

# **Evidence Reports of Kampo Treatment (EKAT)**

## **Appendix 2015**

漢方治療エビデンスレポート(EKAT) Appendix 2015

**31 March 2017**

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

## History of version upgrades

- 31 Mar. 2017: Kampo Chiryō Ebidensu Repoto Appendix 2015 (Evidence Reports of Kampo Treatment Appendix 2015)  
 6 Jun. 2015: Kampo Chiryō Ebidensu Repoto Appendix 2014 (Evidence Reports of Kampo Treatment Appendix 2014)  
 31 Dec. 2013: Kampo Chiryō Ebidensu Repoto 2013 – 402 no RCT (Evidence Reports of Kampo Treatment 2013: 402 Randomized Controlled Trials)  
 31 Dec. 2012: Kampo Chiryō Ebidensu Repoto Appendix 2012 (Evidence Reports of Kampo Treatment Appendix 2012)  
 1 Oct. 2011: Kampo Chiryō Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)  
 1 Jun. 2010: Kampo Chiryō Ebidensu Repoto 2010 – 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)  
 1 Jun. 2009: Kampo Chiryō Ebidensu Repoto 2009 – 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)  
 1 Apr. 2008: Kampo Chiryō Ebidensu Repoto Dai 2-han – RC T 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 Chiryō Ebidensu Repoto Dai 2-han –RC T wo Shu ni Shite- Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007)  
 20 Jul. 2005: Kampo Chiryō niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (*Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2005: 56, EBM supplementary issue)  
 20 Sept. 2002: Kampo Chiryō 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
2017.3.31	Evidence Reports of Kampo Treatment, Appendix 2015 (EKAT appendix 2015)	From EKAT 2014 2014	545 <sup>2)</sup>	447 <sup>1), 2)</sup>	177
2015.6.6	Evidence Reports of Kampo Treatment, Appendix 2014 (EKAT appendix 2014)	From EKAT 2013 2013 (First half)	513 <sup>3)</sup>	418 <sup>1), 3)</sup>	167
2013.12.31	Evidence Reports of Kampo Treatment, 2013 - 402 Randomized Controlled Trials	1986-2012 (First half)	494 <sup>4)</sup>	403 <sup>1), 4)</sup>	159
2012.12.31	Evidence Reports of Kampo Treatment, Appendix 2012 (EKAT appendix 2012)	From EKAT 2011 2011 (First half)	457	379 <sup>1), 5)</sup>	150 <sup>5)</sup>
2011.10.1	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT appendix 2011)	From EKAT 2010 2010 (First half)	432	360 <sup>1), 6)</sup>	-
2010.6.1	Evidence Reports of Kampo Treatment, 2010 - 345 Randomized Controlled Trials (EKAT 2010)	1986-2009 (First half)	416	346 <sup>1)</sup>	132
2009.6.1	Evidence Reports of Kampo Treatment, 2009 - 320 Randomized Controlled Trials (EKAT 2009)	1986-2008 (First half)	385	321 <sup>1)</sup>	111
2008.4.1	Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs - Interim Report 2007 ver1.1	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

<sup>1)</sup> Including 1 meta-analysis

<sup>2)</sup> Total of all references added or removed in EKAT 2013, EKAT Appendix 2014 and EKAT Appendix 2015.

<sup>3)</sup> Total of all references added or removed in EKAT 2013, EKAT Appendix 2014.

<sup>4)</sup> Because literature search methods were improved in EKAT 2013, the additions subsequent to EKAT Appendix 2012 may not necessarily be references subsequent to the first half of 2011.

<sup>5)</sup> Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012.

<sup>6)</sup> 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 as Evidence Reports of Kampo Treatment (EKAT). The ER-TF started working with the Task Force for Clinical Practice Guidelines in June 2009, because data obtained in RCTs of Kampo formulations were used in the preparation of the Clinical Practice Guidelines and the two task forces were therefore considered to be closely related. However, for project management reasons, since June 2014, the ER-TF, consisting of fifth-generation members, has been working as a separate body once again.

As indicated in the "History of version upgrades" on the previous page, "Evidence Reports of Kampo Treatment 2013 – 402 RCTs" (EKAT 2013) was published on December 31, 2013. EKAT 2013 states the results of 402 RCTs and a meta-analysis performed between 1986, when the current quality specifications for Kampo formulations for medical use were established, and the first half of 2012. On June 6, 2015, EKAT Appendix 2014 was published and additionally states only SAs of RCT reports published for approximately one year after the publication of EKAT 2013.

EKAT Appendix 2015 contains SAs of 31 of the RCT reports published within approximately one year after the publication of EKAT Appendix 2014 and two revised SAs published before the publication. Even though the ER-TF website has not been updated since the publication of the EKAT 2013, the Google search engine available on the website allows users to access all SAs in EKAT 2013, EKAT Appendix 2014, and EKAT Appendix 2015.

To enable the inclusion of the results of all RCTs on Kampo formulations in the EKAT, a wide range of documents and reports were referred to: even articles about academic societies were referred to, provided that the articles stated the names of the authors and provided sufficient information to use as basis to prepare SAs. However, issues of authorship and conflict of interest (COI) in regard to medical reports have gained interest since the 2010s. In March 2015, the Japanese Association of Medical Sciences and the Japanese Association of Medical Journal Editors published the Medical Journal Editing Guidelines (<http://jams.med.or.jp/guideline>), which require that articles written by journalists regarding RCTs on Kampo formulations should not be included in EKAT Appendix 2014 or subsequent EKAT appendices, and that SAs based on such articles should be reviewed and complemented by relevant RCT reports or replaced with new SAs, because the number of subjects and the results of RCTs differed between some articles and relevant RCT reports, and some RCTs in such articles were not linked to relevant RCT reports. EKAT Appendix 2015 has been reviewed in accordance with the guidelines, and two SAs (two RCT reports) have been deleted. EKAT Appendix 2015 contains the results of 445 RCTs and two meta-analyses.

Even though the objective of the EKAT and the methods to prepare the EKAT have basically remained the same since EKAT 2013, the time to carry out a search for RCT reports necessary for EKAT Appendix 2015 has been changed from November to April, because there were discrepancies in the title of the EKAT and the time of publication. Although the ER-TF planned to carry out a search for RCT reports necessary for the present EKAT in April 2015, to prepare SAs of RCT reports published in most medical journals in 2014, and to publish a Japanese version under the name of "EKAT Appendix 2015" by the end of 2015, the ER-TF actually published it in 2017. However, the ER-TF will carry out a search for RCT reports in April of each year going forward.

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

**Fifth Phase (September 2015 -)**  
**Task Force for Evidence Reports (ER-TF)**  
**Committee for Evidence-based Medicine (EBM)**  
**The Japan Society for Oriental Medicine (JSOM)**

**Organization**

**Chair and chairperson of Committee for EBM:**

Yoshiharu MOTOO     Department of Medical Oncology, Kanazawa Medical University

**Members (12 persons, order of the Japanese syllabary):**

Ichiro ARAI             Department of Pharmaceutical Sciences, Nihon Pharmaceutical University

Takahisa  
USHIROYAMA             Health Science Clinic, Osaka Medical College

Hiroshi KOIKE             Department of General Internal Medicine, Tokyo Saiseikai Central Hospital  
Center for Kampo Medicine, Keio University School of Medicine

Toshiaki KOGURE         Department of Japanese Oriental Medicine, Gunma Central General Hospital

Hirozo GOTO             Department of Kampo Medicine, Hokusei Hospital

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

Koki TSURUOKA             Graduate School of Social Service Management, Japan College of Social Work

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

Michio FUJISAWA         Division for Health Service Promotion, University of Tokyo (-2016.2)

Etsuo HOSHINO  
Miyuki MINARI             Division of Kampo Support, Cancer Institute Ariake Hospital  
Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association

**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)

Yukio KANEKO             Kaneko Clinic (vice-trustee in charge of Committee for EBM)

**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

# Lists of Structured Abstracts

## <<EKAT Appendix 2015: Structured Abstracts describing RCTs and the References Reporting Them>>

Note: Original English titles assigned by authors were used in these lists and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (\*).

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
A31.0	To evaluate the effectiveness of hochuekkito (補中益氣湯) as an adjunct to conventional treatment for progressed refractory pulmonary Mycobacterium avium complex (MAC) disease.	hochuekkito (補中益氣湯)	Enomoto Y, Hagiwara E, Komatsu S, et al. Pilot quasi-randomized controlled study of herbal medicine hochuekkito as an adjunct to conventional treatment for progressed pulmonary mycobacterium avium complex disease. PLOS ONE 2014; 9: 1-8.	quasi-RCT	C&N	9
E14	To evaluate the efficacy and safety of goshajinkigan (牛車腎氣丸) for treatment of diabetic complications.	goshajinkigan (牛車腎氣丸)	Watanabe K, Shimada A, Miyaki K, et al. Long-term effects of goshajinkigan in prevention of diabetic complications: A randomized open-labeled clinical trial. Evidence-Based Complementary and Alternative Medicine 2014: 1-8. doi: 10.1155/2014/128726	RCT	C&N	10
E88.9	To evaluate the effects of co-administration of probiotics with bofutsushosan (防風通聖散) on obesity.	bofutsushosan (防風通聖散)	Lee S J, Bose S, Seo J-G, et al. The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial. Clinical Nutrition 2014; 33: 973-81.	DB-RCT	N	11
F41.1	To evaluate the effectiveness and safety of yokukansan (抑肝散) in preoperative sedation.	yokukansan (抑肝散)	Arai YC, Kawanishi J, Sakakima Y, et al. The effect of the kampo medicine yokukansan on preoperative anxiety and sedation levels. Evidence-Based Complementary and Alternative Medicine 2014: 1-4. doi: 10.1155/2014/965045	RCT	N	12
F43.1	To evaluate the efficacy and safety of saikokeishikankyoto (柴胡桂枝乾姜湯) for posttraumatic stress disorder (PTSD).	saikokeishikankyoto (柴胡桂枝乾姜湯)	Numata T, Gunfan S, Takayama S, et al. Treatment of posttraumatic stress disorder using the traditional Japanese herbal medicine saikokeishikankyoto: A randomized observer-blinded controlled trial in survivors of the great East Japan earthquake and tsunami. Evidence-Based Complementary and Alternative Medicine 2014: 1-6. doi:10.1155/2014/683293	RCT	C&N	13
F45.9	To evaluate the efficacy and safety of kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) for otorhinolaryngological symptoms with a strong psychosomatic element.	kamikihito (加味帰脾湯)	Tanaka H. Problems and approaches to treatment of psychosomatic disease by an otorhinolaryngologist, and Kampo treatment for psychosomatic cases with depressive tendency – Focusing on kamikihito (加味帰脾湯) –. Phil Kampo 2014; 47: 20-2.	RCT-cross over	I	14
F52.2	To compare the efficacy of LEOPIN ROYAL with that of Kampo medicines for aging in males.	kamishoyosan (加味逍遙散) hangekobokuto (半夏厚朴湯) saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) hochuekkito (補中益氣湯) gosyajinkigan (牛車腎氣丸) hachimijiogan (八味地黄丸)	Nishimatsu H, Kitamura T, Yamada D, et al. Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines-comparison with traditional herbal medicines (Kampo). Aging male 2014; 17: 112-6.	RCT	C&N	15

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
G30.1	To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia (BPSD).	yokukansan (抑肝散)	Teranishi M, Kurita M, Nisiho S, et al. Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: A blinded, randomized trial. <i>Journal of Clinical Psychopharmacology</i> 2014; 33: 600-7.	RCT	N	16
G62.9	To evaluate the efficacy of the carbonate spring foot bath and goshajinkigan (牛車腎気丸) for lower-extremity peripheral neuropathy due to cancer chemotherapy.	goshajinkigan (牛車腎気丸)	Kawabata K, Nakano T, Tsutsumi J, et al. Evaluation of alleviation for lower-extremity peripheral neuropathy due to cancer chemotherapy. Effectiveness of the carbonate spring foot bath and goshajinkigan*. <i>Journal of the Japanese Society of Footcare</i> . 2014; 12: 145-50 (in Japanese).	RCT-envelope	I	17
G62.9	To verify the effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy during chemotherapy for breast cancer.	goshajinkigan (牛車腎気丸)	Abe H, Kawai Y, Mori T, et al. The Kampo medicine goshajinkigan prevents neuropathy in breast cancer patients treated with docetaxel. <i>Asian Pacific Journal of Cancer Prevention</i> 2014; 14: 6351-6.	RCT	N	18
H66.9	To evaluate the efficacy and safety of jumentaihoto (十全大補湯) in children with recurrent otitis media.	jumentaihoto (十全大補湯)	Yoshizaki T. A multicenter, double-blind, randomized controlled trial on the usefulness of jumentaihoto 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).	DB-RCT	N	19
I63.9	To evaluate the effectiveness of saireito (柴苓湯) for acute ischemic stroke.	saireito (柴苓湯)	Nakae Y. Effectiveness of saireito in acute ischemic stroke. <i>Kampo to Saishin Chiryō (Kampo &amp; the Newest Therapy)</i> 2013; 22: 329-32.	RCT	I&N	20
J00	To evaluate the efficacy of Kakkonto (葛根湯) for alleviating early cold symptoms.	kakkonto (葛根湯)	Okabayashi S, Goto M, Kawamura T, et al. Non-superiority of Kakkonto, a Japanese herbal medicine, to a representative multiple cold medicine with respect to anti-aggravation effects on the common cold: a randomized controlled trial. <i>Internal Medicine</i> 2014; 53: 949-56.	RCT	N	21
J00	To evaluate the efficacy and safety of shimpito (神秘湯) for treatment of cough associated with cold syndrome.	shimpito (神秘湯)	Itagaki K. Efficacy of shimpito for treatment of cough associated with cold syndrome.* <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2013; 70: 813-6 (in Japanese).	quasi-RCT	I&N	22
J10.1	To evaluate the long-term effects of jumentaihoto (十全大補湯) on maintenance of the anti-influenza antibody titer in elderly people after influenza vaccination.	jumentaihoto (十全大補湯)	Saiki I, Koizumi K, Goto H, et al. The long-term effects of a Kampo medicine, jumentaihoto, on maintenance of antibody titer in elderly people after influenza vaccination. <i>Evidence-Based Complementary and Alternative Medicine</i> 2013: 1-8. doi: 10.1155/2013/568074.	RCT	N	23
K12.1	To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for gastric cancer chemotherapy-induced oral mucositis.	hangeshashinto (半夏瀉心湯)	Aoyama T, Nishikawa K, Takiguchi N, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. <i>Cancer Chemotherapy and Pharmacology</i> 2014; 73: 1047-54.	DB-RCT	C&N	24
K21.9	To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton-pump inhibitor (PPI)-refractory laryngopharyngeal reflux (LPR).	rikkunshito (六君子湯)	Tokashiki R, Okamoto I, Funato N, et al. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. <i>World Journal of Gastroenterology</i> 2013; 19: 5118-24.	RCT	N	25
K21.9	To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton pump inhibitor-refractory non-erosive reflux disease.	rikkunshito (六君子湯)	Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. <i>Journal of Gastroenterology</i> 2014; 49: 1392-405.	DB-RCT	N	26
			Sakata Y, Tominaga K, Kato M, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from the G-PRIDE study who responded to rikkunshito. <i>BMC Gastroenterology</i> 2014; 14: 116.	RCT		
K30.0	To evaluate the treatment effects of rikkunshito (六君子湯) on functional dyspepsia.	rikkunshito (六君子湯)	Suzuki H, Matsuzaki J, Fukushima Y, et al. Randomized clinical trial: rikkunshito in the treatment of functional dyspepsia - a multicenter, double-blind, randomized, placebo-controlled study. <i>Neurogastroenterology and Motility</i> 2014; 26: 950-61.	DB-RCT	C&N	27

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K30.0	To evaluate the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms following endoscopic submucosal dissection (ESD) of early gastric cancer.	rikkunshito (六君子湯)	Uehara R, Isomoto H, Minami H, et al. Characteristics of gastrointestinal symptoms and function following endoscopic submucosal dissection and treatment of the gastrointestinal symptoms using rikkunshito. <i>Experimental and Therapeutic Medicine</i> 2013; 6: 1083-8.	RCT	N	28
K59.0	To evaluate the efficacy and safety of daikenchuto (大建中湯) as treatment for functional constipation in poststroke patients.	daikenchuto (大建中湯)	Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. <i>Evidence-Based Complementary and Alternative Medicine</i> 2014; 1-8. doi: 10.1155/2014/231258	RCT	C&N	29
K73.9	To evaluate whether use of Kampo medicines (Shimbuto [真武湯] and Ninjinto [人參湯]) in combination with pegylated interferon $\alpha$ plus ribavirin promotes therapeutic responses in patients with chronic hepatitis C.	shimbuto (真武湯) ninjinto (人參湯)	Kainuma M, Furusyo N, Murata M, et al. The effectiveness of traditional Japanese medicine (Kampo), in combination with pegylated interferon $\alpha$ plus ribavirin for patients with chronic hepatitis C: A pilot study. <i>Journal of Traditional Medicines</i> 2013; 30: 132-9.	RCT	I	30
M79.2	To evaluate the efficacy of maobushisaishinto (麻黄附子細辛湯) for treatment of occipital neuralgia.	maobushisaishinto (麻黄附子細辛湯)	Nakajima K, Sato H, Ooyama K, Is maobushisaishinto effective for neuropathic pain? Effect of maobushisaishinto on occipital neuralgia* Itami to Kampo (Pain and Kampo Medicine) 2014; 24: 31-7 (in Japanese with English abstract).	RCT-envelope	I&N	31
N95.1	To evaluate clinical effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women.	tokisyakuyakusan (当帰芍薬散)	Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on climacteric symptoms in peri- and postmenopausal women. <i>Climacteric</i> 2013; 16: 28-35.	RCT	N	32
R13	To evaluate the nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding.	hochuekkito (補中益気湯)	Sasaki S, Oumi A, Kumeda M, et al. Evaluation of nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding. <i>Science of Kampo Medicine</i> 2014 (in Japanese), 38: 263-6.	RCT	I	33
T67.8	To evaluate the efficacy of Kampo therapy in patients with heat illness requiring hospitalization.	hochuekkito (補中益気湯) rikkunshito (六君子湯) daikenchuto (大建中湯) yokukansan (抑肝散)	Nimura T, Yamada S, Ohwaki T, et al. Evaluation of the efficacy of Kampo therapy in patients with heat illness requiring hospitalization*. <i>Kampo Igaku (Kampo Medicine)</i> 2014; 38: 178-81 (in Japanese).	quasi-RCT	I&N	34
T67.8	To evaluate the effect of Kampo extract preparations as an adjunct to the standard therapy to shorten the symptom resolution time in patients with heat illness.	shakuyakukanzoto (芍薬甘草湯)	Takamura M, Effectiveness of Kampo extract preparations for the treatment of heat illness.* <i>Kampo to Saishinchiryō (Kampo &amp; the Newest Therapy)</i> 2014; 23: 121-4 (in Japanese).	RCT	N	35
T88.8	To evaluate pre-and post-operative analgesic effects of shakuyakukanzoto (芍薬甘草湯) for treatment of pain after hemorrhoidectomy.	shakuyakukanzoto (芍薬甘草湯)	Fukuda Y, Azuma M, Novel pain reliever shakuyaku-kanzo-to after hemorrhoidectomy, <i>Journal of the Japan Society of Coloproctology</i> , 2014; 67: 324-9.	RCT	I&N	36
Z01.0	To evaluate the ability of tokishakuyakusan (当帰芍薬散) yokukansan (抑肝散) keishibukuryogan (桂枝茯苓丸) hachimijiogan (八味地黄丸) to increase ocular blood flow.	tokishakuyakusan (当帰芍薬散) yokukansan (抑肝散) keishibukuryogan (桂枝茯苓丸) hachimijiogan (八味地黄丸)	Takayama S, Shiga Y, Kokubun T, et al. The traditional kampo medicine Tokishakuyakusan increases ocular blood flow in healthy subjects. <i>Evidence-Based Complementary and Alternative Medicine</i> 2014; 1-8. doi: 10.1155/2014/586857	RCT cross-over	C&N	37
Z04.8	To isolate the indicator ingredients of Kampo medicines and evaluate their equivalence with extract and decoction.	kakkonto (葛根湯)	Horii C, Okonogi A, Okubo T, et al. Studies on bioequivalence of kakkonto decoction and its extract preparation (I)*. <i>Shoyakugaku zasshi</i> 2014; 68: 9-12 (in Japanese).	RCT cross-over	N	38
Z04.8	To evaluate the bioequivalence of shoseiryuto (小青竜湯) extract and its decoction.	shoseiryuto (小青竜湯)	Horii C, Okonogi A, Studies on bioequivalence of shoseiryuto decoction and its extract preparation (I), <i>Shoyakugaku zasshi (Journal of Natural Medicines)</i> 2014; 68: 65-9.	RCT cross-over	I&N	39

## Revisions of Already Included References

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
J00	To compare the efficacy of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.	group of Kampo formulations (maoto[麻黄湯], keimakakuhanto[桂麻各半湯]etc.)	Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine) 1993; 10: 19–23 (in Japanese). Abe K, Takagi K. Comparison of treatment results between Kampo medicine-treated group and Western medicine-treated group for upper respiratory tract inflammation in children, Kampo medicine 1993; 43: 509-15.	quasi-RCT	N	40
K59.8	To evaluate the effectiveness of daikenchuto (大建中湯) for perioperative intestinal paralysis following laparoscopic colon cancer surgery.	daikenchuto (大建中湯)	Yaegashi M, Otsuka K, Itabashi T, et al. Applying a Kampo medication to lower gastrointestinal tract surgery*. Shokaki Geka (Gastroenterological Surgery) 2013; 36: 1315-24. Yaegashi M, Otsuka K, Itabashi T, et al. Daikenchuto stimulates colonic motility after laparoscopic -associated colectomy. Hepato-Gastroenterology 2014; 61: 85-9.	RCT	N C&N	41

## 1. Infections (including Viral Hepatitis)

### Reference

Enomoto Y, Hagiwara E, Komatsu S, et al. Pilot quasi-randomized controlled study of herbal medicine hochuekkito as an adjunct to conventional treatment for progressed pulmonary *mycobacterium avium* complex disease. *PLOS ONE* 2014; 9: 1-8. CENTRAL ID: CN- 00998327, Pubmed ID: 25093868

### 1. Objectives

To evaluate the effectiveness of hochuekkito (補中益気湯) as an adjunct to conventional treatment for progressed refractory pulmonary *Mycobacterium avium* complex (MAC) disease.

### 2. Design

Quasi-randomized controlled trial (quasi-RCT).

### 3. Setting

One hospital, Japan.

### 4. Participants

Eighteen pulmonary MAC disease patients aged 20 years or older who were treated for at least one year but persistently culture-positive, or who were difficult to treat with antibiotics due to drug allergy.

### 5. Intervention

Prior treatment: Combination of rifampicin, ethambutol, clarithromycin, levofloxacin, kanamycin, and streptomycin or no treatment.

Arm 1: Hochuekkito (補中益気湯) (manufacturer unknown) administered orally 2.5 g b.i.d. or 2.5 g t.i.d. + prior treatment for up to 24 weeks (n=9) (one subject untreated).

Arm 2: Prior treatment (n=9) (one subject untreated).

### 6. Main outcome measures

Sputum conversion rate at 24 weeks and number of MAC colonies.

Change in shadow size in the lungs at 24 weeks.

Chronic obstructive pulmonary disease assessment test (CAT) scores and serum albumin level, serum C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

### 7. Main results

The sputum of all subjects remained positive for bacteria throughout the study. The number of colonies from baseline to 24 weeks remained essentially unchanged in Arm 1 or 2. Chest X-ray revealed improvement or no change in 8 subjects in Arm 1, and 3 subjects in Arm 2, showing that the MAC disease had a significantly more favorable course in the hochuekkito arm. CAT scores and ESR and CRP levels were worsened in most subjects in the two arms, but body weight and serum albumin level tended to increase in Arm 1. Interestingly, body weight increased in all subjects with radiographic improvement and decreased in most subjects with radiographic progression.

### 8. Conclusions

Although patients in the hochuekkito group had higher baseline ESR level and lower baseline blood albumin level, they showed chest radiographic improvement and increased body weight. Thus hochuekkito is useful as a therapeutic drug for pulmonary MAC disease.

### 9. From Kampo medicine perspective

Hochuekkito is indicated for patients in poor general condition.

### 10. Safety assessment in the article

No serious adverse events were noted.

### 11. Abstractor's comments

This RCT selected study subjects from a group of 155 patients with pulmonary MAC disease. These days, the number of pulmonary MAC disease patients is increasing. Since patients are not always responsive to general treatment, this study treatment seems meaningful. Establishing true outcome measures will improve the quality of evidence in a future RCT. Further development of this research is anticipated.

### 12. Abstractor and date

Fujisawa M, 31 March 2017.

#### 4. Metabolism and Endocrine Diseases

##### Reference

Watanabe K, Shimada A, Miyaki K, et al. Long-term effects of goshajinkigan in prevention of diabetic complications: A randomized open-labeled clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2014; 1-8. doi: 10.1155/2014/128726 CENTRAL ID: CN-00993596, Pubmed ID: 24812564

##### 1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for treatment of diabetic complications.

##### 2. Design

Randomized controlled trial (RCT).

##### 3. Setting

Nine hospitals, Japan.

##### 4. Participants

A total of 149 type 2 diabetic patients with HbA1c of  $\geq 6.5\%$ , aged 40 to 75 years. Exclusion criteria were macroangiopathies including cerebral infarction, myocardial infarction, angina pectoris, leg gangrene, and arteriosclerosis obliterans; nephropathy associated with microalbuminuria or serum creatinine of 1.0 mg/dL; and proliferative or pre-proliferative retinopathy. Other exclusion criteria were related to *sho* (証, pattern) for goshajinkigan and included BMI of 30 kg/m<sup>2</sup> or more; two or more digestive system symptoms including gastrointestinal weakness, anorexia, nausea, and diarrhea; and three or more symptoms or activities indicative of sensitivity to heat such as a preference for dressing lightly, sweating upwards from the neck, a tendency to drink cold water, flushed face, congestion of the eyeballs, and a high body temperature of 36.7°C or higher.

##### 5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules administered orally at 2.5 g t.i.d. (n=100).

Arm 2: No treatment (n=49).

##### 6. Main outcome measures

The primary outcome measures were occurrence of nonfatal myocardial infarction or cerebral infarction and frequency of diabetic nephropathy or retinopathy; the progression of diabetic nephropathy as indicated by a new onset of renal failure or an increase in urinary protein; and the progression of diabetic retinopathy as evaluated by fundus photography performed annually by ophthalmologists. Secondary outcome measures were body weight, blood pressure, fasting blood glucose, glycosylated hemoglobin, blood insulin, diabetic neuropathy, etc. Diabetic neuropathy was evaluated on the basis of characteristic symptoms: ankle reflex, lightheadedness, abnormal sweating, occurrence of constipation or diarrhea, etc.

##### 7. Main results

A total of 116 subjects, i.e., 149 subjects minus 33 subjects who stopped visiting the hospital, were included in the analysis (74 subjects in the goshajinkigan arm; 42 subjects in the no treatment arm). The mean observation period was 28 months in Arm 1, and 15 months in Arm 2. No macroangiopathies such as myocardial infarction and cerebral infarction occurred in the two arms. The occurrence of diabetic nephropathy and retinopathy was not significantly different between arms. The deterioration of ankle reflex was significantly more frequent in Arm 2 than in Arm 1 ( $P=0.04$ ). Glycosylated hemoglobin level was significantly lower in Arm 1 than in Arm 2 at 60 months ( $P<0.05$ ). The fasting blood glucose level was significantly decreased from baseline in Arm 1 at 36 months ( $P<0.05$ ).

##### 8. Conclusions

Goshajinkigan inhibits worsening of ankle reflex and improves glycosylated hemoglobin and fasting blood glucose levels.

##### 9. From Kampo medicine perspective

To evaluate patients with *sho* (証, pattern) for goshajinkigan, patients with obesity, gastrointestinal weakness, and sensitivity to heat were excluded from the study.

##### 10. Safety assessment in the article

No dropouts due to adverse reactions to goshajinkigan were noted.

##### 11. Abstractor's comments

This is an interesting clinical study planned to elucidate the long-term effects of goshajinkigan, which is frequently used for treatment of diabetes mellitus. As stated by the authors, however, the desired number of subjects could not be included in the study and the available macroangiopathies occurrence data were inadequate. On the other hand, there were data suggesting that goshajinkigan was effective. Future studies with more subjects are anticipated.

##### 12. Abstractor and date

Goto H, 31 March 2017.

#### 4. Metabolism and Endocrine Diseases

##### Reference

Lee S J, Bose S, Seo J-G, et al. The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial. *Clinical Nutrition* 2014; 33: 973-81. Pubmed ID: 24411490

##### 1. Objectives

To evaluate the effects of co-administration of probiotics with bofutsushosan (防風通聖散) on obesity.

##### 2. Design

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

##### 3. Setting

One university hospital in Seoul, the Republic of Korea.

##### 4. Participants

Fifty females aged 19 to 65 years with BMI of  $>25 \text{ kg/m}^2$  and waist circumference of  $>85 \text{ cm}$ . Exclusion criteria were hypothyroidism, Cushing's syndrome, heart diseases, cancer, lung diseases, severe renal dysfunction ( $\text{Cr} >2.0 \text{ mg/dL}$ ), hepatic dysfunction, non-insulin dependent diabetes mellitus (fasting blood sugar level [FBS]  $>140 \text{ mg/dL}$ ), eating disorders, pregnancy, breast feeding, and body weight decrease by 10% within 6 months of the study.

##### 5. Intervention

Arm 1: TSUMURA Bofutsushosan (防風通聖散) Extract Granules 3 g b.i.d. + probiotics twice daily (Duolac7 capsules) for 8 weeks ( $n=25$ ).

Arm 2: TSUMURA Bofutsushosan (防風通聖散) Extract Granules 3 g b.i.d. + placebo twice daily (identical to Duolac7 capsules) for 8 weeks ( $n=25$ ).

##### 6. Main outcome measures

The main outcome measures were body weight and gut permeability. The secondary outcome measures were BMI, blood pressure, blood parameters (e.g., lipid levels), fecal bacteria count, endotoxin level, body fat level (as measured by bioelectrical impedance), and quality of life (as measured using the Korean version of obesity-related quality of life [KOQOL] scale). In the article, parameters including body weight, waist circumference, BMI, and body fat level (bioelectrical impedance) were termed "body composition parameters," while other parameters including blood parameters, fecal bacteria count, and endotoxin level were termed "metabolic biomarkers."

##### 7. Main results

Although body weight and waist circumference were significantly decreased in both arms ( $P=0.000$ ), no inter-arm difference in the body composition parameters or metabolic biomarkers were found. Correlation analysis revealed that change in body composition was positively correlated with endotoxin level ( $\gamma=0.441$ ,  $P<0.05$  for body weight;  $\gamma=0.350$ ,  $P<0.05$  for fat mass) and lactic acid bacteria count ( $\gamma=0.425$ ,  $P<0.05$  for body weight;  $\gamma=0.407$ ,  $P<0.05$  for BMI). The body composition parameters, waist circumference and total cholesterol level were positively correlated with Gram negative bacteria count ( $\gamma=0.359$  and  $\gamma=0.393$ , respectively;  $P<0.05$  for both) and *Bifidobacterium breve* count was negatively correlated with endotoxin level ( $\gamma=-0.350$ ,  $P<0.05$ ).

##### 8. Conclusions

Correlation between gut microbiota and change in body composition shows that probiotics affect energy metabolism in obese subjects. Correlation between endotoxin level and body weight decrease suggests that probiotics play a role in preventing the growth of endotoxin-producing bacteria in gut microbiota that promote obesity-associated dysbiosis.

##### 9. From Kampo medicine perspective

None.

##### 10. Safety assessment in the article

Not mentioned.

##### 11. Abstractor's comments

This DB-RCT was conducted in the Republic of Korea and evaluated the effects of co-administration of bofutsushosan and probiotics on obesity. This study was a registered clinical trial of the Korean National Institute of Health (NIH) and seems to be a well-designed study. Although body weight was decreased in both arms, the body weight decrease was not significantly different between arms. Therefore, the efficacy of adding bofutsushosan to probiotics remains unknown. In the article, the authors focused mainly on the results of correlation analyses rather than the effectiveness of probiotics. Research questions posed at the time of the study's design seem to remain unanswered. The significance and effects of co-administration of bofutsushosan were poorly described. More explanation is needed. Further development of this research is anticipated.

##### 12. Abstractor and date

Tsuruoka K, 31 March 2017.

## 5. Psychiatric/Behavioral Disorders

### Reference

Arai YC, Kawanishi J, Sakakima Y, et al. The effect of the kampo medicine yokukansan on preoperative anxiety and sedation levels. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-4. doi: 10.1155/2014/965045 Pubmed ID: 24799947

#### 1. Objectives

To evaluate the effectiveness and safety of yokukansan (抑肝散) in preoperative sedation.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

Single facility (hospital surgery department).

#### 4. Participants

Seventy patients whose physical status was rated I or II (American Society of Anesthesiologists) before hemicolectomy (ages: 30-85; 23 females and 47 males).

#### 5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) extract granules (2.5 g) taken orally 1.5 hours before general anesthetic (n=36).

Arm 2: Diazepam (5 mg) taken orally 1.5 hours before general anesthetic (n=34).

#### 6. Main outcome measures

Intensity of anxiety immediately prior to anesthesia, using a verbal rating scale (VRS); Level of sedation using the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S).

#### 7. Main results

There was no significant difference between arms 1 and 2 in the intensity of anxiety on the VRS. The levels of sedation on the OAA/S showed statistically significant sedation in arm 2 compared to arm 1 ( $P<0.05$ ).

#### 8. Conclusions

Compared to diazepam, yokukansan does not excessively sedate patients.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

There were no adverse drug reactions in either the yokukansan group or the diazepam group.

#### 11. Abstractor's comments

This clinical trial evaluated the significance of using yokukansan in sedation prior to hemicolectomy. The authors concluded that sedation with yokukansan prior to surgery under general anesthesia is not excessive. However, because the trial was not designed as a non-inferiority study, it does not clarify whether diazepam and yokukansan have the same level of effectiveness in suppressing anxiety. Hopefully the authors will conduct a trial that indicates non-inferiority by comparing yokukansan administration with diazepam administration for the suppression of anxiety prior to surgery under general anesthesia, and indicates the effectiveness of yokukansan administration for the suppression of anxiety prior to surgery under general anesthesia in comparison with the use of placebo or no preoperative drugs prior to surgery, as the next stage of their research.

#### 12. Abstractor and date

Koike H, 31 March 2017.

## 5. Psychiatric/Behavioral Disorders

### Reference

Numata T, Gunfan S, Takayama S, et al. Treatment of posttraumatic stress disorder using the traditional Japanese herbal medicine saikokeishikankyoto: A randomized observer-blinded controlled trial in survivors of the great East Japan earthquake and tsunami. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-6. doi:10.1155/2014/683293 CENTRAL ID: CN-00988474, Pubmed ID: 24790634

#### 1. Objectives

To evaluate the efficacy and safety of saikokeishikankyoto (柴胡桂枝乾姜湯) for posttraumatic stress disorder (PTSD).

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One hospital, Japan.

#### 4. Participants

Forty-three patients aged 20 years or older who survived the Great East Japan Earthquake and tsunami and had a diagnosis of PTSD according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (text revision) (DSM-IV TR), with an Impact of Event Scale-Revised Questionnaire (IES-R) score of  $\geq 25$ . The patients meeting any of the following four criteria were excluded from the study: 1) major medical illness such as neoplastic disease, acute inflammation, and any other disease precluding successful completion of the study; 2) psychosis due to other disorders such as schizophrenia, depression, and dementia; 3) delirium due to drugs, alcohol; and 4) use of neuroleptics, antianxiety drugs, antiepileptic drugs, antidepressants, or herbal remedies during the past 2 months.

#### 5. Intervention

Arm 1: TSUMURA Saikokeishikankyoto (柴胡桂枝乾姜湯) Extract Granules 2.5 g t.i.d. for 2 weeks orally (n=21).

Arm 2: No administration (n=22).

#### 6. Main outcome measures

The primary outcome measure was severity of PTSD as measured on the total IES-R scale. The secondary outcome measures were scores on three IES-R subscales: the intrusion subscale of 8 items, Questions 1, 2, 3, 6, 9, 14, 16, and 20; the avoidance subscale of 8 items, Questions 5, 7, 8, 11, 12, 13, 17, and 22; and the hyperarousal subscale of 6 items, Questions 4, 10, 15, 18, 19, and 21.

#### 7. Main results

Twenty-one subjects in Arm 1 and 22 subjects in Arm 2 were included in the analysis. One subject in Arm 1 dropped out of the study due to cough on Day 3. Changes in total IES-R scores were significantly different between the two arms ( $P < 0.001$ ). Total IES-R scores were significantly improved from baseline to the completion of the study in Arm 1 ( $P < 0.001$ ) but not in Arm 2. The between-arm differences in all three subscales were significant ( $P = 0.025$  for avoidance subscale;  $P = 0.005$  for hyperarousal subscale;  $P < 0.001$  for intrusion subscale). From baseline to the completion of the study, there was a significant improvement in three subscale scores in Arm 1 ( $P = 0.003$  for avoidance sub-scale;  $P < 0.001$  for hyperarousal subscale;  $P < 0.001$  for intrusion sub-scale) and a significant improvement in one subscale score in Arm 2 ( $P = 0.032$  for avoidance subscale). There were significant inter-arm differences in the scores on Questions 1, 3, 6, 14, 19, 20, and 21 ( $P < 0.001$  for Question 1;  $P = 0.005$  for Question 3;  $P < 0.001$  for Question 6;  $P = 0.003$  for Question 14;  $P = 0.001$  for Question 19;  $P = 0.002$  for Question 20;  $P = 0.001$  for Question 21).

#### 8. Conclusions

Saikokeishikankyoto is effective for alleviation of PTSD.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

One subject in the saikokeishikankyoto arm was withdrawn from the study on Day 3 due to mild cough.

#### 11. Abstractor's comments

This was an innovative clinical study evaluating the efficacy of a Kampo product for treatment of post-disaster PTSD, and a valuable study given the rarity of this type of disaster. However, as mentioned by the authors, the small number of subjects, the influence of placebo effect, and the absence of control drugs for comparison seems to preclude adequate evaluation of the efficacy. Although there are many limitations to the conduct of this type of study, based on this study's findings, further development of clinical studies with longer follow-up and inclusion of positive and negative controls for comparison is anticipated.

#### 12. Abstractor and date

Goto H, 31 March 2017.

## 5. Psychiatric/Behavioral Disorders

### Reference

Tanaka H. Problems and approaches to treatment of psychosomatic disease by an otorhinolaryngologist, and Kampo treatment for psychosomatic cases with depressive tendency – Focusing on kamikihito (加味帰脾湯) –. *Phil Kampo* 2014; 47: 20-2. Ichushi Web ID: 2014238207

#### 1. Objectives

To evaluate the efficacy and safety of kamikihito (加味帰脾湯) and kamishoyosan (加味逍遙散) for otorhinolaryngological symptoms with a strong psychosomatic element.

#### 2. Design

Quasi-randomized controlled trial (quasi-RCT).

#### 3. Setting

Single facility (hospital otorhinolaryngology department).

#### 4. Participants

Thirty patients who presented at the otorhinolaryngology department with dizziness, tinnitus or hypopharyngeal globus sensation; who scored at least 11 points on the Toho University Self-Rating Questionnaire for Depression, SRQ-D; and whose psychosomatic factors appeared to aggravate symptoms.

#### 5. Intervention

Arm 1: Kamikihito (加味帰脾湯) (manufacturer and dose unknown) taken for four weeks then kamishoyosan (加味逍遙散) (manufacturer and dose unknown) taken for four weeks (n=15).

Arm 2: Kamishoyosan (加味逍遙散) (manufacturer and dose unknown) taken for four weeks then kamikihito (加味帰脾湯) (manufacturer and dose unknown) taken for four weeks (n=15).

#### 6. Main outcome measures

Change in chief complaint following the change of Kampo medication.

#### 7. Main results

Efficacy was relatively high in 6.7% and low in 33.3% of patients in arm 1 after the change of Kampo medication. Efficacy was not high in any and it was low in 50.0% of the 10 patients who scored 16 or more on the SRQ-D, which is an indicator of possible depression. Of the 5 patients who scored 11-15 on the SRQ-D, which is on the borderline of depression, efficacy was high in 20.0% and it was not low in any patient. In arm 2, efficacy was high in 26.7% and low in 6.7% of patients. Of the 10 patients who scored 16 or more on the SRQ-D, efficacy was high in 40.0% and it was not low in any patient. Of the 5 patients who scored 11-15 on the SRQ-D, efficacy was not high in any and it was low in 20.0%.

#### 8. Conclusions

Kamikihito was more effective than kamishoyosan for dizziness, tinnitus and hypopharyngeal globus sensation aggravated by psychosomatic factors in patients with an SRQ-D score of 16 or more and kamishoyosan was more effective than kamikihito in patients with an SRQ-D score of 11-15.

#### 9. From Kampo medicine perspective

Kamikihito appears to be more appropriate than kamishoyosan for patients with severe depressive tendency.

#### 10. Safety assessment in the article

No adverse effect induced by kamishoyosan or kamikihito was observed.

#### 11. Abstractor's comments

This study was a cross-over comparison to evaluate whether kamikihito or kamishoyosan is more effective for otorhinolaryngological symptoms in which psychosomatic factors exist. The study suggests that kamikihito is effective for patients with severe depression and that kamishoyosan is effective for patients with slightly mild depression. It suggests that the SRQ-D could be a tool when selecting these two prescriptions. However, this study alone does not conclusively prove that kamikihito and kamishoyosan are effective for otorhinolaryngological symptoms. As the next stage of research to clarify which patient group responds to kamikihito and kamishoyosan, the author should prospectively study in a randomized controlled trial whether kamikihito is effective for patients with severely depressive otorhinolaryngological symptoms and whether kamishoyosan is effective for patients with mild depressive otorhinolaryngological symptoms.

#### 12. Abstractor and date

Koike H, 31 March 2017.

## 5. Psychiatric/Behavioral Disorders

### Reference

Nishimatsu H, Kitamura T, Yamada D, et al. Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines-comparison with traditional herbal medicines (Kampo). *Aging male* 2014; 17: 112-6. CENTRAL ID: CN-00992899, Pubmed ID: 24844765

#### 1. Objectives

To compare the efficacy of LEOPIN ROYAL with that of Kampo medicines for aging in males.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One department of urology in a university hospital and one department of urology in a hospital, Japan.

#### 4. Participants

Forty-nine males who complained of aging symptoms and underwent physical examinations at the Department of Urology, Faculty of Medicine, University of Tokyo.

#### 5. Intervention

Arm 1: LEOPIN ROYAL for 6 months (n=24).

Arm 2: Kamishoyosan (加味逍遙散) (n=20), hangekobokuto (半夏厚朴湯) (n=1), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) (n=1), hochuekkito (補中益気湯) (n=1), goshajinkigan (牛車腎気丸) (n=1), and hachimijiogan (八味地黄丸) for 6 months (n=1) (manufacturers unknown).

#### 6. Main outcome measures

Aging Males' Symptoms (AMS) scale; International Index of Erectile Function with 5 questions (IIEF-5); Androgen Deficiency in the Aging Male (ADAM) score; Self-Rating Questionnaire for Depression (SRQ-D) score; and serum levels of the following hormones: total testosterone, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and estradiol (E2).

#### 7. Main results

In the LEOPIN ROYAL arm compared to the Kampo arm, somatic and psychological subscores and the total score in the AMS scale were significantly lower ( $P<0.01$  for somatic sub-score;  $P<0.01$  for psychological subscore;  $P<0.01$  for total score), and the AMS somatic score and IIEF-5 score were significantly improved ( $P<0.01$  for somatic subscore;  $P=0.019$  for IIEF-5 score). Blood levels of total testosterone, free testosterone, FSH, LH, PRL, or E2 remained unchanged in the two arms.

#### 8. Conclusions

LEOPIN ROYAL is more effective than kamishoyosan for symptoms of aging in males.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No special problems were noted.

#### 11. Abstractor's comments

In this study, kamishoyosan was the control for LEOPIN ROYAL, but hangekobokuto, saikokaryukotsuboreito, hochuekkito, goshajinkigan, and hachimijiogan were also used as controls in one subject each, depending on their symptoms. For symptoms such as decreased libido, hachimijiogan was presumably more effective than LEOPIN ROYAL; therefore, presenting in this article information about each Kampo formulation, rather than information about the group of Kampo formulations, would have been more valuable.

#### 12. Abstractor and date

Nakata H, 31 March 2017.

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

### Reference

Teranishi M, Kurita M, Nisiho S, et al. Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: A blinded, randomized trial. *Journal of Clinical Psychopharmacology* 2014; 33: 600-7. Pubmed ID: 23948783

#### 1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for behavioral and psychological symptoms of dementia (BPSD).

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One psychiatric hospital, Japan.

#### 4. Participants

Eighty-two patients who met the diagnostic criteria of dementia according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) with total score on the Mini-Mental State Examination (MMSE) of <19 and at least one symptom score of >4 in the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). Patients meeting any of the following criteria were excluded from the study: participation in any other drug study within 4 weeks of the study; hypersensitivity to risperidone, yokukansan, or fluvoxamine; evidence of chronic and/or severe disease that could interfere with the study.

#### 5. Intervention

Arm 1: Yokukansan (抑肝散) (manufacturer unknown) 2.5 to 7.5 g/day for 8 weeks (n=27).

Arm 2: Risperidone 0.5 to 2.0 g/day for 8 weeks (n=27).

Arm 3: Fluvoxamine 25 to 200 mg/day for 8 weeks (n=28).

The study was initiated after a 1-week washout of drugs used for treatment of BPSD. The dose of each drug was adjusted at the discretion of the investigator and based on his/her analysis of NPI-NH subscales.

#### 6. Main outcome measures

At baseline and Weeks 2, 4, 6, and 8, an assessment was made of neuropsychiatric symptoms using the NPI-NH, cognitive function using the MMSE, and daily life function using the Functional Independence Measure (FIM). To evaluate drug tolerability, blood and other tests and the Drug-induced Extra-pyramidal Symptoms Scale (DIEPSS) were performed.

#### 7. Main results

Of the 82 subjects, 76 were included in the analysis. NPI-NH scores were significantly improved from baseline to Week 8 in all arms ( $P=0.034$  in Arm 1;  $P=0.022$  in Arm 2;  $P<0.001$  in Arm 3), but with no significant difference among the three arms. MMSE and FIM scores did not change significantly in the three arms.

#### 8. Conclusions

Yokukansan is as effective as risperidone and fluvoxamine for BPSD but safer to use than risperidone.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

DIEPSS scores were similar between the yokukansan and fluvoxamine arms, but significantly higher in the risperidone arm than in the yokukansan and fluvoxamine arms. One subject in the risperidone arm died suddenly during the study.

#### 11. Abstractor's comments

BPSDs are important symptoms to treat, but there are no good drugs for BPSD treatment at this time. This clinically meaningful study evaluated the efficacy and safety of risperidone and yokukansan, which are frequently used in clinical settings, and fluvoxamine used by the authors. However, as acknowledged by the authors, no placebo was used in this study; the investigator's assessment might have been affected by this omission. In addition, since hospitalized patients were included in this study, care by staff members might have improved NPI-NH scores in all arms. However, the intent of this study was to improve the state of current treatment. It is anticipated that similar future studies will be conducted to establish the guidelines for treatment of BPSD with Kampo medicines.

#### 12. Abstractor and date

Goto H, 31 March 2017.

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

### Reference

Kawabata K, Nakano T, Tsutsumi J, et al. Evaluation of alleviation for lower-extremity peripheral neuropathy due to cancer chemotherapy. Effectiveness of the carbonate spring foot bath and goshajinkigan\*. *Journal of the Japanese Society of Footcare*. 2014; 12: 145-50 (in Japanese). Ichushi Web ID: 2015126257

#### 1. Objectives

To evaluate the efficacy of the carbonate spring foot bath and goshajinkigan (牛車腎気丸) for lower-extremity peripheral neuropathy due to cancer chemotherapy.

#### 2. Design

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

#### 3. Setting

One university hospital, Japan.

#### 4. Participants

Eighteen females with breast cancer aged <75 years who were to receive preoperative chemotherapy with paclitaxel (80 mg/m<sup>2</sup> once weekly, infused for 12 consecutive weeks).

#### 5. Intervention

Arm 1: Spring foot bath with Kao carbonated tablets (炭酸足浴剤) diluted in 6 L of warm water maintained at 38°C to 40°C and administered for 15 minutes daily at a convenient time for 12 weeks (n=8).

Arm 2: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules orally administered at 2.5 g t.i.d. for 12 weeks (n=4).

Arm 3: No treatment (n=6).

#### 6. Main outcome measures

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), peripheral neuropathy (i.e., numbness measured on the CTC-AE version 4.0 grading scale), and foot skin temperature (measured by thermography) at Weeks 4, 8, and 12.

#### 7. Main results

Peripheral neuropathy in the lower extremity (all grade 2 or less) occurred in 11 of the 18 subjects (61%). In the carbonate spring foot bath arm (n=8), the 4 subjects with no numbness compared to the remaining 4 subjects with numbness had higher median skin temperature (34.8°C vs. 31.1°C) and higher percent change in foot skin temperature over time. At Week 12 of paclitaxel chemotherapy, 4 subjects in the carbonate spring foot bath arm, 0 subjects in the goshajinkigan arm, and 3 subjects in the control arm had no numbness, and 2 subjects in the carbonate spring foot bath arm had no numbness for 12 consecutive weeks.

#### 8. Conclusions

Lower-extremity numbness caused by preoperative once-weekly paclitaxel chemotherapy may be alleviated by bathing in carbonate spring foot bath; however, the number of subjects in this study was too small to draw clear conclusions.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

Not mentioned.

#### 11. Abstractor's comments

This was a unique study evaluating the effects of carbonate spring foot bath on vasodilation, such as increased muscle blood flow, increased skin temperature, and alleviation of numbness. Presented only at the convention of the Japanese Society of Footcare, the study suggested that carbonate spring foot bath was effective for numbness in patients with non-small-cell lung cancer (NSCLC). Although there were 2 control arms (a goshajinkigan arm and no treatment arm), the number of subjects in each arm was small and no statistical analysis was mentioned in the article. Skin temperature should have been measured at baseline. Although the authors valued that the severity of peripheral neuropathy at the completion of the scheduled 12-week treatment was Grade 2 or lower in all subjects, it was not mentioned whether the treatment could be effective without dose reduction of paclitaxel. In addition, the description of the carbonate spring foot bath arm was mistakenly replaced by the description of the goshajinkigan arm in the third line of the Results section, and the number of subjects in the carbonate spring foot bath arm should be 8 instead of 6 in Table 4. It is anticipated that statistical evaluation of the efficacy of the carbonate spring foot bath will be possible once the number of subjects is increased.

#### 12. Abstractor and date

Motoo Y, 31 March 2017.

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

### Reference

Abe H, Kawai Y, Mori T, et al. The Kampo medicine goshajinkigan prevents neuropathy in breast cancer patients treated with docetaxel. *Asian Pacific Journal of Cancer Prevention* 2014; 14: 6351-6. Pubmed ID: 24377531

#### 1. Objectives

To verify the effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy during chemotherapy for breast cancer.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

Single facility (hospital).

#### 4. Participants

Sixty women aged 20-70 who were receiving chemotherapy with docetaxel for invasive breast cancer.

#### 5. Intervention

Arm 1: GJG group: TSUMURA Goshajinkigan Extract Granules (7.5 g divided in two to three doses per day) taken either before or between meals (n=33).

Arm 2: B12 group: Mecobalamin (1500µg/day) taken after meals (n=27).

#### 6. Main outcome measures

Assessment of the frequency of peripheral neuropathy (Neurotoxicity Criteria of Debiopharm [DEB-NTC], Common Terminology Criteria for Adverse Events [CTC-AE], and Visual analogue scale [VAS]).

#### 7. Main results

The incidence of chemotherapy-induced peripheral neuropathy in the GJG group was 39.3% compared to 88.9% in the B12 group, which was significantly ( $P<0.01$ ) lower. Twelve patients in the B12 group were assessed as DEB-NTC grade 3, a severe assessment, while 5 patients in the GJG group received that assessment, which was a significant difference ( $P<0.01$ ). Similarly, 12 patients were assessed as CTC-AE grade 2 and 1 as grade 3 in the B12 group, while 6 patients in the GJG group were assessed as grade 2 and none as grade 3, which was a significant difference ( $P<0.01$ ). The VAS scores for subjective symptom assessment were also significantly lower ( $P<0.01$ ) in the GJG group ( $2.7\pm 2.2$ ) compared to the B12 group ( $4.9\pm 2.4$ ). Taking goshajinkigan during chemotherapy with docetaxel significantly reduced not only the occurrence of peripheral neuropathy but also the severity of subjective symptoms.

#### 8. Conclusions

Preventive oral administration of goshajinkigan suppresses the occurrence of peripheral neuropathy and even when such neuropathy does occur, it reduces symptom severity, during chemotherapy with docetaxel for invasive breast cancer in female patients.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

There was no clinically problematic adverse effect.

#### 11. Abstractor's comments

This study confirmed the preventive effects of goshajinkigan for peripheral neuropathy, an inevitable adverse effect of chemotherapy for invasive breast cancer. It has great significance in clinical medicine and is a valuable study. Confirmation of this significant effect through a randomized trial, not based on the *zuisho* (随証, patterns) of Kampo medicine, means the results are worthy of being included in the guidelines for Western medical treatment. Hopefully the authors will conduct a robust study of its clinical effects under protocols including goshajinkigan's *zuisho* (随証, pattern), or at least whether *jinkyō* (腎虚, kidney deficiency) is present or not. Further research is anticipated.

#### 12. Abstractor and date

Ushiroyama T, 31 March 2017.

## 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).

#### 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  $\geq$ 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

The mean number of recurrences with acute otitis media per month during the study, and the difference in mean number of recurrences with acute otitis media per month between baseline and endpoint of the study, 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, general condition including nutritional status (e.g., albumin level at the completion of the study, Kaup's index), and anemia improvement (yes or no).

#### 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. Compared with Arm-2 patients, Arm-1 patients had decreased mean number of recurrence with acute otitis media per month (time/month) and coryza per month, and decreased mean frequency of antibiotic use per month. However, there was no significant inter-arm difference in nutritional status or anemia improvement.

#### 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. However, this study was published as a report, many details of the results were not mentioned. A more detailed presentation of the results should be published. As stated by the authors, more evidence of juzentaihoto's efficacy in the treatment of childhood recurrent otitis media is desired and will be sought in the future.

#### 12. Abstractor and date

Goto H, 31 March 2017.

## 9. Cardiovascular Diseases

### Reference

Nakae Y. Effectiveness of saireito in acute ischemic stroke. *Kampo to Saishin Chiryō (Kampo & the Newest Therapy)* 2013; 22: 329-32. Ichushi Web ID: 2014077192

#### 1. Objectives

To evaluate the effectiveness of saireito (柴苓湯) for acute ischemic stroke.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

Single facility (hospital neurology department).

#### 4. Participants

Ninety-nine patients who gave verbal consent out of the acute ischemic stroke patients hospitalized between December 2010 and December 2011.

#### 5. Intervention

Arm 1: Saireito administration group: TSUMURA Saireito (柴苓湯) Extract Granules (3g t.i.d.) administered after each meal for two weeks (n=43).

Arm 2: Non-administration group (n=56)

#### 6. Main outcome measures

NIHSS (National Institutes of Health Stroke Scale) and mRS (modified Rankin Scale) comparison.

#### 7. Main results

The results of a questionnaire taken after the first week of hospitalization showed that symptoms had been significantly alleviated in the saireito administration group. The NIHSS scores showed significant improvement in the saireito administration group compared to the non-administration group after the second week of hospitalization ( $P=0.020$ ). The mRS scores showed significant improvement in the saireito administration group compared to the non-administration group after the first week ( $P=0.020$ ) and the second week ( $P=0.011$ ) of hospitalization.

#### 8. Conclusions

Saireito is effective for acute ischemic stroke.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

None.

#### 11. Abstractor's comments

This study used the NIHSS and the mRS to evaluate the effectiveness of saireito in acute ischemic stroke. It showed that saireito has a certain effect on symptoms after stroke. Much of saireito's mechanism of action has not been elucidated, so comparing the scores for each item may provide clues to its mechanism of action, such as whether it is more effective for lower or upper limb symptoms.

#### 12. Abstractor and date

Nakata H, 31 March 2017

## 10. Respiratory Diseases (including Influenza and Rhinitis)

### Reference

Okabayashi S, Goto M, Kawamura T, et al. Non-superiority of Kakkonto, a Japanese herbal medicine, to a representative multiple cold medicine with respect to anti-aggravation effects on the common cold: a randomized controlled trial. *Internal Medicine* 2014; 53: 949-56. Ichushi Web ID: 2015097387, Pubmed ID: 24785885

#### 1. Objectives

To evaluate the efficacy of Kakkonto (葛根湯) for alleviating early cold symptoms.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

Nine university hospitals and 6 clinics, Japan.

#### 4. Participants

A total of 407 cold patients aged 18 to 65 years with throat discomfort, mild chills, but no sweating who underwent a physical examination within 48 hours of onset. (The patients meeting any of the following criteria were excluded from the study: moderate or severe subjective symptoms, body temperature of 37.5°C or higher, any prior oral treatment or serious underlying disease.)

#### 5. Intervention

Arm 1: Kracie Kakkonto (葛根湯) Extract Granules administered orally at 2.0 g t.i.d. for four days or until the symptoms disappeared (n=209).

Arm 2: Western-style multiple cold medicine (Pabron Gold-A) at 3.6 g/day for four days or until the symptoms disappeared (n=198).

#### 6. Main outcome measures

Worsening of cold symptoms (yes or no) (i) within five days after oral administration and (ii) within seven days after oral administration.

#### 7. Main results

In the Kakkonto arm, 41 subjects dropped out and 168 subjects were included in the analysis. In the Pabron arm, 26 subjects dropped out and 172 subjects were included in the analysis. Worsening occurred by five days in 38 subjects (22.6%) in the Kakkonto arm and 43 (25.0%) in the Pabron arm. The percentage was lower in the Kakkonto arm, but the difference between arms was not significant. Worsening occurred by seven days in 41 subjects (24.4%) in the Kakkonto arm and 52 (30.2%) in the Pabron arm. Again, the percentage was not significantly lower in the Kakkonto arm.

#### 8. Conclusions

There is no significant difference in efficacy between Kakkonto and the multi-symptom cold medicine.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No serious adverse drug reactions were noted in the two arms. The incidence of mild adverse drug reactions including sleepiness and gastrointestinal disorder was lower in the Kakkonto arm (7 subjects [4.2%] vs 12 subjects [7.0 %]), but not significantly so.

#### 11. Abstractor's comments

This is an important study evaluating the efficacy of Kakkonto, which is frequently used for daily treatment of cold symptoms in clinical settings, as compared with a multi-symptom cold medicine. Although the anti-aggravation effects of Kakkonto on cold symptoms were evaluated in the present study with sample size based on the previous study, a significant efficacy was not demonstrated. One of the limitations of the study, according to the authors, was the difficulty with demonstrating evidence based on subjective evaluation. In this study, the efficacy was evaluated in terms of cold symptom prevention, but not symptom improvement in actual clinical settings. The inclusion of patients with mild symptoms may have affected the study's ability to detect a significant difference. Although the study design seemed to be appropriate for determining Kakkonto's efficacy as a self-medication and its safety, more studies are anticipated after re-examining the existing severity classification rules or outcome measures to be evaluated.

#### 12. Abstractor and date

Koike H, 31 March 2017.

## 10. Respiratory Diseases (including Influenza and Rhinitis)

### Reference

Itagaki K, Efficacy of shimpito for treatment of cough associated with cold syndrome.\* *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2013; 70: 813-6 (in Japanese). Ichushi Web ID: 2014063683 [MOL](#), [MOL-Lib](#)

### 1. Objectives

To evaluate the efficacy and safety of shimpito (神秘湯) for treatment of cough associated with cold syndrome.

### 2. Design

Quasi-randomized controlled trial (quasi-RCT).

### 3. Setting

One clinic, Japan.

### 4. Participants

Sixteen patients (3 males and 13 females) who visited the clinic between January 2011 and May 2011 and had a diagnosis of cold syndrome with severe or persistent cough.

### 5. Intervention

Arm 1: Kracie Shimpito (神秘湯) Extract Granules administered orally at 3.0 g b.i.d. before or between meals for 7 days and lysozyme hydrochloride 90 mg t.i.d. + carbocysteine 500 mg t.i.d. after meals for 7 days (n=9).

Arm 2: Lysozyme hydrochloride 90 mg t.i.d. + carbocysteine 500 mg t.i.d. after meals for 7 days (n=7).

### 6. Main outcome measures

The severity of cough was assessed on the following 4-point scale: 0, none; 1, mild; 2, moderate; 3, severe. Subjects recorded the severity scores in a cough diary. The scores on each day were compared to those on Day 1 using the Wilcoxon signed-rank test.

### 7. Main results

The scores improved significantly after Day 4 ( $P<0.05$ ) in Arm 1 and after Day 6 in Arm 2 ( $P<0.05$ ).

### 8. Conclusions

Shimpito is effective for the treatment of refractory cough associated with cold syndrome.

### 9. From Kampo medicine perspective

None.

### 10. Safety assessment in the article

No adverse events were noted.

### 11. Abstractor's comments

This is a meaningful clinical study because the author, a physician at the study site, conducted the study, in the midst of daily busy clinical practice, to evaluate the efficacy of a Kampo medicine in patients with cough due to cold, which is a common symptoms. However, since some subjects with persistent cough were assigned to the control arm, the inter-arm difference in the period from onset to the start of the study investigation was large:  $4.7\pm 1.7$  days in the shimpito arm and  $16.7\pm 18.4$  days in the control arm. Persistent cough might be refractory and affect the results of the study. In addition, intra-arm (but not inter-arm) cough severity scores were compared; therefore, the efficacy of shimpito compared with that of control drugs remains unknown. Since it is very important to make a continuous effort to elucidate the efficacy of Kampo medicine against common symptoms in daily clinical settings, a larger number of such clinical studies are anticipated..

### 12. Abstractor and date

Fujisawa M, 31 March 2017; Goto H, 31 March 2017.

## 10. Respiratory Diseases (including Influenza and Rhinitis)

### Reference

Saiki I, Koizumi K, Goto H, et al. The long-term effects of a Kampo medicine, jumentaihoto, on maintenance of antibody titer in elderly people after influenza vaccination. *Evidence-Based Complementary and Alternative Medicine* 2013: 1-8. doi: 10.1155/2013/568074. Pubmed ID: 24348705

### 1. Objectives

To evaluate the long-term effects of jumentaihoto (十全大補湯) on maintenance of the anti-influenza antibody titer in elderly people after influenza vaccination.

### 2. Design

Randomized controlled trial (RCT).

### 3. Setting

Four long-term care facilities, Japan.

### 4. Participants

Ninety patients aged 65 years or older who were receiving long-term care for cerebrovascular disease, dementia, bone, joint disease, etc.

### 5. Intervention

Arm 1: Kracie Jumentaihoto (十全大補湯) Extract Granules administered orally or through a gastrostomy tube 3.75 g b.i.d. for a total of 28 weeks (i.e., from 4 weeks before influenza vaccination to 24 weeks after influenza vaccination) (n=44).

Arm 2: No administration (n=46).

### 6. Main outcome measures

Antibody titer to influenza virus A (H1N1 and H3N2) and B at Weeks -4, 0, 4, 8, 12, and 24.

### 7. Main results

The H3N2 antibody titer was significantly higher in the jumentaihoto arm (Arm 1) than in the control arm (Arm 2) at 8 weeks after vaccination ( $P=0.0229$ ), and rose still higher at Weeks 4, 12, and 24. In addition, the antibody titer from Weeks 4 to 24 was significantly higher in Arm 1 than in Arm 2 ( $P=0.0468$ ). There was no significant inter-arm difference in antibody titers to H1N1 or B at any post-vaccination week.

### 8. Conclusions

Jumentaihoto increases and maintains the titer of influenza antibodies especially those specific for H3N2.

### 9. From Kampo medicine perspective

None.

### 10. Safety assessment in the article

Epigastric discomfort was reported in one subject after administration of jumentaihoto, but improved after discontinuation of administration. There were no significant changes in serum chemistry values in the two arms.

### 11. Abstractor's comments

Notably, this RCT demonstrated significantly higher anti-H3N2 antibody titers at Week 8 after vaccination in elderly people, at high risk for influenza infection, treated with jumentaihoto from 4 weeks before to 24 weeks after vaccination, a total of 28 weeks. Although a previous RCT of maobushisaishinto had reported that anti-H3N2 antibody titers were significantly higher at Week 4, it did not report this effect after Week 4. In another RCT, hochuekkito did not significantly increase antibody titer. These preceding studies and the present study differed in the Kampo products selected, treatment period, target subjects, etc. Especially, the present study included subjects with the mean age of 85.6 years who had experienced the outbreaks of H3N2 in 1968 to 1969, which elicited a strong post-vaccination response. Previously, the adjuvanticity of jumentaihoto was demonstrated in a basic study. This is the first RCT to clinically evaluate the effect of jumentaihoto on enhancing production of influenza antibody.

### 12. Abstractor and date

Motoo Y, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Aoyama T, Nishikawa K, Takiguchi N, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. *Cancer Chemotherapy and Pharmacology* 2014; 73: 1047-54. CENTRAL ID: CN-00993423, Pubmed ID: 24652604

#### 1. Objectives

To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for gastric cancer chemotherapy-induced oral mucositis.

#### 2. Design

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

#### 3. Setting

Ten facilities (four university hospitals and 6 hospitals).

#### 4. Participants

Ninety-one patients with oral mucositis induced by gastric cancer chemotherapy rated at grade 1 or more on CTC-AE v4.0.

#### 5. Intervention

Arm 1: TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (2.5 g t.i.d.) taken until the start of the next round of chemotherapy (n=45).

Arm 2: Placebo administration group (n=46).

#### 6. Main outcome measures

Severity of oral mucositis, its frequency and duration.

#### 7. Main results

The frequency of oral mucositis of grade 2 or more was 40% in the hangeshashinto group (arm 1) and 41.3% in the control group (arm 2), so no significant between-group difference was found. Nor was any significant between-group difference found for oral mucositis duration (14 days in arm 1 and 16 days in arm 2). However, median oral mucositis duration among all grades was 9.0 days in arm 1 and 17.0 days in arm 2: although this was not a significant difference, oral mucositis duration tended to be shorter in the hangeshashinto group compared to the placebo group ( $P=0.290$ ).

#### 8. Conclusions

Hangeshashinto tends to shorten the duration of oral mucositis induced by gastric cancer chemotherapy.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

Being an adverse effect induced by an anticancer drug, no adverse event attributable to hangeshashinto was observed.

#### 11. Abstractor's comments

Being a double-blind RCT using placebo, this is a high-quality study that tested the effects of hangeshashinto for oral mucositis induced by gastric cancer chemotherapy. Unfortunately there was no significant difference in frequency or duration of oral mucositis of grade 2 or more, although hangeshashinto did tend to shorten oral mucositis duration among all grades. The authors point to a decrease in the anticancer dose as a possible reason why no significant difference was found. Yet the authors mention the need for a larger scale phase III trial in which the anticancer drug dose is not decreased, which is a valid observation. This follows the principle of "Kampo for the successful accomplishment of standard treatment": alleviating the oral mucositis with hangeshashinto allows for the anticancer drug to demonstrate its inherent effect to the full, without the need to decrease the dose. Further progress in this research is anticipated.

#### 12. Abstractor and date

Motoo Y, 31 March 2017

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Tokashiki R, Okamoto I, Funato N, et al. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. *World Journal of Gastroenterology* 2013; 19: 5118-24. Pubmed ID: 23964146

#### 1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton-pump inhibitor (PPI)-refractory laryngopharyngeal reflux (LPR).

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

Single facility (university hospital otorhinolaryngology department), Japan.

#### 4. Participants

In total, 22 patients with PPI-refractory LPR aged 20-76, between March 2007 and December 2008.

#### 5. Intervention

Following administration of lansoprazole (30 mg) once daily for 2 weeks, patients with LPR symptoms and at least a score of 3 for acid reflux, abdominal pain, and dyspepsia on the gastrointestinal symptom rating scale (GSRS) were assigned to two groups using the envelope method. Excluded from the study were patients taking psychoactive or other gastrointestinal drugs, during pregnancy, breastfeeding mothers, and patients with sinusitis, asthma, or organic disease.

Arm 1: TSUMURA Rikkunshito (六君子湯) (2.5 g t.i.d) alone for four weeks (n=11).

Arm 2: TSUMURA Rikkunshito (六君子湯) (2.5 g t.i.d) plus lansoprazole (30 mg/day) for four weeks (n=11).

Outcome measures were compared before and four weeks after administration.

#### 6. Main outcome measures

(1) LPR symptoms (globus sensation, sore throat, and excessive laryngeal care) were assessed using a Visual Analogue Scale (VAS). (2) Gastrointestinal symptoms were assessed on the GSRS (comprised of five domains including abdominal and reflux symptoms). (3) Gastric emptying was assessed with a radio-opaque marker (carried out on 18 patients).

#### 7. Main results

LPR symptoms (VAS score) decreased significantly in both groups after four weeks, but there was no significant difference between the groups. Of the LPR symptoms, sore throat decreased significantly in the rikkunshito plus PPI group compared to the rikkunshito-alone group, however, there was no significant difference between the two groups for excessive laryngeal care. Gastrointestinal symptoms decreased significantly on the GSRS in both groups. Gastric emptying improved in the rikkunshito-alone group, but there was no significant before-after difference, while significant improvement was observed in the rikkunshito plus PPI group, however, there was no significant difference between the two groups. Examination of the relation between gastric emptying and globus sensation improvement found a significant correlation between the two.

#### 8. Conclusions

Rikkunshito is effective for PPI-refractory LPR (especially globus sensation). Gastric emptying capacity may be involved in the mechanism of action.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No adverse event or reaction was observed during the protocol period.

#### 11. Abstractor's comments

While PPI is effective for LPR, quite a few patients do not respond. The protocols for this study provided for a two-week PPI administration period before non-responsive patients were randomly assigned to a rikkunshito-alone group or a PPI combined with rikkunshito group for the four-week clinical trial, which made for a highly precise design. As well as obtaining significant clinical outcomes in relation to efficacy, the authors suggest the involvement of improvement in gastric emptying in the mechanism of action. Hopefully the authors will carry out further clinical trials with larger samples in future.

#### 12. Abstractor and date

Kogure T, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### References

**Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. *Journal of Gastroenterology* 2014; 49: 1392-405. Pubmed ID: 24535455**

Sakata Y, Tominaga K, Kato M, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from the G-PRIDE study who responded to rikkunshito. *BMC Gastroenterology* 2014; 14: 116. Pubmed ID: 24990161

#### 1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton pump inhibitor-refractory non-erosive reflux disease.

#### 2. Design

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

#### 3. Setting

One university hospital department of gastroenterology and 48 other medical institutions (including university hospitals, non-university hospitals, clinics), Japan.

#### 4. Participants

Two hundred and forty-two patients with PPI-refractory (FSSG [Frequency Scale for the Symptoms of gastroesophageal reflux disease {GERD}]] scores greater than 8 after treatment with regular use of rabeprazole (RPZ), omeprazole, and lansoprazole for 4 weeks or longer) for non-erosive reflux disease (NERD).

#### 5. Intervention

Arm 1: Oral administration of RPZ 10mg/day + TSUMURA Rikkunshito (六君子湯) 7.5g/day in 3 divided doses (administration period: 8 weeks) (n=109).

Arm 2: Oral administration of RPZ 10mg/day + placebo (granules that have a taste and scent similar to rikkunshito and are packaged similarly to rikkunshito [六君子湯]) 7.5g/day in 3 divided doses (n=108).

#### 6. Main outcome measures

FSSG, GSRS (Gastrointestinal Symptom Rating Scale), and SF-8 (Short-Form Health survey-8) scores. Each domain of the SF-8.

#### 7. Main results

Sixteen patients in the rikkunshito-administered group and 9 patients in the placebo-administered group were excluded due to invalid results or drop out due to adverse events. Both groups showed no significant improvement in FSSG and GSRS scores at week 4 and week 8. Mental component Summary (MCS) scores improved significantly in the rikkunshito group at week 4 compared to the placebo group ( $P<0.05$ ). In patients aged over 65, acid-related dysmotility symptoms (ARD) improved significantly in the rikkunshito group at week 8.

#### 8. Conclusions

Administration of rikkunshito in addition to RPZ improved subjective symptoms of PPI-refractory NERD; however, the difference compared to placebo was not statistically significant.

#### 9. From Kampo medicine perspective

None. However, the improvement in the SF-8 MCS score was prominent in patients with BMI below 22.

#### 10. Safety assessment in the article

There were no differences in serious complications related to the treatment drugs.

#### 11. Abstractor's comments

Conducting a multi-center placebo-controlled trial in patients with PPI-refractory NERD deserves praise. However, the improvement in subjective symptoms of PPI-refractory NERD due to administration of rikkunshito plus RPZ (when compared with placebo) was not statistically significant. A sub-analysis and supplementary paper demonstrated that rikkunshito is effective in improving MCS score and ARD (manifesting as abdominal distension, stomach feeling heavy, and indigestion after meals) in elderly patients. Future analysis of its intended use should be anticipated.

#### 12. Abstractor and date

Kogure T, 31 March 2017

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Suzuki H, Matsuzaki J, Fukushima Y, et al. Randomized clinical trial: rikkunshito in the treatment of functional dyspepsia - a multicenter, double-blind, randomized, placebo-controlled study. *Neurogastroenterology and Motility* 2014; 26: 950-61. CENTRAL ID: CN-00995379, Pubmed ID: 24766295

#### 1. Objectives

To evaluate the treatment effects of rikkunshito (六君子湯) on functional dyspepsia.

#### 2. Design

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

#### 3. Setting

Multi-center study in 20 general hospitals and 11 clinics, Japan.

#### 4. Participants

Two hundred forty-seven patients aged 20 years or older who had diagnosis of functional dyspepsia.

#### 5. Intervention

Arm 1: Rikkunshito (六君子湯) extract granules (manufacturer unknown) 2.5 g t.i.d. before meals for 8 weeks (n=125).

Arm 2: Placebo before meals for 8 weeks (n=122).

#### 6. Main outcome measures

Weekly change in the global patient assessment (GPA) score and Likert scale after rikkunshito administration; change in the Gastrointestinal Symptom Rating Scale (GSRS) score, anti-*Helicobacter pylori* IgG antibody level, and blood ghrelin concentrations from baseline to post-administration.

#### 7. Main results

The proportion of participants showing symptom improvement as reflected in the GPA score was higher in the rikkunshito arm than in the placebo arm, but not significantly (33.6% vs. 23.8%;  $P=0.09$ ). However, stomach pain was significantly more improved in the rikkunshito arm than in the placebo arm ( $P=0.04$ ); postprandial abdominal distension also tended to improve ( $P=0.06$ ), with greater improvement in the *H. pylori*-positive patients (40.0%) than in *H. pylori*-negative patients (20.0%) ( $P=0.07$ ). The change in blood ghrelin concentration from baseline to post-administration was similar between the two arms.

#### 8. Conclusions

Eight-week administration of rikkunshito improved dyspepsia symptoms especially stomach pain and postprandial distension. This indicated that rikkunshito has strong treatment effects on functional dyspepsia.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No clinically significant adverse drug reactions were reported. However, mild adverse drug reactions including diarrhea and nausea were found in 15.2% of subjects in the rikkunshito arm and 11.5% of subjects in the placebo arm (no significant difference).

#### 11. Abstractor's comments

The main value of this study was its clinical evaluation of the treatment effects of rikkunshito for functional dyspepsia, which is widely used for upper gastrointestinal tract symptoms corresponding to *qi* (気) deficiency. In particular, certain effects of rikkunshito on stomach pain and postprandial distension will enable clinical practitioners to more effectively treat functional dyspepsia in actual clinical settings. Rikkunshito is a Kampo product essential for persons living in modern society who suffer from functional dyspepsia, a psychophysiological disorder known to be difficult to treat. In this study, blood ghrelin concentrations did not change after rikkunshito administration. To elucidate the mechanism of rikkunshito, a formulation with tonic effects for spleen *qi* deficiency or *qi* deficiency affecting upper gastrointestinal tract symptoms, future studies will need to utilize biochemical measures such as biogenic markers and physiological markers including peristaltic movement of the gastrointestinal tract and secretory release of digestive enzymes.

#### 12. Abstractor and date

Ushiroyama T, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Uehara R, Isomoto H, Minami H, et al. Characteristics of gastrointestinal symptoms and function following endoscopic submucosal dissection and treatment of the gastrointestinal symptoms using rikkunshito. *Experimental and Therapeutic Medicine* 2013; 6: 1083-8. Pubmed ID: 24223626

#### 1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms following endoscopic submucosal dissection (ESD) of early gastric cancer.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One university hospital, Japan.

#### 4. Participants

Thirteen patients who experienced upper gastrointestinal symptoms 6 to 8 days following stomach ESD. The patients had at least 3 of the following symptoms: epigastric pain, hunger pain, nausea, borborygmus, abdominal distension, eructation, and increased flatus assessed by the Gastrointestinal Symptom Rating Scale (GSRS) Questionnaire.

#### 5. Intervention

Arm 1: Oral administration of proton pump inhibitor (PPI: rabeprazole) 10 mg b.i.d. and TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 8 weeks (n=8).

Arm 2: Oral administration of PPI for 8 weeks (n=5).

#### 6. Main outcome measures

Gastric emptying (as assessed by the [<sup>13</sup>C]-labeled acetate breath test) at Weeks 0 and 8.

Scores for the following Gastrointestinal Symptom Rating Scale (GSRS) items: epigastric pain, hunger pain, nausea, borborygmus, abdominal distension, eructation, and increased flatus at Weeks 0, 4, and 8.

#### 7. Main results

Gastric emptying was compared between subjects who underwent ESD and healthy volunteers rather than between Arms 1 and 2 and was significantly decreased in subjects who underwent ESD ( $P<0.01$ ). Overall GSRS score was significantly decreased at Week 4 ( $P<0.05$ ) and Week 8 ( $P<0.01$ ) compared to Week 0 in Arm 1 but not Arm 2, and the GSRS subscale score for abdominal pain at Week 0 was significantly decreased at Week 8 in Arm 1 ( $P<0.05$ ).

#### 8. Conclusions

The combination of PPI and rikkunshito may alleviate symptoms (especially abdominal pain) in patients with upper gastrointestinal symptoms following ESD.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

Not mentioned.

#### 11. Abstractor's comments

This RCT evaluated the efficacy of PPI + rikkunshito, which is believed to be effective for functional dyspepsia, in patients with upper gastrointestinal symptoms following ESD using change in subjective symptoms (GSRS score) as indicator. This study showed that gastric emptying was decreased following ESD but failed to measure gastric emptying after coadministration of rikkunshito and PPI. The authors suggested that the mechanism of this combined therapy, which improved abdominal pain following ESD, was associated with improved gastric emptying and increased secretion of ghrelin; however, this suggestion is based only on a literature review and was not verified. Future studies to evaluate the effects on frequency of postoperative bleeding (a complication of ESD) or time needed for mucosal defect (ulcer scarring) repair is anticipated. This structured abstract replaces a previous one (which was based on a convention abstract) and utilizes data from the original article.

#### 12. Abstractor and date

Hoshino E, 31 December 2013; Motoo Y, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. *Evidence-Based Complementary and Alternative Medicine* 2014; 1-8. doi: 10.1155/2014/231258 CENTRAL ID: CN-00999698, Pubmed ID: 25089144

#### 1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) as treatment for functional constipation in poststroke patients.

#### 2. Design

Randomized controlled trial (RCT)

#### 3. Setting

Six hospitals.

#### 4. Participants

Thirty-four patients (17 females / 17 males) who were diagnosed with functional constipation according to Roma III diagnostic criteria from September 2012 to December 2013 and who remained stable over 6 months or longer after having suffered cerebral hemorrhage, cerebral infarct, or subarachnoid hemorrhage.

#### 5. Intervention

Arm 1: Common treatment for relief of constipation including laxative, enema, fecal disimpaction, etc. as well as oral administration of TSUMURA Daikenchuto (大建中湯) Extract Granules 5g divided in three doses per day before each meal or tube administration for 4 weeks (n=17).

Arm 2: Common treatment for relief of constipation including laxative, enema, fecal disimpaction, etc. for 4 weeks (n=17).

#### 6. Main outcome measures

Constipation scoring system (CSS), gas volume score (GVS), calcitonin-gene related peptide (CGRP) concentration in blood.

#### 7. Main results

Patients in arm 1 showed a statistically significant decrease in CSS ( $P<0.01$ ), and also in GVS ( $P=0.03$ ) compared to arm 2. The CGRP concentration in blood was similar between arm 1 and arm 2.

#### 8. Conclusions

Daikenchuto is effective in improvement of constipation and retention of gas in the abdominal cavity in poststroke patients.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

Adverse reaction was not observed in the daikenchuto-administered arm.

#### 11. Abstractor's comments

This paper reports the results of a clinical trial investigating the efficacy of daikenchuto for the treatment of constipation in poststroke patients. This RCT is significant for its demonstration of daikenchuto's efficacy in poststroke patients who often suffer from constipation and distension. Moreover, while hypothetically the effect of daikenchuto on constipation is mediated via CGRP, this RCT found no significant difference in blood levels of CGRP in spite of daikenchuto's clinical efficacy. This conflicting finding has warrants further basic studies of daikenchuto. As mentioned in this paper, some studies report that daikenchuto is not effective for constipation in other circumstances; therefore, further studies are anticipated to determine the efficacy of daikenchuto in a broader spectrum of constipation.

#### 12. Abstractor and date

Koike H, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Kainuma M, Furusyo N, Murata M, et al. The effectiveness of traditional Japanese medicine (Kampo), in combination with pegylated interferon  $\alpha$  plus ribavirin for patients with chronic hepatitis C: A pilot study. *Journal of Traditional Medicines* 2013; 30: 132-9. Ichushi Web ID: 2014095582 [J-STAGE](#)

### 1. Objectives

To evaluate whether use of Kampo medicines (Shimbuto [真武湯] and Ninjinto [人參湯]) in combination with pegylated interferon  $\alpha$  plus ribavirin promotes therapeutic responses in patients with chronic hepatitis C.

### 2. Design

Randomized controlled trial (RCT).

### 3. Setting

General clinical department of a university hospital and 5 related hospitals.

### 4. Participants

Fifty-one patients (20 males and 31 females) diagnosed with chronic hepatitis C. All patients were hepatitis C virus (HCV) antibody-positive and HCV-RNA-positive for more than 6 months. The exclusion criteria were: (1) history of upper gastrointestinal (UGI) bleeding, ascites, hepatocellular carcinoma, hepatic failure, and cirrhosis with a risk of esophageal varices, (2) hemoglobin  $<11.5$  g/dL, leukocyte count  $<3 \times 10^3$ /L, platelet count  $<50 \times 10^9$ /L; (3) hepatitis B surface antigen positive or human immunodeficiency virus (HIV) positive; (4) excessive alcohol use ( $>60$  g/day), drug addiction; (5) severe mental disorder; (6) treatment with an antiviral drug and steroid therapy for 12 months before enrollment.

### 5. Intervention

Arm 1: Patient group treated with Kampo medicines (Group A) (n=26). Oral administration of pegylated interferon  $\alpha$  1.5 $\mu$ g/kg/week plus ribavirin 600–1000 mg/day (600mg for 60kg of body weight or below, 800mg for 60–80kg of body weight, 1000 mg for 80 kg of body weight or over) concurrently with Kampo medicines (mixed formulation of Shimbuto [真武湯] extract and Ninjinto [人參湯] extract, each 5g t.i.d. before each meal).

Arm 2: Control group (Group B)(n=25). Oral administration of pegylated interferon  $\alpha$  1.5 $\mu$ g/kg/week plus ribavirin 600–1000mg/day (600mg for 60kg of body weight or below, 800mg for 60–80kg of body weight, 1000 mg for 80kg of body weight or over) alone.

### 6. Main outcome measures

Early virological response (EVR), Sustained virological response (SVR).

### 7. Main results

EVR rate and SVR rate were significantly higher in Group A than in Group B (EVR, 22/26 patients [84.6%] vs 14/25 patients [56.0%],  $P=0.034$ ; SVR, 20/26 patients [76.9%] vs 12/25 patients [48.0%],  $P=0.033$ ). The minimum dose (80% or higher of pegylated interferon  $\alpha$  and 60% or higher of ribavirin) was given to 22/26 patients (84.6%) in Group A and 18/25 patients (72.0%) in Group B. SVR rate showed no differences between arms. The dropout rate was significantly different between Group B (5/25 patients [20.0%]) and Group A (0/26 patients;  $P=0.0023$ ).

### 8. Conclusions

Administration of a mixed formulation of Shimbuto and Ninjinto to patients with chronic hepatitis C who received concurrent administration of pegylated interferon  $\alpha$  plus ribavirin decreases the dropout rate and promotes treatment efficacy.

### 9. From Kampo medicine perspective

The reason for the efficacy of Shimbuto and Ninjinto in patients with chronic hepatitis C has not been identified.

### 10. Safety assessment in the article

No adverse events were observed in the Kampo-administered group. Five patients dropped out in the control group. Adverse events, vomiting (week 4), interstitial pneumonia (week 10), hyperthyroidism (week 22), and hepatocellular carcinoma (week 19) were observed in 1 patient each. The remaining patient stopped treatment, as no clinical efficacy was observed at week 44.

### 11. Abstractor's comments

This RCT demonstrated the efficacy of concurrent use of Kampo medicines (mixed formulation of Shimbuto and Ninjinto) with pegylated interferon  $\alpha$  plus ribavirin in patients with chronic hepatitis C. The study showed that the treatment decreased the onset rate of adverse events and increased the rate of early virological response and concluded that Kampo medicines were effective. In the original abstract, the line "Kampo medicines were given to Group B" was considered a misprint. This trial was carefully designed including the intent-to-treat (ITT) analysis; however blinding was not mentioned. If the trial had used measures such as blinding to reduce bias, it would have increased confidence in the results. We anticipate further developments.

### 12. Abstractor and date

Tsuruoka H, 31 March 2017.

### 13. Diseases of the Musculo Skeletal System and Connective Tissue

#### Reference

Nakajima K, Sato H, Ooyama K, Is maobushisaishinto effective for neuropathic pain? Effect of maobushisaishinto on occipital neuralgia\* *Itami to Kampo (Pain and Kampo Medicine)* 2014; 24: 31-7 (in Japanese with English abstract). Ichushi Web ID: 2015016097

#### 1. Objectives

To evaluate the efficacy of maobushisaishinto (麻黄附子細辛湯) for treatment of occipital neuralgia.

#### 2. Design

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

#### 3. Setting

Three clinics, Japan.

#### 4. Participants

Twenty-two patients with occipital neuralgia who visited three clinics between November 2011 and April 2012, a total of 6 months.

#### 5. Intervention

Arm 1: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules administered at 2.5 g t.i.d. before or between meals (n=12).

Arm 2: A loxoprofen tablet administered orally at a dose of 60 mg up to three times daily (n=10).

The longest treatment period was 21 days in both Arms 1 and 2. Treatment was discontinued if the patient's pain disappeared or if an adverse drug reaction occurred.

#### 6. Main outcome measures

Treatment period. Pain assessed on a visual analogue Scale (VAS). A subject who reported a change in VAS value of 50 mm or more within 1 week of the last dose was regarded as "very responsive"; 50 mm or more 8 or more days after the last dose or of 20–49 mm, as "responsive"; and of 20 mm or less, as "nonresponsive."

#### 7. Main results

No significant inter-arm difference was found for treatment period. The VAS value was 51.8±16.1 mm (standard deviation: SD) before treatment and 7.8±14.3 mm (SD) after treatment in the maobushisaishinto arm, showing a significant decrease ( $P=0.0001$  in the U-test), and 56.0±19.6 mm (SD) before treatment and 10.1±17.5 mm (SD) after treatment in the loxoprofen arm, showing a significant decrease ( $P=0.0001$  in the U-test). The number of subjects assessed as very responsive, responsive, and nonresponsive was 4, 7, and 1 to maobushisaishinto, and 5, 4, and 1 to loxoprofen, respectively.

#### 8. Conclusions

Maobushisaishinto is effective for the treatment of occipital neuralgia.

#### 9. From Kampo medicine perspective

The relationship between the efficacy of maobushisaishinto and *kan-sho* (寒証, cold pattern) was not found.

#### 10. Safety assessment in the article

No description of adverse drug reactions were provided. Since discontinuation due to adverse drug reactions was not mentioned, there seemed to be no adverse responses.

#### 11. Abstractor's comments

This study is very meaningful from the standpoint of clinical practice because it was a randomized controlled clinical trial using envelopes for allocation and evaluated the efficacy of maobushisaishinto for treatment of occipital neuralgia, as compared with loxoprofen. An evaluation of the outcomes suggests that maobushisaishinto has a similar or higher efficacy than loxoprofen. Considering the randomized controlled design of the trial, it is regrettable that the statistical procedures used to analyze between-arm differences were insufficient. In the Kampo medicine perspective section, the authors suggested that the diagnosis of *hyo-sho* (表証, exterior pattern) was appropriate in study subjects because the disease period was short (around 10 days). However, most occipital neuralgia lesions generally are considered to be appeared on the exterior surface of the body. Given these, further evaluation in a larger number of subjects is anticipated.

#### 12. Abstractor and date

Kogure T, 31 March 2017.

#### 14. Genitourinary Tract Disorders (including Climacteric Disorders)

##### Reference

Koike K, Yamamoto Y, Suzuki N, et al. Efficacy of porcine placental extract on climacteric symptoms in peri- and postmenopausal women. *Climacteric* 2013; 16: 28-35. Pubmed ID: 22920723

##### 1. Objectives

To evaluate clinical effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women.

##### 2. Design

Randomized controlled trial (RCT).

##### 3. Setting

One university hospital and 1 clinic, Japan.

##### 4. Participants

Seventy-six women with climacteric symptoms.

##### 5. Intervention

Arm 1: TSUMURA Tokishaykuyakusan (当帰芍薬散) Extract Granules administered orally at 7.5 g/day for 24 weeks (n=38).

Arm 2: Porcine placental extract (350 mg/capsule) administered orally 3 capsules/day for 12 weeks followed by 6 capsules/day for 12 weeks (n=38).

##### 6. Main outcome measures

Severity (scores) of climacteric symptoms assessed by the simplified menopausal index (SMI), Zung self rating depression scale (ZSDS), and Spielberger state-trait anxiety inventory (STAI).

##### 7. Main results

Compared with the tokishaykuyakusan alone group (control), the porcine placental extract group had significantly lower SMI and scores on the ZSDS and STAI ( $P<0.01$ ).

##### 8. Conclusions

Porcine placental extract may be an effective option for the treatment of climacteric symptoms in peri-postmenopausal women.

##### 9. From Kampo medicine perspective

None.

##### 10. Safety assessment in the article

During the study period, porcine placental extract treatment did not affect other variables including serum chemistry levels and BMI and caused no adverse drug reactions.

##### 11. Abstractor's comments

Placental extracts have been commercialized and used as a supplement to alleviate climacteric symptoms. This article is valuable because treatment effects of porcine placental extract on climacteric symptoms in peri-postmenopausal women were clinically evaluated using SMI, ZSDS score, and STAI score. Placental extract contains many bioactive substances, including low-molecular-weight peptides, which appear to be absorbed from the gastrointestinal tract into systemic circulation, where they affect targeted organs. However, their mechanisms are unknown. Although the influence of prior treatment with tokishaykuyakusan could not be ruled out, further studies on the relation and difference between these biopharmaceuticals and Kampo medicines are anticipated.

##### 12. Abstractor and date

Ushiroyama T, 31 March 2017.

## 18. Symptoms and Signs

### Reference

Sasaki S, Oumi A, Kumeda M, et al. Evaluation of nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding. *Science of Kampo Medicine 2014 (in Japanese)*, 38: 263-6. Ichushi Web ID: 2015111016

#### 1. Objectives

To evaluate the nutrition improvement effects of hochuekkito (補中益気湯) in patients with tube feeding.

#### 2. Design

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

#### 3. Setting

One hospital.

#### 4. Participants

Twenty-four patients with tube feeding.

#### 5. Intervention

Arm 1: Administration of TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5g t.i.d. for 3 months (n=12).

Arm 2: Lactose 2.5g colored with decaffeinated coffee t.i.d. for 3 months (n=12).

#### 6. Main outcome measures

Serum albumin value, prognostic nutritional index, area of the brachial muscle, controlling nutritional status (CONUT) score, rate of fever of 37°C or higher 3 months before and after the administration.

#### 7. Main results

As 1 and 3 patients dropped out in arm 1 and in arm 2, respectively, 11 patients in arm 1 and 9 patients in arm 2 were studied. Serum albumin level was significantly higher in arm 1 than arm 2 at month 3 ( $P=0.032$ ). There were no significant between-arm differences in prognostic nutritional index, area of the brachial muscle, CONUT score after administration, and rate of fever of 37°C or higher for 3 months before and after the administration.

#### 8. Conclusions

Hochuekkito increases serum albumin levels in patients with tube feeding.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

In the hochuekkito-administered group, 1 patient died, and in placebo-administered group, 2 patients died.

#### 11. Abstractor's comments

This paper reports nutrition improvement after hochuekkito administration in patients with tube feeding. A number of retrospective studies have suggested the efficacy of hochuekkito and other Kampo medicines to improve nutrition rationally; however, this study was significant because it was an actual double-blind prospective study showing the efficacy of hochuekkito. In the study, the endpoints had not been defined either primary or secondary endpoints and designed to detect any endpoints with statistical significance among the 5 endpoints. Therefore, we have to admit that improvement in serum albumin level (the only endpoint with statistical significance) may be accidental. In addition, the number of patients in the study was insufficient and the investigators appeared to proceed through the trial in a disorganized undisciplined manner without knowing the appropriate duration of evaluation. Thus the trial is only important as an exploratory study, and a new trial with defined primary endpoints, appropriate number of patients, and appropriate evaluation period is anticipated as a next step.

#### 12. Abstractor and date

Koike H, 31 March 2017.

## 19. Post-anesthesia and Postoperative Pain

### Reference

Nimura T, Yamada S, Ohwaki T, et al. Evaluation of the efficacy of Kampo therapy in patients with heat illness requiring hospitalization\*. *Kampo Igaku (Kampo Medicine)* 2014; 38; 178-81 (in Japanese). Ichushi Web ID: 2015015844

#### 1. Objectives

To evaluate the efficacy of Kampo therapy in patients with heat illness requiring hospitalization.

#### 2. Design

Randomized controlled trial (RCT). However, the attending physicians were randomly assigned.

#### 3. Setting

A department of internal medicine in a general hospital in Aichi Prefecture, Japan.

#### 4. Participants

Thirty-four patients who were admitted to the hospital due to hyperthermia during the summer seasons (July to September) from 20xx to 20xx (2 years).

Hyperthermia was diagnosed and its severity was graded according to the severity classification (Classes I to III) of the Japanese Congress on Neurological Emergencies.

#### 5. Intervention

Arm 1: Kampo arm (fluid replacement + Kampo medicine). Four physicians who routinely prescribe Kampo medicines were randomly assigned to this arm. (n=20)

Arm 2: Non-Kampo arm. Only fluid replacement was administered. Four physicians who do not routinely prescribe Kampo medicines were randomly assigned to this arm. (n=14)

#### 6. Main outcome measures

Number of hospitalization days.

#### 7. Main results

No inter-arm differences in age, sex, presence or absence of primary disease, laboratory data on admission, or severity of hyperthermia were found. Kampo medicines used in the Kampo arm were hochuekkito (n=17), rikkunshito (n=1), daikenchuto (n=1), and yokukansan (n=1). The hospitalization period was significantly shorter in the Kampo arm ( $5.1 \pm 3.7$  days) than in the non-Kampo arm ( $15.8 \pm 16.1$  days) for all hyperthermia severity Classes I to III ( $P < 0.05$ ) and for severity Class III ( $4.9 \pm 3.6$  days in the Kampo arm vs.  $20.5 \pm 18.5$  days in the non-Kampo arm;  $P < 0.05$ ).

#### 8. Conclusions

Kampo medicines shorten the period of hospitalization for hyperthermia.

#### 9. From Kampo medicine perspective

No differences were found in effects of four Kampo medicines used in the study: hochuekkito, rikkunshito, daikenchuto, and yokukansan. According to the article, Kampo medicines (seishoekkito, hochuekkito, rikkunshito, ninjinto, goreisan, and ireito) had previously been used for treating summer fatigue and heat exhaustion, but not for hyperthermia requiring hospitalization.

#### 10. Safety assessment in the article

One subject in each arm died in the study, but these deaths had no causal relationship with Kampo medicines.

#### 11. Abstractor's comments

This study is important because the efficacy of Kampo medicines in subjects with hyperthermia requiring hospitalization was evaluated in an RCT. Since this article is a short report, the study methods and the results were not fully described. The study design was an RCT; however, the prescribing physicians (Arm 1: physicians who routinely prescribe Kampo medicines, Arm 2: physicians who do not routinely prescribe Kampo medicines) were randomly assigned to each study arm. Therefore, neither the physicians nor the subjects were blinded. As in the usual RCT design, which would be preferable, just one Kampo medicine was used for evaluation and comparison between the Kampo and placebo control arms. The development of future studies is anticipated.

#### 12. Abstractor and date

Tsuruoka K, 31 March 2017.

## 19. Post-anesthesia and Postoperative Pain

### Reference

Takamura M, Effectiveness of Kampo extract preparations for the treatment of heat illness.\* *Kampo to Saishinchiryō (Kampo & the Newest Therapy)* 2014; 23: 121-4 (in Japanese).

#### 1. Objectives

To evaluate the effect of Kampo extract preparations as an adjunct to the standard therapy to shorten the symptom resolution time in patients with heat illness.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One clinic, Japan.

#### 4. Participants

Eleven male patients with heat illness assessed as Class II (moderate) in severity, occurring at manufacturing sites of companies with around 3000 employees (including exterior and interior sites) between June and September in 2010 and 2011, who were able to drink water.

#### 5. Intervention

For Kampo medicines, one packet (2.5 g) of TSUMURA Shyakuyakukanzoto (芍薬甘草湯) Extract Granules was used as a single dose for subjects with muscle cramp or myalgia. Otherwise, one packet (3.0 g) of TSUMURA Byakkokaninjinto (白虎加人参湯) Extract Granules was used as a single dose.

Arm 1: Cooling + oral rehydration solution (Otsuka OS-1) + saline infusion + Kampo extract preparation (n=5).

Arm 2: Cooling + oral rehydration solution (Otsuka OS-1) + saline infusion (n=6).

#### 6. Main outcome measures

Time from onset to symptom resolution.

#### 7. Main results

Symptoms in all subjects improved after treatment. Time to symptom resolution was significantly shorter in the Kampo arm (48.0±13.5 minutes vs 80.8±21.8 minutes;  $P=0.017$ ). No significant difference in age, blood pressure, body temperature, fluid replacement, or total water requirement was found between the arms.

#### 8. Conclusions

Adding shyakuyakukanzoto or byakkokaninjinto extract to the standard rehydration therapy (of cooling and salt and water supplementation) may shorten the time to symptom improvement in patients with heat illness.

#### 9. From Kampo medicine perspective

In Kampo therapy, byakkokaninjinto is believed to be effective for treatment of the following symptoms: *etsu* (暍, summerheat stroke), sweating, feeling hot in the body and thirsty. Shyakuyakukanzoto is used for treatment of myalgia and muscle stiffening symptoms.

#### 10. Safety assessment in the article

No adverse events were noted.

#### 11. Abstractor's comments

This is an interesting clinical study because the addition of one packet of Kampo extract preparations to the standard therapy for heat illness significantly shortened the time to symptom resolution by 30 minutes. On the other hand, since the number of subjects was small and two types of Kampo medicines were used in the study, the results in this study should be reviewed in the future. Meanwhile, the author's efforts to obtain randomized data from a population requiring emergency medical attention, which is difficult in actual clinical settings, should be respected. Although each subject's *sho* (証, pattern) was not diagnosed, shyakuyakukanzoto and byakkokaninjinto were appropriate for heat illness. As stated by the author, shortening of the time to symptom resolution in patients with mild to moderate heat illness, which is estimated to affect 30,000 patients annually in Japan, is meaningful from a medical cost standpoint. Further development is anticipated in future studies assessing the efficacy and safety of Kampo medicines added to the standard therapy.

#### 12. Abstractor and date

Fujisawa M, 31 March 2017.

## 19. Post-anesthesia and Postoperative Pain

### Reference

Fukuda Y, Azuma M, Novel pain reliever shakuyaku-kanzo-to after hemorrhoidectomy, *Journal of the Japan Society of Coloproctology*, 2014; 67: 324-9. Ichushi Web ID: 2014256564 [J-STAGE](#)

#### 1. Objectives

To evaluate pre-and post-operative analgesic effects of shakuyakukanzoto (芍薬甘草湯) for treatment of pain after hemorrhoidectomy.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One clinic, Japan.

#### 4. Participants

A total of 103 patients who visited the clinic after hemorrhoidectomy between April 2011 and September 2012.

#### 5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules administered orally at 2.5 g t.i.d. before meals before and after hemorrhoidectomy for 14 days (n=34).

Arm 2: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules administered orally at 2.5 g t.i.d. before meals only after hemorrhoidectomy for 7 days (n=37).

Arm 3: No treatment with TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (n=32).

#### 6. Main outcome measures

Maximum pain scored on a visual analogue scale (VAS).

#### 7. Main results

Over a 7-day post-operative period, the pain VAS score was significantly lower in Arm 1 than in Arm 3 ( $P<0.05$ ) on Day 2 after hemorrhoidectomy; in Arm 2 than in Arm 3 on Day 5 after hemorrhoidectomy ( $P<0.05$ ); and in Arm 1 than in Arm 3 ( $P<0.05$ ) on the day of hemorrhoidectomy. If VAS score of 3 or lower is defined as pain relief, the mean time to achieving pain relief was significantly shorter in Arm 1 than in Arm 3 ( $P<0.05$ ). The degree of pain alleviation was higher in Arm 1 than in Arm 3 on Day 6, but not in Arm 2 than in Arm 3, although it tended to be higher in Arm 2.

#### 8. Conclusions

Pre- and post-operative treatment with shakuyakukanzoto is effective for pain alleviation after hemorrhoidectomy.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No evident adverse events were noted.

#### 11. Abstractor's comments

This article demonstrated that continuous treatment with shakuyakukanzoto at the start of the pre-operative period is effective for post-operative pain alleviation. Although partial alleviation of pain was noted after the post-operative treatment, it is interesting that pre- and post-operative treatment was more effective. In general, since the effect of shakuyakukanzoto is apparent immediately after administration, it is also used as needed. As stated in the Discussion, careful monitoring is needed to prevent Glycyrrhiza-induced pseudoaldosteronism after continuous treatment. Since post-hemorrhoidectomy pain is most severe on the day of surgery, it is meaningful that oral administration of shakuyakukanzoto before the pain developed was more effective. Interestingly, mechanisms of pain development (increase in anal resting pressure and spasm of the anal sphincter) may explain why shakuyakukanzoto tended to be more effective in male and young subjects.

#### 12. Abstractor and date

Nakata H, 31 March 2017.

## 21. Others

### Reference

Takayama S, Shiga Y, Kokubun T, et al. The traditional kampo medicine Tokishakuyakusan increases ocular blood flow in healthy subjects. *Evidence-Based Complementary and Alternative Medicine* 2014; 1-8. doi: 10.1155/2014/586857 CENTRAL ID: CN-00993227, Pubmed ID: 24872835

#### 1. Objectives

To evaluate the ability of tokishakuyakusan (当帰芍薬散) to increase ocular blood flow.

#### 2. Design

Study 1: Double-blind, randomized controlled trial (cross-over) (DB-RCT cross-over).

#### 3. Setting

A university department of ophthalmology, Japan.

#### 4. Participants

Study 1: Thirteen healthy volunteers aged 20 to 70 years (mean age, 37.3±12.3 years; 6 males, 7 females) with intraocular pressure of ≤22 mmHg in both eyes (exclusion criteria: abnormal ocular fundus, history of ocular incisional surgery in either eye, history of systemic disease including hypertension and diabetes mellitus, and smoking history).

Study 2: Nineteen healthy volunteers (38 eyes) (mean age, 32.0±11.0 years; 8 males, 11 females).

#### 5. Intervention

Study 1: Four Kampo medicines (TSUMURA Yokukansan [抑肝散] Extract Granules, TSUMURA Tokishakuyakusan [当帰芍薬散] Extract Granules, TSUMURA Keishibukuryogan [桂枝茯苓丸] Extract Granules, and TSUMURA Hachimijiogan [八味地黄丸] Extract Granules) at 5 g each were orally administered with 50 mL of warm water in a single arm. All subjects randomly received these 4 Kampo medicines in a blinded manner for 2 months. Subjects received 1 Kampo medicine, followed by at least 1 week of washout, and then received next Kampo medicine. Clinical tests were performed before and after administration (n=13).

Study 2: TSUMURA Tokishakuyakusan [当帰芍薬散] Extract Granules at 5 g was orally administered with 50 mL of warm water. Tests were performed at 15, 30, 45, and 60 minutes post-dose. After at least 1 week of washout, the control (50 mL of warm water) was administered to the same group (n=19) of subjects who were then evaluated in the same manner.

#### 6. Main outcome measures

Intraocular pressure, blood pressure, pulse rate, and mean blur rate (MBR; a measure of ocular blood flow [OBF]) measured by laser speckle flowgraphy (LSFG) in both Studies 1 and 2.

#### 7. Main results

Study 1: The four Kampo medicines did not cause intraocular pressure or blood pressure differences. The OBF was significantly increased 30 minutes after the administration of tokishakuyakusan (100% to 103.6%±6.9%;  $P<0.01$ ).

Study 2: The OBF was significantly increased after the administration of tokishakuyakusan as compared with the control ( $P<0.01$ ). In addition, intraocular pressure significantly increased from baseline to 30 to 60 minutes after the administration of tokishakuyakusan ( $P<0.01$ ).

#### 8. Conclusions

Tokishakuyakusan increases ocular blood flow irrespective of blood pressure and intraocular pressure in healthy volunteers.

#### 9. From Kampo medicine perspective

The Kampo diagnostic questionnaire was used to reveal the conditions of "qi (気)," "blood," and "fluid" in subjects who received tokishakuyakusan in Study 2.

#### 10. Safety assessment in the article

Not mentioned.

#### 11. Abstractor's comments

The results of Study 1 (which had a crossover design) showed that only one of the four Kampo medicines, tokishakuyakusan, increased the ocular blood flow. The results of Study 2 showed the ability of tokishakuyakusan to increase ocular blood flow over time. Furthermore, ocular blood flow was increased after tokishakuyakusan administration irrespective of blood pressure and intraocular pressure especially in subjects who met the *sho* (証, pattern) for tokishakuyakusan in accordance with Kampo diagnosis. Since the study uses a surrogate endpoint (i.e., ocular blood flow in healthy subjects) to determine outcome, the evidence provided by this study is still not clinically robust. However, this study has potential. RCTs with the true endpoint (i.e., ocular blood flow in patients) are anticipated as a next step.

#### 12. Abstractor and date

Tsuruoka K, 31 March 2017.

## 21. Others

### Reference

Horii C, Okonogi A, Okubo T, et al. Studies on bioequivalence of kakkonto decoction and its extract preparation (I)\*. *Shoyakugaku zasshi* 2014; 68: 9-12 (in Japanese). Ichushi Web ID: 2014173073 [MOL](#), [MOL-Lib](#)

#### 1. Objectives

To isolate the indicator ingredients of Kampo medicines and evaluate their equivalence with extract and decoction.

#### 2. Design

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

#### 3. Setting

Public recruitment of healthy volunteers from a clinical study registry of a university hospital medical information network center, Japan.

#### 4. Participants

Six healthy volunteers.

#### 5. Intervention

Since the method of allocation to treatment arms was not described in the article, the treatment arms are described in terms of treatment regimen.

Arm 1: Administration orally of kakkonto (葛根湯) decoction (of Pueraria Root 8 g, Ephedra Herb 4 g, Jujube 4 g, Cinnamon Bark 3 g, Peony Root 3 g, Glycyrrhiza 2 g, and ginger 1 g heated and extracted in 500 mL of water, filtered through 4 layers of gauze, and adjusted to 250 mL), washout for 2 weeks, and finally administration of Kracie Kakkonto (葛根湯) Extract Fine Granules 7.5 g (n=6).

Arm 2: Administration orally of Kracie Kakkonto (葛根湯) Extract Fine Granules 7.5 g, washout for 2 weeks, and administration of its decoction (n=6).

#### 6. Main outcome measures

Blood concentrations of ephedrine and pseudoephedrine at 15, 30, 60, 120, and 240 minutes after treatment.

#### 7. Main results

No inter-arm difference in post-dose blood concentrations of ephedrine and pseudoephedrine and absorption parameters (Tmax, Cmax, AUC, and MRT) was found.

#### 8. Conclusions

The equivalence with kakkonto extract and decoction can be established from blood levels of ephedrine and pseudoephedrine, which are indicator ingredients according to the Japanese Pharmacopeia.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

Not mentioned.

#### 11. Abstractor's comments

This study was conducted to evaluate the equivalence of Kampo extract with decoction, the predominant form of this Kampo treatment in daily use. When ephedrine and pseudoephedrine, the main ingredients in kakkonto, were selected as indicator ingredients, their post-dose blood concentrations and absorption rates were similar between the extract and decoction formulation. These results suggested that the various drug formulations prescribed in clinical settings were equally effective and that these indicator ingredients selected from the Japanese Pharmacopeia may be used to show the equivalence between formulations. This study is a pilot study of just six subjects assigned to two groups. , Considering the differences in treatment response between individuals, an increased number of study subjects will be required to obtain more generalizable results. ePilot studies, such as this study, which evaluate pharmacokinetics of Kampo crude ingredient absorption, are of major importance to clinicians who need to anticipate the possible effects of Kampo medicines in daily practice. Further studies are anticipated.

#### 12. Abstractor and date

Ushiroyama T, 31 March 2017.

## 21. Others

### Reference

Horii C, Okonogi A, Studies on bioequivalence of shoseiryuto decoction and its extract preparation (I), *Shoyakugaku zasshi (Journal of Natural Medicines)* 2014; 68: 65-9. Ichushi Web ID: 2014391859 [MOL](#), [MOL-Lib](#)

#### 1. Objectives

To evaluate the bioequivalence of shoseiryuto (小青竜湯) extract and its decoction.

#### 2. Design

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

#### 3. Setting

A university hospital medical center, Japan.

#### 4. Participants

Six volunteers recruited publicly.

#### 5. Intervention

Since the method of treatment assignment was not apparent from the article, treatment arms are defined by drug formulation.

Arm 1: Kracie Shoseiryuto (小青竜湯) Extract Fine Granules at 6.0 g for 2 weeks.

Arm 2: Shoseiryuto (小青竜湯) decoction (Ephedra Herb 3 g, Peony Root 3 g, Processed Ginger 3 g, Glycyrrhiza 3 g, Cinnamon Bark 3 g, Asiasarum Root 3 g, Schisandra Fruit 3 g, and Pinellia Tuber 6 g)

#### 6. Main outcome measures

Blood concentrations of ephedrine and pseudoephedrine (indicator constituents of Ephedra Herb).

#### 7. Main results

There was no significant difference in blood concentrations of ephedrine and pseudoephedrine between Arm 1 and Arm 2 at each timepoint.

#### 8. Conclusions

Concentrations of the indicator constituents in Ephedra Herb seem to be equivalent between the shoseiryuto decoction and shoseiryuto extract.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No special problems were noted.

#### 11. Abstractor's comments

This article showed no significant difference in blood levels of ephedrine and pseudoephedrine between the decoction and extract. As mentioned in the Discussion in this article, however, additional comparisons including comparison of paeoniflorin of Peony Root and glycyrrhizic acid of Glycyrrhiza and an examination of the influence of absorption and metabolism would make this article's results more meaningful. However, even though the decoction and extract produced the same blood levels of the indicator constituents of Ephedra Herb, the efficacy of the extract was not fully demonstrated.

#### 12. Abstractor and date

Nakata H, 31 March 2017.

## 10. Respiratory Diseases (including Influenza and Rhinitis)

### References

Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine\*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine)* 1993; 10: 19–23 (in Japanese).

**Abe K, Takagi K, Comparison of treatment results between Kampo medicine-treated group and Western medicine-treated group for upper respiratory tract inflammation in children, *Kampo medicine* 1993; 43: 509-15. J-STAGE**

#### 1. Objectives

To compare the efficacy of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.

#### 2. Design

Quasi-randomized controlled trial (quasi-RCT).

#### 3. Setting

One pediatric internal medicine clinic.

#### 4. Participants

Four hundred and nineteen children who presented with summer-time cold at the same clinic between 1 and 31 July 1991 were allocated to two groups in the order of presentation. High frequency rates of Coxsackie A2 and Coxsackie A4 were detected in the region at the time.

#### 5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified; n=212): including those treated with keimakakuhanto (桂麻各半湯) (n=76), maoto (麻黃湯) (n=63), keishinimaoitto (桂枝二麻黃一湯) (n=14), keishinieppiiitto (桂枝二越婢一湯) (n=9), gingyosan (銀翹散) (n=8), saikokeishito (柴胡桂枝湯) (n=5), shoseiryuto (小青竜湯) (n=4), and shoseiryutogohangekobokuto (小青竜湯合半夏厚朴湯) (n=4).

Arm 2: Western medicine group (n=207). The drugs administered were not mentioned.

#### 6. Main outcome measures

Number of consultations, and outcome assessed by the quantity of antibiotics used (oral and drip infusion), and incidence of asthmatic bronchitis, acute bronchitis, and pneumonia.

#### 7. Main results

The numbers of consultations were one (159 patients), two (37), three (12), four (3), and five (1) in arm 1 and one (132 patients), two (44), three (14), four (7), five (6), six (2), seven (1), and eight (1) in arm 2. There were fewer consultations in arm 1. Eleven patients in arm 2 and 179 patients in arm 2 used oral antibiotics. No patients in arm 1 and 12 patients in arm 2 used intravenous drip antibiotics. Nine patients in arm 1 and eight in arm 2 suffered asthmatic bronchitis. One patient in arm 1 and 10 in arm 2 suffered acute bronchitis. No cases of pneumonia were observed in either group.

#### 8. Conclusions

There were fewer consultations for upper airway inflammation in arm 1, which suggests that Kampo medicine accelerates recovery. There was less antibiotics use and fewer cases of acute bronchitis in arm 2.

#### 9. From Kampo medicine perspective

The author discusses Kampo *sho* (証, pattern) in hypothetical terms, but appears to make no mention of the criteria used in this study for the selection of Kampo medicines for each patient.

#### 10. Safety assessment in the article

Not mentioned.

#### 11. Abstractor's comments

Allocating participants by order of consultation made this a quasi-randomized controlled trial. This clinical trial was conducted before evidence-based medicine became widespread in Japan and before the introduction of the Consolidated Standards of Reporting Trials Statement. It is difficult to interpret the results because participants' ages or genders, details of the Western medicine interventions, or the criteria for administration of the Kampo medicines are not clearly specified. For its time, it was an advanced undertaking and may be considered a valuable report.

#### 12. Abstractor and date

Tsuruoka K. 31 December 2013, 31 March 2017.

## 11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference

Yaegashi M, Otsuka K, Itabashi T, et al. Applying a Kampo medication to lower gastrointestinal tract surgery. *Shokaki Geka (Gastroenterological Surgery)* 2013; 36: 1315-24.

**Yaegashi M, Otsuka K, Itabashi T, et al. Daikenchuto stimulates colonic motility after laparoscopic-associated colectomy. *Hepato-Gastroenterology* 2014; 61: 85-9. CENTRAL ID: CN-00991603, Pubmed ID: 24895799**

#### 1. Objectives

To evaluate the effectiveness of daikenchuto (大建中湯) for perioperative intestinal paralysis following laparoscopic colon cancer surgery.

#### 2. Design

Randomized controlled trial (RCT).

#### 3. Setting

One center: Department of Surgery, Iwate Medical University, Japan.

#### 4. Participants

Fifty-four cases of laparoscopic colon cancer surgery (aged between 43 and 89 years).

#### 5. Intervention

Arm 1: Daikenchuto (大建中湯) (manufacturer unknown) 7.5 g/day two days before surgery then from the first day after surgery until discharge from hospital (n=27, aged 51 to 83 years).

Arm 2: Intestinal disorder medication two days before surgery then from the first day after surgery until discharge from hospital (n=27, aged 43 to 89 years).

#### 6. Main outcome measures

Time until first flatus and until bowel movement. Time to the first toleration of solid food (50% rice gruel diet). Colonic transit time with radiopaque markers.

#### 7. Main results

Since 1 patient in arm 1 and 2 patients in arm 2 dropped out of the study, the efficacy analysis set included 26 and 25 patients in arm 1 and arm 2, respectively. Greater acceleration of first flatus and bowel movement from post-operative extubation was observed in arm 1 compared to arm 2 ( $P<0.05$ ). Time to toleration of the first solid food was similar between the arms. Colonic transit time was significantly shorter in arm 1 (no description of P-value). White blood cell count and CRP showed no significant difference between arms.

#### 8. Conclusions

Daikenchuto is effective for accelerating improvement of intestinal paralysis following laparoscopic surgery.

#### 9. From Kampo medicine perspective

None.

#### 10. Safety assessment in the article

No adverse drug reactions were observed.

#### 11. Abstractor's comments

This paper is a randomized controlled trial (RCT) investigating the effectiveness of daikenchuto in improving intestinal paralysis after laparoscopic surgery. Previous papers have reported early administration of daikenchuto to be effective in improving gastrointestinal dysfunction, however, this paper suggests even greater efficacy by commencing administration before surgery. Although 7.5 g/day was selected in this RCT as the standard dose of daikenchuto, the authors should have recognized that the usual dose is 15.0 g/day. In the DISCUSSION, the authors state that doses depending on body weight should have been considered if daikenchuto had dose-dependent effects. However, since body weight-dependent dosing is impossible in actual clinical settings, an RCT selecting the dose of 15.0 g/day should be conducted at first. A larger clinical trial evaluating the effectiveness of daikenchuto and its administration timing in the perioperative period is anticipated in the future.

#### 12. Abstractor and date

Okabe T, 6 June 2015; Motoo Y, 31 March 2017

# List of Excluded References (Appendix 2015)

**Note:** Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (\*).

**Abbreviations:** C, The Cochrane Library (CENTRAL); I, *Igaku Chuo Zasshi (Japan Centra Revuo Medicana, Ichushi)*; N, Database 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
F95.2	Regulation of dopamine, serotonin and gamma-amino butyric acid with Ningdong Granule in Tourette syndrome	ningdong granule (寧動顆粒)	Wang S, Qi F, Li J, et al. Effects of Chinese herbal medicine Ningdong Granule on regulating dopamine (DA)/serotonin (5-TH) and gamma-amino butyric acid (GABA) in patients with Tourette syndrome. <i>BioScience Trends</i> 2012; 6: 212-8.	2)	I
G20	Effectiveness of Zen-xiao An-shen Zhi-chan for sleep disorder in Parkinson's disease	zen-xiao an-shen zhi-chan 1 (増効安神止顫 1号)	Liu Y, Ohnishi R, Aiko S, et al. The efficacy of the recipe of Zen-xiao An-shen Zhi-chan 1 (ZAZ1) using actigraph quantitative analysis to treat sleeping dysfunction of early onset PD. <i>Nihon Chui Gakkai Zasshi (Journal of Japan Traditional Chinese Medicine Association)</i> 2012; 2: 8-18.	2)	I
J84.1	Evaluation of the effectiveness of Rikkunshito for gastrointestinal symptoms when Pirfenidone is administered for idiopathic pulmonary fibrosis	rikkunshito (六君子湯)	Shimizu Y, Shimoyama Y, Kawada A, et al. Gastrointestinal symptoms in idiopathic pulmonary fibrosis patients treated with Pirfenidone and herbal medicine. <i>Journal of Biological Regulators Homeostatic Agents</i> 2014; 28: 433-42.	1)	N
K12.1	Effectiveness of Hangeshashinto for oral mucositis induced by chemotherapy for colorectal cancer	hangeshashinto (半夏瀉心湯)	Matsuda C, Kono T, Munemoto Y. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. <i>Annals of Cancer Research and Therapy</i> 2013; 21: 26-30.	5) The article contained protocols only.	N
K30.0	Evaluation of the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms after endoscopic submucosal dissection (ESD) for early gastric cancer	rikkunshito (六君子湯)	Uehara R. An evaluation of gastrointestinal symptoms and gastric mobility after endoscopic submucosal dissection (ESD) and an investigation of the usefulness of Rikkunshito (TJ-43)*. <i>Dai 8 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai Workshop 4 PROCEEDING Jobu Shokaki Shojo to Kampo (Workshop 4 Proceedings of the 8th Annual Meeting of the Japanese Gastroenterological Association: Upper Gastrointestinal Symptoms and Kampo)</i> 2012: 16-7 (in Japanese).	6) Reported in article form. Although published as structured abstract (-EKAT2014), a new SA being prepared based on a newly published article.	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K59.0	Effects of complementary and alternative medicine on constipation in the elderly	-	Cherniack E. P. Use of complementary and alternative medicine to treat constipation in the elderly. <i>Geriatrics &amp; Gerontology International</i> 2013; 13: 533-8.	2) Complementary and alternative medicine other than Kampo formulation.	I
K59.8	Evaluation of the efficacy and safety of daikenchuto (大建中湯) for intestinal dysmotility after laparoscopic surgery	daikenchuto (大建中湯)	Yaegashi M. Usefulness of daikenchuto in the laparoscopic colorectal cancer perioperative period. <i>Progress in Medicine</i> 2012; 32: 616-7 (in Japanese).	6) Reported in article form. Although published as structured abstract (-EKAT2014), a new SA being prepared based on a newly published article.	N
M81.9	Preventive effect of Fufang for postmenopausal osteoporosis and fragility fractures	fufang	Deng W-M, Zhang P, Huang H, et al. Five-year follow-up study of a kidney-tonifying herbal Fufang for prevention of postmenopausal osteoporosis and fragility fractures. <i>Journal of Bone and Mineral Metabolism</i> 2012; 30: 517-24.	2)	I
R51	Effectiveness of Yangxue Qingnao for chronic cerebral circulation insufficiency	yangxue qingnao (養血清腦)	Wu C, Liao L, Yan X, et al. Effects of Yangxue Qingnao Granules on chronic cerebral circulation insufficiency: a randomized, double-blind, double-dummy, controlled multicentre trial. <i>Psychogeriatrics</i> 2013; 13: 29-34.	2)	I
T14.0	Effectiveness of hochuekkito for ultraviolet-irradiated skin damage	hochuekkito (補中益氣湯)	Kobayashi H, Yanagihara S, Tamiya Y, et al. Histopathological study of the effects of astragalus bupleurum and ginseng combination formula bupleurum and ginseng combination formula hochuekkito a traditional japanese herbal medicine on ultraviolet-irradiated skin damage in hairless mice. <i>American Journal of dermatopathology</i> 2014; 36: e40-1	6) This was a basic study.	C