improving effect of drinking Yamatotokicha (大和当帰茶) on oversensitivity to cold in young women	toki (当帰)	Kitano N, Nagasawa T, Improving effect of continuous drinking of Yamatotokicha (大和当帰茶) on oversensitivity to cold in young women. *Trace Nutrients Research* 2016; 33:1-8.	2)	I
S06	Effect of Zhoubo and uncaria tincture in the treatment of concussion sequelae	Zhoubo	Liang J, Wang Y, Liang B. Zhoubo plus uncaria tincture in the treatment of cerebral concussion sequelae. Journal of *Physical Therapy Science* 2017: 28: 2027-30.	2)	I
Z04.8	A study of the essential oil components of kamishoyousan extract (加味逍遙散料)	components of kamishoyousan extract (加味逍遙散料)	Yomoda S, Kawashima T. A study on essential oil components of kamishoyousan extract (加味逍遙散料), *Phil Kampo.* 2017; 63:30-2.	2)	I
Z04.8	Evaluation of the clinical utility of ephedrine alkaloid free ephedra extract (EFE)	ephedrine alkaloid free ephedra extract	Odaguchi H. A clinical study to evaluate the clinical utility of ephedrine alkaloid free ephedra extract (EFE). *Journal of the Pharmaceutical Society of Japan* 2017; 137:195-7.	2)	C
None	Results of a survey of Chinese medicine education for training hospitals and residents	Chinese medicine education	Arai M, Nakada Y, Izumi S, et al. The education of traditional Japanese (Kampo) medicine: surveys of training hospitals and residents. *BMC Complementary and Alternative Medicine.* 2017: 17:134; 1-11. doi: 10.1186/s12906-017-1634-2.	6) Reference to Chinese medicine education	C