Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials (EKAT 2009)

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

Edited by
Tetsuro OKABE, Kiichiro TSUTANI

1 June 2009
Task Force for Evidence Reports (ER-TF),
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Kiichiro TSUTANI
Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, the University of Tokyo
Executive Summary

The Special Committee for Evidence Based Medicine (EBM), established in June 2001 by the Japan Society for Oriental Medicine (JSOM), issued the “EBM in Kampo 2002, Interim Report” (Nihon Toyo Igaku Zasshi [Japanese Journal of Oriental Medicine] 2002: 53 (5), supplementary issue) in 2002, followed by “Evidence Reports of Kampo Treatment” (Nihon Toyo Igaku Zasshi [Kampo Medicine] 2005: 56, EBM supplementary issue) in 2005. These publications were intended to present the evidence from “good” studies, including randomized controlled trials (RCTs), of Kampo products published between 1986 and 2002. However, those studies had several weaknesses, such as lack of clear inclusion/exclusion criteria. Thus questions were raised by readers such as why particular articles had or had not been included.

Accordingly, the following improvements were made in the second phase, starting in 2005:

1. Although all RCTs for the period 1986–2008 were reviewed, only some of these were included.
2. The “systematic review” approach was adopted in literature search, and evidence appraisal was adopted to enhance comprehensiveness, accuracy, and transparency of the review.
3. The structure of the abstracts included eight standard items, i.e., “objectives,” “design,” “setting,” “participants,” “intervention,” “main outcome measures,” “main results,” and “conclusions”, and four additional items, i.e., “from Kampo medicine perspective,” “safety assessment in the article,” “abstractor’s comments,” and “abstractor’s name and date.”
4. Excluded references along with the reasons for their exclusion were listed.
5. Because the main mission of the task force was to develop structured abstracts, recommendations were not made. Recommendations will be dealt with during the development of clinical practice guidelines (CPG) in the future.
6. A system to enable feedback from readers through the internet and other media on the current reports was established.
7. In order to have transparency and accountability, conflicts of interests (COI) of the members of the Task Force were disclosed.

This phase 2 report includes only RCTs of Kampo products (extract granules, tablets, and capsules, or pills, approved for sale as ethical Kampo prescriptions in Japan). It excludes studies of in-house formulations such as decoctions, since no quality control criteria have been established.

The data sources of searches were 1) the Cochrane Library (CENTRAL), 2) Igaku Chuo Zasshi (Japana Centra Revuo Medicana [JCRM], Ichushi) web, and 3) the database offered by the Japan Kampo Medicines Manufacturers Association (JKMA).

Structured abstracts were arranged in the order used in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10).


We would appreciate your comments on the contents, methodology, relevant references, and other matters. Please send your comments to ebm-er@jsom.or.jp. We will review and respond to them in the final report.
## Lists of Structured Abstracts

### 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: Cochrane Library (CENTRAL), I: Igaku Chuo Zasshi (Japan Centra Revuo Medicana, Ichushi), N: Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association), UC: Under Construction.

<<Structured Abstracts describing RCTs and the References Reporting Them>>

### Infections (including Viral Hepatitis) (18 abstracts, 23 references)

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<thead>
<tr>
<th><a href="#">ICD-10</a></th>
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<tr>
<td>B18.2</td>
<td>Efficacy for reducing adverse effects of interferon therapy in patients with chronic hepatitis C</td>
<td>maoto (麻黄湯) + keishi (桂枝湯) + kojinmatsu (知母麥冬)</td>
<td>Isai H. Efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C`. Shindan to Chiryo (Diagnosis and Treatment) 1996; 84: 1505-9 (in Japanese).</td>
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<td>C57.9</td>
<td>To determine the efficacy of ninjin'yoeito for reducing myelosuppression due to chemotherapy for gynecologic cancer.</td>
<td>ninjin'yoeito (人参養気湯)</td>
<td>Oda T. My prescription – clinical application of ninjin'yoeito in gynecologic cancer – a preventive effect on bone marrow suppression–’. <em>WE</em> 2004; 9: 5-6.</td>
<td>quasi-RCT</td>
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</table>
Efficacy and safety of saireito for relieving the adverse urological effects of anticancer drugs

saireito (柴苓湯)


RCT-envelope  

I  

UC

Efficacy of juzentaihoto for reducing adverse effects and improving QOL in postoperative patients undergoing chemotherapy for gastric, colorectal, or breast cancer

juzentaihoto (十全大補湯)


RCT-envelope  

I  

UC

Efficacy and safety for reducing adverse reactions during cancer radiotherapy

juzentaihoto (十全大補湯)


RCT-envelope  

I  

UC

Effect on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer

juzentaihoto (十全大補湯)


RCT-envelope  

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UC

Clinical effects in patients undergoing chemotherapy (tegafur)

hochuukkito (補中益気湯), ninjin’yoeito (人参養榮湯)


RCT-envelope  

I  

UC

To determine whether preoperative administration of hochuukkito relieves surgical stress in patients with gastric or colorectal cancer.

hochuukkito (補中益気湯)


RCT  

I  

51

To evaluate the anti-tumor effect of keishibukuryogan in patients with hysteromyoma/uterine adenomyosis.

keishibukuryogan (桂枝茯苓丸)


RCT  

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52

Blood Diseases including Anaemia (14 abstracts, 17 references)

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**Metabolism and Endocrine Diseases (10 abstracts, 12 references)**

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<tr>
<td>E28.2</td>
<td>To evaluate the switch to unkei-to from treatment based on the traditional diagnostic criterion “eight-principle pattern identification” in women with polycystic ovary syndrome (PCOS).</td>
<td>unkei-to (温経湯), tokiyakuyakusan (当帰芎藺散), keishibukuryogan (桂枝茯苓丸)</td>
<td>Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. <em>The American Journal of Chinese Medicine</em> 2006; 34: 177-87.</td>
<td>RCT-envelope</td>
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<td>58</td>
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<td>E78.5</td>
<td>Efficacy and safety of daisaikoto combined with bezafibrate in patients with hyperlipidemia</td>
<td>daisaikoto (大柴胡湯)</td>
<td>Muramatsu N, Okayasu M. Clinical study on hyperlipidemia at bezafibrate and Da-chai-hu-tang (Dai-saiko-to) for the combination therapy. <em>Shigaku (Odontology)</em> 1993; 81: 94-9 (text in Japanese with English abstract).</td>
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### Psychiatric/Behavioral Disorders (10 abstracts, 12 references)

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### ICD-10 Research Question

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### Nervous System Diseases (including Alzheimer's Disease) (9 abstracts, 10 references)

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### Eye Diseases (4 abstracts, 5 references)

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### Ear Diseases (5 abstracts, 5 references)

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<td>I67.9</td>
<td>Efficacy and safety of hachimijigohan in patients with hypertension or cerebrovascular disease and their concomitant symptoms</td>
<td>hachimijigohan (八味地黄丸)</td>
<td>Ito K, Yamamoto H, Saibara T, et al. The usefulness of Kaneo Hachimijigohan in patients with hypertension or cerebrovascular disease (excluding acute phase symptoms) and their concomitant symptoms: a multicenter, double-blind, crossover study. Shindan to Chiryo (Diagnosis and Treatment) 1988; 76: 1096-114 (in Japanese).</td>
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<td>I89.0</td>
<td>To evaluate the efficacy and safety of goshajinkigan in the treatment of lymphedema.</td>
<td>goshajinkigan (牛車腎気丸)</td>
<td>Abe Y. The efficacy of goshajinkigan against lymphedema*. <em>Kampo Igaku (Kampo Medicine)</em> 2002; 25: 285-7 (in Japanese).</td>
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Respiratory Diseases (42 abstracts, 52 references)

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<tr>
<td>J00</td>
<td>To evaluate the efficacy and safety of bakumondoto for postinfectious cough.</td>
<td>bakumondoto (麥門冬湯)</td>
<td>Fujimori K, Suzuki E, Simojo F. Comparison between bakumondoto (mai men dong tang) and dextromethorphan hydrobromide in terms of effect on postinfectious cough: a pilot study. <em>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</em> 2000; 51: 725-32</td>
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<td>J69.0</td>
<td>To investigate whether hangekobokuto (banxia houp tang) improves cough reflex in elderly patients likely to have aspiration pneumonia.</td>
<td>hangekobokuto (半夏厚朴湯)</td>
<td>Iwasaki K, Cyong JC, Kitada S, et al. A traditional Chinese herbal medicine, banxia houp tang, improves cough reflex of patients with aspiration pneumonia. <em>Journal of the American Geriatrics Society</em> 2002; 50: 1751-2.</td>
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<td>J98.8</td>
<td>To determine the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampō combination therapy for bacterial respiratory infections.</td>
<td>juzentaihoto (十全大補湯), hakkontou (葛根湯), keishiton (桂枝湯), kosanontou (香蘇散), shosaikotou (小柴胡湯), hochuekkotou (補中益気湯)</td>
<td>Mikamo H, Tamaya T. Usefulness of Kampō medicine for the treatment of infections from the perspective of medical economics. <em>Sanfujinka Kampō Kenkyu no Ayumi (Recent Progress of Kampō Medicine in Obstetrics and Gynecology)</em> 2007; 24: 105-8 (in Japanese).</td>
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**Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (49 abstracts, 62 references)**

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<td>To determine the efficacy of rikkunshito combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).</td>
<td>rikkunshito (六君子湯)</td>
<td>Koida A. Effect and role of TJ-43: rikkun-shi-to from the aspects of endoscopic findings and QOL improvement in GERD patients. <em>Medical Tribune Online (Digestive Disease Week: DDW)</em> 2005: 6-7 (in Japanese).</td>
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<td>K30</td>
<td>Efficacy of rikkunshito for treating indefinite complaints of epigastric distress</td>
<td>rikkunshito (六君子湯)</td>
<td>Komatsu O. Clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress - comparison with a control agent, and assessment mainly based on the endoscopic findings and the histology of gastric mucosal biopsy specimens before and after the treatment -. Kampo Igaku (Kampo Medicine) 1993; 17: 120-31 (in Japanese).</td>
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<td>Efficacy of junchoto and mashiningan for atonic constipation in the elderly</td>
<td>junchoto (潤腸湯), mashiningan (麻子仁丸)</td>
<td>Ishioka T. Comparison of the efficacy of junchoto and mashiningan for atonic constipation in the elderly stratified by physical strength -. Kameno Rinsho (Journal of Kampo Medicine) 1996; 43: 1431-7 (in Japanese).</td>
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<td>K82.8</td>
<td>Efficacy of goreisan and tokishakuyakusan on urinary 6-keto-prostaglandin F1α level in patients with gallbladder stones or polyps</td>
<td>goreisan (五苓散), tokishakuyakusan (当帰芍薬散), shosaikoto (小柴胡湯)</td>
<td>Takagi S. Increase of urinary 6-keto-prostaglandin F1α level by preoperative administration of Gorei-san or Toki-shakuyaku-san to the patients of gallbladder stones or polyps. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU) 1992; 9: 32-9 (text in Japanese with English abstract).</td>
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<td>K92.9</td>
<td>To determine the clinical effect of rikkunshito on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.</td>
<td>rikkunshito (六君子湯)</td>
<td>Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshito attenuates adverse gastrointestinal symptoms induced by fluvoxamine. Biopsychosocial Medicine 2007; 1.</td>
<td>RCT</td>
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**Skin Diseases (13 abstracts, 14 references)**

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Diseases of the musculoskeletal system and connective tissue (19 abstracts, 18 references)

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<td>M54.56</td>
<td>Effects on nonspecific lumbago in women during menopause</td>
<td>keishibukuryogun (桂枝茯苓丸), keishibukuryogun (桂枝茯苓丸) + shuchubushimatsu (修治附子未)</td>
<td>Ohta H, Makita K. Lumbago - with emphasis on nonspecific lumbago, which obstetricians and gynecologists think is the most common form in women <em>- Chiyo (The Journal of Therapy)</em> 1995; 77: 1646-57 (in Japanese).</td>
<td>RCT</td>
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<tr>
<td>M81.1</td>
<td>Combined effect of keishibukuryogun or tokishakuyakusan and vitamin D3 on osteopenia in women during menopause</td>
<td>keishibukuryogun (桂枝茯苓丸), tokishakuyakusan (当帰芍薬散)</td>
<td>Ohta H, Nemoto K. Preventive effect of 1α-hydroxyvitamin D3 plus Kampo medicine combination therapy on osteopenia following oophorectomy - comparison between keishibukuryogun and tokishakuyakusan -. <em>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</em> 1990; 7: 65-70 (in Japanese).</td>
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**Genitourinary Tract Disorders (including Climacteric Disorders) (30 abstracts, 37 references)**

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<td>N95.1</td>
<td>To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.</td>
<td>Kampo therapy (keishibukuryogan (桂枝茯苓丸), kamishoyosan (加味逍遥散), goshajinkigan (牛車腎気丸), etc.)</td>
<td>Ota H. Positioning of Kampo therapy and hormone replacement therapy in treatment of climacteric disorders*. <em>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</em> 2001; 18: 21-9 (in Japanese).</td>
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<td>N95.1</td>
<td>To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-sho-based (非随証) Kampo medicines for gynecological disease.</td>
<td>tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遥散), keishibukuryogan (桂枝茯苓丸)</td>
<td>Takamatsu K, Kusunoki M, Komori M, et al. Study of the usefulness of Kampo therapy for climacteric disorders – a randomized trial of three major Kampo medicines for treatment of gynecological disease-. <em>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</em> 2006; 23: 35-42 (in Japanese).</td>
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<td>142</td>
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<td>N95.1</td>
<td>To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-sho-based (非随証) Kampo medicines for gynecological disease.</td>
<td>kamishoyosan (加味逍遥散), tokishakuyakusan (当帰芍薬散), keishibukuryogan (桂枝茯苓丸)</td>
<td>Takamatsu K, Musha C, Okano H, et al. Study of usefulness of Kampo therapy for climacteric disorders*. <em>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</em> 2002; 19: 111-6 (in Japanese).</td>
<td>quasi-RCT</td>
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<td>N95.1</td>
<td>To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-sho-based (非随証) Kampo medicines for gynecological disease.</td>
<td>tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遥散), keishibukuryogan (桂枝茯苓丸)</td>
<td>Takamatsu K, Makita K, Tanabe K, et al. HRT and Kampo medicine*. <em>Rinsho Kensa (Journal of Medical Technology)</em> 2004; 48: 877-84 (in Japanese).</td>
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<td>N95.1</td>
<td>To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-sho-based (非随証) Kampo medicines for gynecological disease.</td>
<td>tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遥散), keishibukuryogan (桂枝茯苓丸)</td>
<td>Takamatsu K, Tanabe K. Efficacy of Kampo medicine against climacteric disorders*. <em>Sanfujinka Chiryo (Obstetrical and Gynecological Therapy)</em> 2004; 89: 408-15 (in Japanese).</td>
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<td>N95.8</td>
<td>To compare the effects of unkeito and vitamin E on peripheral blood flow.</td>
<td>unkeito (温経湯)</td>
<td>Ushiroyma T, Sakuma K, Nosaka S. Comparison of effects of vitamin E and wen-jing-tang (unkei-to), an herbal medicine, on peripheral blood flow in post-menopausal women with chilly sensation in the lower extremities: a randomized prospective study. <em>The American Journal of Chinese Medicine</em> 2006; 34: 969-79.</td>
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**Ante/Post-partum Diseases (10 abstracts, 11 references)**

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<td>O92.5</td>
<td>To determine a Kampo medicine effective for relieving the feeling of lactation deficiency.</td>
<td>kakkonto (葛根湯), Juzentaihoto (十全大補湯), kyukichoketsuin (キユウ帰調血飲), and combination of these Kampo formulations</td>
<td>Kawakami S, Nishimura J, Umeki M, et al. Kampo therapy for feeling of lactation deficiency*. Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology) 2003; 20: 140-3.</td>
<td>RCT</td>
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<td>154</td>
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<td>O99.0</td>
<td>To determine whether rikkunshito combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.</td>
<td>rikkunshito (六君子湯)</td>
<td>Fushiki H, Saeki A, Shiozaki A. Attempt to reduce adverse reactions associated with oral iron preparation for anemia in pregnancy by combination with rikkunshito (TJ-43)*. Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology) 2003; 20: 138-9 (in Japanese).</td>
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**Symptoms and Signs (19 abstracts, 27 references)**

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<td>R60.0</td>
<td>Efficacy of goreisan and saireito for mild edema of the dorsum of the foot in the elderly</td>
<td>saireito (柴苓湯)</td>
<td>Ishioka T. Comparison of the efficacy of goreisan and saireito for mild edema of the dorsum of the foot in elderly subjects stratified by physical strength*. <em>Kampo no Rinsho (Journal of Kampo Medicine)</em> 1997; 44: 1091-5 (in Japanese).</td>
<td>RCT-cross over</td>
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<td>R60.9</td>
<td>To investigate the efficacy and safety of saireito on postoperative edema and inflammation after total hip arthroplasty (THA).</td>
<td>saireito (柴苓湯)</td>
<td>Kishida Y, Miki H, Nishii T, et al. Therapeutic effects of Saireito (TJ-114), a traditional Japanese herbal medicine, on postoperative edema and inflammation after total hip arthroplasty. <em>Phytomedicine</em> 2007; 14: 581-6.</td>
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<td>Hioki C, Arai M. Bofutsushosan use for obesity with IGT: search for scientific basis and development of effective therapy with Kampo medicine. Journal of Traditional Medicines 2007; 24: 115-27.</td>
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**Post-anesthesia and Postoperative Pain (2 abstracts, 2 references)**

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**Others (26 abstracts, 28 references)**

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<tr>
<td>Z01.8</td>
<td>To evaluate the effect of bakumondoto on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.</td>
<td>bakumondoto (麦門冬湯)</td>
<td>Saruwatari J, Hisaeda S, Higa Y, et al. The in-vivo effect of bakumondo-to (TJ-29), a traditional Japanese medicine used for treatment of chronic airway disease, on cytochrome P450 1A2, xanthine oxidase and N-acetyltransferase 2 activity in man. Journal of Pharmacy and Pharmacology 2004; 56: 1171-7.</td>
<td>RCT- cross over</td>
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<tr>
<td>Z01.8</td>
<td>To evaluate the effect of shoseiryuto on blood carbamazepine concentration.</td>
<td>shoseiryuto (小青竜湯)</td>
<td>Ohnishi N, Yonekawa Y, Fumihara T. et al. Studies on interactions between traditional herbal and Western medicines, II. Lack of pharmacokinetic interaction between Shosieiryu-to and carbamazepine in healthy volunteers. TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring) 1999; 16: 399-404.</td>
<td>RCT- cross over</td>
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<td>Z03.8</td>
<td>To evaluate the efficacy of directly sprayed shakuyakukanzoto on large bowel spasm.</td>
<td>Ai M. Assessment of the antispasmodic effect of peppermint oil and shakuyaku-kanzo-to (TJ-68); a Chinese herbal medicine on the colonic wall. <em>Medical Tribune Online (Digestive Disease Week: DDW)</em> 2005: 10-1 (in Japanese).</td>
<td>RCT</td>
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<<A Structured Abstract describing Meta-analysis and the Reference Reporting It>>

**Ante/Post-partum Diseases (1 abstract, 1 reference)**

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Structured Abstracts
(320 abstracts describing RCTs)

Each bibliographic item is followed by its ID No. from a particular searched database (CENTRAL ID, PubMed ID, or Ichushi web ID).

Articles published on the Web are indicated along with the site.

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Institutions that subscribe to the Medical Online Library have access to articles via the above URL.
Infections (including Viral Hepatitis)

Reference

1. Objectives
To determine whether hochuekkito has efficacy in preventing colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

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

3. Setting
Department of Traumatology and Critical Care Medicine, Dokkyo Medical University Koshigaya Hospital

4. Participants
Ninety-five patients admitted to the above hospital.

5. Intervention
Arm 1: treatment with hochuekkito (補中益気湯) (2.5 g, t.i.d.) per os (p.o.) or using a nasogastric tube; every day from the third day of hospitalization.
Arm 2: no treatment with hochuekkito.

6. Main outcome measures
From all patients, nasal, throat, and urine specimens were cultured for MRSA on the second hospital day, one week later, and then once a week. Sputum was also cultured from patients who underwent endotracheal intubation or tracheotomy and from those who were able to provide sputum. Similarly wound cultures were performed for patients with wound infection. When at least one culture of any specimen was positive for MRSA, the patient was considered to be MRSA-positive.

7. Main results
A total of 63 patients - 30 of 48 in arm 1 and 33 of 47 in arm 2 - withdrew from the study. Among these withdrawals, 25 patients in arm 1 and 32 in arm 2 were transferred to other wards or died, 3 received no hochuekkito, and 3 underwent no laboratory follow-up (cultures). Thus, 18 patients in arm 1 and 14 in arm 2 were examined and compared. The most common disease was trauma, followed by cerebrovascular disorder. There was no significant difference in MRSA positivity between arm 1 (8 of 18 patients) and arm 2 (9 of 14 patients). Among the trauma patients, however, there was a trend toward lower MRSA positivity in hochuekkito-treated patients (5 of 11 [45.5%] being positive), compared with hochuekkito-untreated patients (5 of 7 [71.4%] being positive). A similar trend toward lower MRSA positivity in hochuekkito-treated patients was found among patients who required mechanical ventilation.

8. Conclusions
It is suggested that administration of hochuekkito could prevent MRSA infection.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
The authors deserve praise for conducting this RCT in an emergency care setting. Given the setting, it is not surprising that many patients (66%) withdrew from the study. But the authors’ reasons for the withdrawals provide readers with very useful information. They also described gown use and hand washing by medical personnel and visitors, reflecting their consideration of bias and confounding factors. Unfortunately, this study included only a small number of patients. If it had employed a blinded, placebo-controlled design, the report would have been more reliable. The development of future studies is expected.

12. Abstractor and date
### Infections (including Viral Hepatitis)

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#### 1. Objectives
To determine whether hochuekkito (補中益気湯) can improve immune and nutritional status in immuno-compromised hosts.

#### 2. Design
Randomized controlled trial (RCT).

#### 3. Setting
Critical Care and Emergency Center, Yokohama City University Medical Center.

#### 4. Participants
Twenty-six immuno-compromised patients who were admitted to the above center. Of these, 13 patients received hochuekkito or placebo for three weeks or longer.

#### 5. Intervention
- **Arm 1**: oral or enteral administration of hochuekkito (補中益気湯) (2.5 g t.i.d.) in 7 patients (all males; mean age 53.3±5.6 years).
- **Arm 2**: administration of the same amount of lactose (placebo) in 6 patients (4 males and 2 females; mean age 53.0±7.7 years).

#### 6. Main outcome measures
- Serum albumin level and peripheral lymphocyte count (at baseline, 1, 2, 3, and 4 weeks after the start of the treatment).
- Change in prognostic nutrition index (PNI=[albumin level]×10+[peripheral lymphocyte count]×0.005).

#### 7. Main results
There was no significant difference between the two arms in serum albumin level and peripheral lymphocyte count. In placebo-treated patients, PNI increased 1 week after the start of treatment, but decreased in the following week, then increased again. PNI was significantly higher in hochuekkito-treated patients than in placebo-treated patients (P<0.05).

#### 8. Conclusions
PNI value was significantly increased by hochuekkito treatment.

#### 9. From Kampo medicine perspective
None.

#### 10. Safety assessment in the article
None.

#### 11. Abstractor's comments
The authors deserve praise for attempting the RCT in an emergency care setting. Since PNI is a surrogate outcome measure, future trials focusing on outcomes that involve the presence or absence of infection and quantity of nutrition, as mentioned in the last part of the present results, are anticipated. Although the number of patients in this study is small, future studies are expected to be larger and confirmatory. In the results of this paper, MRSA infection was identified in 4 of 9 previously non-infected patients in the lactose arm and only 1 of 8 in the hochuekkito arm.

#### 12. Abstractor and date
Infections (including Viral Hepatitis)

Reference

1. Objectives
To determine the efficacy and safety of triple therapy with proton pump inhibitor, antibiotic, and goshuyuto (呉茱萸湯) for Helicobacter pylori (H. pylori) infection.

2. Design
Randomized controlled trial (RCT).

3. Setting
No description of the setting is available; the authors belong to the Third Department of Internal Medicine, Osaka City University Medical School.

4. Participants
Sixty-three patients infected with H. pylori.

5. Intervention
Arm 1: treatment with omeprazole (40 mg/day), amoxicillin (1,500 mg/day), and goshuyuto (呉茱萸湯) (7.5 g/day), n=32.
Arm 2: treatment with omeprazole (40 mg/day) and amoxicillin (1,500 mg/day), n=31.
The duration of treatment was 2 weeks.

6. Main outcome measures
Histologic evaluation of gastric biopsy specimen and rapid urease test were performed. The outcomes were evaluated at 4 weeks after the treatment.

7. Main results
H. pylori eradication rates were 60% in the double therapy arm and 80% in the triple therapy arm. There was no emergence of goshuyuto- or amoxicillin-resistant bacteria even in cases where treatment failed to eradicate H. pylori.

8. Conclusions
The novel triple therapy containing goshuyuto improves the eradication rate without increasing incidences of adverse effects and treatment resistance by H. pylori. This therapy is a useful tool for eradicating H. pylori.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Side effects were similar in arm 1 (4 patients with diarrhea) and in arm 2 (4 patients with diarrhea and 1 with abdominal pain). No serious adverse effects were observed.

11. Abstractor’s comments
In this study, goshuyuto was used differently from its original application of Kampo medicine. This article, as a Letter to the Editor, lacks adequate descriptions, so the submission as an original article is desired.

12. Abstractor and date
Infections (including Viral Hepatitis)

Reference

1. Objectives
To determine whether hochuekkito (補中益気湯) has a preventive effect on postherpetic neuralgia (PHN).

2. Design
Randomized controlled trial (RCT).

3. Setting
One hospital (one department of dermatology).

4. Participants
Fifty-seven patients with acute-phase herpes zoster.

5. Intervention
Arm 1: oral administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 mg t.i.d.) for 12 weeks (42 patients: 12 males and 30 females; mean age, 69.2 years).
Arm 2: no treatment with hochuekkito (補中益気湯) (15 patients: 5 males and 10 females; mean age, 66.9 years).

6. Main outcome measures
Pain intensity was evaluated by visual analogue scale (VAS) at baseline, and 12 and 24 weeks after the start of treatment. Obtained data are expressed as median (25 percentile, 75 percentile).

7. Main results
VAS score in the hochuekkito arm and control arm was respectively 7.1 (6.5, 7.4) and 6.9 (5.5, 7.9) at baseline, 4.1 (3.0, 5.4) and 3.5 (1.7, 5.1) at 12 weeks, 1.4 (0.5, 2.3) and 2.9 (1.7, 4.2) at 24 weeks. The ratio of VAS score at 24 weeks to that at baseline (rVAS) was significantly different between the hochuekkito arm (0.20 [0.09, 0.30]) and control arm (0.42 [0.33, 0.53]).

8. Conclusions
During the acute phase of herpes zoster, 12-week oral administration of hochuekkito significantly controlled PHN at 24 weeks. Hochuekkito therefore has a preventive effect on PHN.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
In one of the 42 hochuekkito-treated patients, transient stomach discomfort developed, which did not interfere with continuation of the treatment.

11. Abstractor’s comments
Many patients suffer from PHN for years. This study provides valuable insight. Since similar results were described in “Taniguchi S, Terai T, Kono T, et al. The effect of hochuekkito on postherpetic neuralgia*. Hifu no Rinsho (Clinical Practice of Dermatology) 1999; 41: 601-3 (in Japanese)”, I would include a comment on that finding in the present study. Although the authors found no between-group difference in age, affected area, number of days with symptoms, underlying disease, and concomitant medications, there was a between-group difference in the number of cases. This problem is related to the incidence of PHN, so an examination of the influence of incidence of PHN on the study results is needed. The outcomes of these studies are clinically relevant, and results of further studies are expected.

12. Abstractor and date
Infections (including Viral Hepatitis)

Reference

1. Objectives
To confirm the efficacy of shosaikoto (小柴胡湯) for interferon-resistant chronic hepatitis C.

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

3. Setting
One university hospital and general hospitals.

4. Participants
One hundred patients with chronic active hepatitis C who completed interferon therapy.

5. Intervention
Arm 1: treatment with squalene 1500 mg/day. (n=33)
Arm 2: treatment with cepharanthine (1 mg/kg body weight per day). (n=33)
Arm 3: treatment with shosaikoto (小柴胡湯) 6.0 g/day. (n=34)
In all arms, study drugs were orally administered in three divided daily doses before meals for 5 years.

6. Main outcome measures
Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), procollagen III peptide (PIIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. Main results
AST and ALT showed overall significant decreases, except for transient elevations after 6 and 30 months of treatment. Type IV collagen, PIIIP, and HCV-RNA also decreased significantly in all arms. No significant differences in these variables were observed among the three arms. AST and ALT were significantly decreased at 50 months in arm 3, but not in arms 1 and 2. Choline esterase (Ch-E) did not change in arm 3, but decreased significantly in arms 1 and 2. Type IV collagen and HCV-RNA decreased significantly in arm 3 and increased significantly in arms 1 and 2. Changes in PIIIP were similar to those of type IV collagen.

8. Conclusions
Shosaikoto is effective for the treatment of chronic hepatitis C and its efficacy is equivalent to that of squalene or cepharanthine.

9. From Kampo medicine perspective
One patient with “in-sho (陰証, yin pattern)” and “kyo-sho (虛証, deficiency pattern)” was excluded before the allocation, and the study was actually conducted in 99 patients.

10. Safety assessment in the article
None.

11. Abstractor's comments
This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. Abstractor and date
**Infections (including Viral Hepatitis)**

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1. **Objectives**
   To confirm the efficacy of shosaikoto (小柴胡湯) for chronic hepatitis C.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   Multiple general hospitals.

4. **Participants**
   Ninety-nine patients with chronic active hepatitis C who completed interferon therapy.

5. **Intervention**
   Arm 1: oral administration of Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 6 g/day, t.i.d. (n=49)
   Arm 2: oral administration of one of the commonly used liver protectors. (n=50)
   Patients were followed for 50 months in both arms.

6. **Main outcome measures**
   Level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), choline esterase (Ch-E), procollagen III peptide (PIIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. **Main results**
   AST and ALT were significantly decreased at 50 months in arm 1, but not in arm 2. Ch-E did not change in arm 1, but decreased significantly in arm 2. Type IV collagen and HCV-RNA decreased significantly in arm 1, and increased significantly in arm 2. Changes in PIIIP were similar to those of type IV collagen.

8. **Conclusions**
   Shosaikoto is effective for the treatment of chronic hepatitis C, and its prevention of the progression to cirrhosis is implied.

9. **From Kampo medicine perspective**
   Patients with “in-sho (陰証, yin pattern)” and “kyo-sho (虛証, deficiency pattern)” were excluded before the allocation.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. **Abstractor and date**
Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

1. Objectives
To evaluate the efficacy of juzentaihoto (十全大補湯; TJ-48) combined with oral 5-FU as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.

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

3. Setting
Fifteen hospitals associated with Gifu University.

4. Participants
Ninety-four patients with surgically treated gastric cancer satisfying the following 8 criteria were included: (1) curability A or B; (2) no serious complications; (3) no preoperative treatment; (4) no double or multiple cancer; (5) WBC ≥3,000/mm³, Plt ≥70,000/mm³, total protein ≥6.0g/dL, AST/ALT ≤60 IU/L, and urinary protein (-), before the start of chemotherapy; (6) no possibility of pregnancy; (7) performance status of grade 0 or 1; (8) receipt of consent to participate in the study from patient or family member.

5. Intervention
Arm 1: monotherapy group; continuous treatment with 5-FU tablets (200 mg/day) for 2 years starting 2 weeks after surgery; 51 patients.
Arm 2: combination therapy group; continuous treatment with 5-FU tablets (200 mg/day) combined with TSUMURA Juzentaihoto (十全大補湯) Extract Granules (TJ-48; 7.5 g/day) for 2 years starting 2 weeks after surgery; 43 patients.

6. Main outcome measures
Five-year survival rate, 5-year survival rate by clinical stage.

7. Main results
Five-year survival rate was 74.3% in arm 1 and 73.5% in arm 2, indicating no significant difference between arms. By clinical stage, patients with stage I or II had 2-year and 5-year survival rates of 92% and 90%, respectively, in arm 1 (n=42), and 91% and 83%, respectively, in arm 2 (n=35), indicating no significant difference between arms. In contrast, patients with stage III or IV had 2-year and 5-year survival rates of 22% and 0%, respectively, in arm 1 (n=9), and 87% and 25%, respectively, in arm 2 (n=8), with median survival of 35.1 months in arm 2 and 14.2 months in arm 1, demonstrating significantly extended survival of patients treated with juzentaihoto.

8. Conclusions
Combination of juzentaihoto with oral 5-FU was effective for patients with surgically treated stage III or IV gastric cancer.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
The finding that the combination with juzentaihoto extends the postoperative survival of patients with surgically treated gastric cancer is clinically very impressive. The adverse drug reactions (ADRs) associated with this anticancer treatment are also of interest. Also, some information on study design (such as blinding) is lacking, making further evaluation difficult. Publication of the original paper is awaited.

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

1. Objectives
To determine the clinical efficacy of juzentaihoto （十全大補湯）for the prevention of postoperative recurrence of colorectal cancer.

2. Design
Randomized controlled trial (RCT).

3. Setting
The First Department of Surgery of Sapporo Medical University and other institutions (their names, unspecified).

4. Participants
One hundred and sixty-eight patients (mean age, 65 years) with stage II or III colorectal cancer who received curative resection and adjuvant chemotherapy between July 2001 and March 2005.

5. Intervention
Arm 1: treatment with oral 5-FU and juzentaihoto （十全大補湯）(manufacturer, not specified) 7.5 g/day, n=86.
Arm 2: treatment with oral 5-FU, n=82.

6. Main outcome measures
Recurrence rate, time to recurrence, and survival time.

7. Main results
Mean postoperative follow-up was 38.6 months. Recurrence rate for patients with stage II disease was slightly, though not significantly, more favorable in arm 1 (6.9%) than in arm 2 (14.0%). Mean times to recurrence were 18.2 months in arm 1 and 16.9 months in arm 2. The 3-year recurrence-free survival rate was slightly, though not significantly, better in arm 1: 92.2% in arm 1 and 85.9% in arm 2 for patients with stage II disease, and 67.5% and 62.9%, respectively, for patients with stage III disease.

8. Conclusions
Juzentaihoto may have a metastasis-suppressive effect, but since these are interim reports, the follow-up is still ongoing.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
These two papers are interim reports on a multicenter clinical study that evaluated the clinical efficacy of juzentaihoto for the prevention of postoperative recurrence of colorectal cancer. The data from slightly less than 100 patients in each arm were analyzed. At this point, no clear difference is observed between the juzentaihoto-treated arm and the control arm, although the outcomes tend to be slightly more favorable in the former. A final report is anticipated. This abstract summarized mainly data from the second, recently published, paper mentioned above.

12. Abstractor and date

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

Reference

1. Objectives
To determine the effects of daikenchuto (大建中湯) on intestinal obstruction following colorectal cancer surgery.

2. Design
Randomized controlled trial (RCT).

3. Setting
Second Department of Surgery, Dokkyo University School of Medicine.

4. Participants
One hundred and seventy-five patients who underwent surgery for colorectal cancer (cecal colon [n=119] or rectal [n=56] cancer).

5. Intervention
Arm 1: treatment with daikenchuto (大建中湯) (manufacturer, not specified) 27 g/day (n=86).
Arm 2: no treatment (n=87).

6. Main outcome measures
The percentage of patients who postsurgically developed each of the following: ileus, abdominal pain, abdominal distention, and irregular bowel movements.

7. Main results
The between-arm difference in the percentage of patients who developed ileus in arms 1 (1.16%) and 2 (5.75%) or who experienced abdominal distension in arms 1 (2.33%) and 2 (6.90%) was not significant. A significantly smaller percentage of patients in arm 1 developed abdominal pain (1.16% vs 9.20% [for arm 2]; P=0.042) or experienced irregular bowel movements (3.49% vs 13.79% [for arm 2]; P=0.033).

8. Conclusions
Daikenchuto extract fine granules did not prevent ileus following colorectal cancer surgery, but did result in the reduction of postoperative abdominal pain and irregular bowel movements.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor's comments
The description of the study method in the present paper is extremely inadequate, and the protocol itself is problematic. Details, such as duration of treatment with daikenchuto extract fine granules, outpatient or inpatient setting, length of follow-up, and definitions of abdominal pain, abdominal distention, or irregular bowel movement are not given. Significant results would have been obtained if the authors had defined these specifics. Therefore, I recommend a rewrite of this paper after these details are clarified and the results are reviewed.

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

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1. **Objectives**
   To evaluate the efficacy of hochuekkito (補中益気湯) combined with clarithromycin (CAM) for improvement in the prognosis of lung cancer.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   A university hospital (Department of Internal Medicine, Dokkyo Medical University Hospital).

4. **Participants**
   Thirty-five patients with primary lung cancer lesions that responded to chemotherapy or radiotherapy either partially or completely (21 males, 14 females; mean age, 63.2±6.7 years; performance status [P.S.] 0-2; baseline clinical stage Ia [n=5], Ib [n=21], and II [n=9]; squamous cell carcinoma [n=14], adenocarcinoma [n=21]).

5. **Intervention**
   Arm 1: combination therapy group; 400 mg/day of CAM + 7.5 g/day of hochuekkito (補中益気湯) extract granules administered to 17 patients (10 males, 7 females; mean size reduction of the primary lesion, 62.8 ± 11.2%).
   Arm 2: monotherapy group; 400 mg/day of CAM administered to 18 patients (11 males, 7 females; mean size reduction of the primary lesion, 66.7±8.6%).

6. **Main outcome measures**
   Tumor markers, NK cell activity (at baseline, and 2 and 12 months after the start of treatment), and 1-year survival.

7. **Main results**
   Serum levels of tumor markers were significantly elevated in both treatment groups compared with the control group. In patients surviving 1 year after the start of treatment, NK cell activity, representing immunoreactivity, was elevated in both treatment groups, and was significantly higher in the combination therapy group than the control group.

8. **Conclusions**
   The combination (hochuekkito plus CAM) seems to be effective for maintaining the efficacy of chemotherapy and radiotherapy.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This study deserves praise for attempting to conduct RCT targeting a difficult-to-treat pathology of lung cancer prognosis. Regrettably, however, it is unclear whether “the control group” mentioned here refers to the CAM monotherapy group or yet another group, or to a before-after comparison in the same group. Clarification of the study is expected.

12. **Abstractor and date**
### Evidence Reports of Kampo Treatment 2009

**Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine**

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

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1. **Objectives**
   To determine the efficacy of ninjin’yoeito (人参養栄湯) for reducing myelosuppression due to chemotherapy for gynecologic cancer.

2. **Design**
   Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
   One hospital.

4. **Participants**
   Eight patients who underwent surgery for gynecologic cancer (ovarian [n=6], uterine [n=1], or fallopian tube [n=1] cancer) and received granulocyte colony-stimulating factor (G-CSF) for neutropenia during the first cycle of chemotherapy (CAP: cyclophosphamide, Farmorubicin [epirubicin], cisplatin).

5. **Intervention**
   Arm 1: treatment with Kanebo Ninjin’yoeito (人参養栄湯) Extract Fine Granules (7.5 g/day in two divided doses) continuously from 1 to 2 weeks prior to the start of the second cycle of chemotherapy (n=4).
   Arm 2: no treatment with ninjin’yoeito (n=4).

6. **Main outcome measures**
   The following measures during the second and third cycles of chemotherapy: nadir leukocyte and neutrophil counts, the length of time for neutrophil count to fall below 1,000/µL, total dose of G-CSF, duration of neutrophil counts under 1,000/µL, and nadir hemoglobin level and platelet count.

7. **Main results**
   There were no significant between-arm differences in nadir leukocyte, neutrophil, and platelet counts or in the length of time for the neutrophil count to fall below 1,000/µL. Duration of neutrophil count under 1,000/µL tended to be shorter in arm 1 than in arm 2 during the second cycle, and became significantly shorter during the third cycle. Total dose of G-CSF tended to be lower in arm 1 than in arm 2 during the second cycle, and became significantly lower during the third cycle. Nadir hemoglobin level during the second cycle, compared with that during the first cycle, was significantly lower in arm 1, but not in arm 2.

8. **Conclusions**
   It is strongly suggested that Kanebo Ninjin’yoeito Extract Fine Granules may exert neutropenia-preventing effects by inducing pluripotent stem cells to multiply and differentiate and by increasing the activity of G-CSF.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    Because of the small sample size (only four in each arm), it seems difficult to address the statistical significance of differences observed in this study. Furthermore, although G-CSF administration affects “total dose of G-CSF” and “duration of neutrophil counts under 1,000/µL,” administration criteria for G-CSF are not described. Thus the data are not objective. The significant decrease in hemoglobin level in arm 1 may indicate that Kanebo Ninjin’yoeito Extract Fine Granules is effective against neutrophil suppression, but not against suppression of erythropoietic cells. It is necessary to include more patients and to investigate not only the efficacy, but also the adverse events induced by G-CSF.

12. **Abstractor and date**
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

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

Reference

1. Objectives
To determine whether preoperative administration of hochuekkito (補中益気湯) relieves surgical stress in patients with gastric or colorectal cancer.

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

3. Setting
Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Okayama University, and six other institutions.

4. Participants
Forty-eight patients who underwent surgery for gastric (n=10) or colorectal (n=38) cancer.

5. Intervention
Arm 1: treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g, t.i.d. for 1 week prior to surgery (n=22).
Arm 2: no preoperative treatment (n=26).

6. Main outcome measures
The levels of cortisol, soluble tumor necrosis factor receptor (sTNF-R), and soluble interleukin-2 receptor (sIL-2R) measured right before surgery and on postoperative day 1; total and differential white blood cell counts measured preoperatively and postoperatively at days 1 and 7; C-reactive protein level measured preoperatively and postoperatively at days 1, 3, and 7; postoperative course of body temperature and pulse rate; length of postoperative stay; the number of patients who received therapeutic antibiotics after surgery.

7. Main results
There were no significant between-arm differences in total and differential white blood cell counts, CRP level, and rates of increase in sTNF-R and sIL-2R from before to after surgery. The rate of increase in cortisol from before to after surgery was significantly lower in arm 1. The body temperature from postoperative day 6 was significantly lower in arm 1. The pulse rate on postoperative days 6 and 7 was significantly lower in arm 1. The number of patients who received therapeutic antibiotics after surgery was significantly smaller in arm 1 (3/22) than in arm 2 (11/22).

8. Conclusions
Preoperative administration of TSUMURA Hochuekkito Extract Granules reduces the response to surgical stress and may be helpful for accelerating postoperative recovery.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse events: no adverse drug reactions occurred in arm 1.

11. Abstractor’s comments
The authors postulate that preoperative administration of hochuekkito improves quality of life, helps control body temperature and heart rate, and reduces therapeutic administration of antibiotics in patients during postoperative recovery, and thus may lead to reduction of medical costs. They also suggest that the mechanism underlying these effects may involve Kampo medicine-induced attenuation of the increase in cortisol blood level. The principle of this treatment is similar to that of “immunonutrition,” which involves omega-3 fatty acids, arginine, and nucleic acids. These approaches attempt to reduce postoperative surgical complications by means of preoperative nutritional supplementation. Cancer patients before surgery are in a state of *qikyo* (氣虚, qi deficiency) with various anxieties, and at the same time in a relatively mild state of *kekkyo* (血虚, blood deficiency) if they are operable. Hochuekkito and other comparable *hozai* (補剤; formulations with tonic effects) seem to be suitable for these patients. The investigation of hochuekkito combined with the immunonutritional approach and further elucidation of the mechanism are anticipated in the future.

12. Abstractor and date
## Evidence Reports of Kampo Treatment 2009

Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

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

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1. **Objectives**
   To evaluate the anti-tumor effect of keishibukuryogan (桂枝茯苓丸) in patients with hysteromyoma/uterine adenomyosis.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   Single hospital (Department of Obstetrics and Gynecology, Sakai Hospital, Kinki University School of Medicine).

4. **Participants**
   The 24 patients seen at the above institution and diagnosed with hysteromyoma or uterine adenomyosis were randomized into two arms: 1) the gonadotropin-releasing hormone (GnRH) analogue + keishibukuryogan arm (mean age, 45.9 years; mean tumor diameter, 35.7 mm) and 2) the GnRH analogue arm (mean age, 46.3 years; mean tumor diameter, 34.1 mm).

5. **Intervention**
   Arm 1: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months + oral administration of a sachet of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (2.5 g) t.i.d (before meals) for 12 months (n=14).
   Arm 2: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months (n=10).

6. **Main outcome measures**
   Tumor response was evaluated on a 3-point scale: tumor diameter reduction: remarkably effective, ≥50%; effective, >0 - 50%; not effective, 0%. Evaluation was performed at baseline, 4, 8, and 12 months after intervention.

7. **Main results**
   Four months after treatment, complete response was achieved in 42.9% (6/14) of arm 1 and 10% (1/10) of arm 2, showing that GnRH + keishibukuryogan tended to have a higher anti-tumor effect although there were no between-group differences in tumor size reduction 8 or 12 months after treatment. Analysis limited to hysteromyoma revealed that 4-month treatment produced complete response in a significantly higher percentage of arm 1 (50%) than arm 2 (0%) (P=0.012). When the analysis was limited to the GnRH analogue leuprorelin, 4-month treatment produced a significantly higher complete response rate in arm 1 (62.5%) than in arm 2 (0%) (P=0.016). GnRH + keishibukuryogan exerted clinical efficacy in the short-term but not in the long-term (8 or 12 months after treatment).

8. **Conclusion**

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    As the contents of this paper have also been described in several previous case reports and clinical studies, the present study provided additional supportive evidence. Nevertheless, the present results are not sufficient to conclude that the effect can be generalized beyond the study sample because of the small sample size, but it will serve as a helpful reference in determining the future direction of research. Although the measure of tumor response (use of a 3-point scale) was rather crude, further accumulation of cases may enable more reliable determination — for clinical practice — of mean tumor reduction and differences in tumor reduction with time after administration.

12. **Abstractor and date**
   Ushiroyama T, 1 April 2008, 8 August 2009.
Blood Diseases including Anaemia

Reference

1. Objectives
To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for hypochromic anemia in patients with uterine myoma.

2. Design
Randomized controlled trial (RCT).

3. Setting
A university hospital (Outpatient Department of Obstetrics and Gynecology, Kitasato University Hospital).

4. Participants
Twenty-three patients having hypochromic anemia associated with uterine myoma visiting the above institution between August 1999 and the end of January 2000. Mean age: 45.4±1.99 years in the tokishakuyakusan group; 42.9 ± 1.68 years in the oral iron preparation group. Range of blood hemoglobin concentration: 8 – 12 g/dL.

5. Intervention
Arm 1: oral administration of a sachet of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (2.5 g) t.i.d. (before meals) for 3 months.
Arm 2: oral administration of a tablet containing sodium ferrous citrate (50 mg) q.d or b.i.d. (after meals) for 3 months.

6. Main outcome measures
Laboratory: hematology (RBC, hemoglobin, hematocrit, etc.), blood chemistry (serum iron, ferritin concentration, etc.), blood coagulation function (PT, APTT), evaluated at baseline, and 4 and 8 weeks after dosing. Improvement in subjective symptoms, including pallor, dizziness on standing up, and dizziness/vertigo, evaluated on a 5-point scale at baseline, and 4 and 8 weeks after dosing. Adverse drug reactions (ADRs): incidences of heartburn, nausea/vomiting, diarrhea, etc. during 8-week administration.

7. Main results
Although there was no between-group difference in blood profile, subjective symptoms such as cold, pallor, spoon nail, and dizziness/vertigo were significantly improved with tokishakuyakusan (P<0.05). In particular, cold was improved significantly efficiently in the tokishakuyakusan group (score at 8 weeks: 0.3±0.2 for tokishakuyakusan, 2.0±0.6 for oral iron; P<0.05). ADRs occurred in 80% of patients receiving the oral iron preparation (heartburn and nausea noted with the highest incidences of 46.7% each) but in no patients receiving tokishakuyakusan.

8. Conclusions
Three-month treatment with tokishakuyakusan is more effective in improving subjective symptoms and is safer than an oral iron preparation for mild to moderate anemia in women with uterine myoma.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
ADRs occurred in none of 10 patients receiving tokishakuyakusan, while in 12 (80%) of 15 patients receiving the oral iron preparation.

11. Abstractor’s comments
If clinicians designed a noninvasive antianemic treatment plan for the present study population, i.e., patients with anemia (defined as blood hemoglobin concentration, 8–12 g/dL) and uterine myoma, the oral iron preparation would be the treatment of choice. However, in the present study, tokishakuyakusan had higher efficacy for subjective symptom improvement. In addition, tokishakuyakusan was clinically more efficacious and safer (i.e., had no ADRs). However, since tokishakuyakusan (unlike the oral iron preparation) did not improve the blood profile, a combination of these drugs might be more efficacious. A new research protocol to investigate the efficacy of Kampo formulations combined with oral iron to reduce the severity of anemia is expected in the future.

12. Abstractor and date
Ushiroyama T, 1 April 2008, 8 August 2009.
Blood Diseases including Anaemia

Reference

1. Objectives
To evaluate the efficacy of juzentaihoto (十全大補湯) and ninjin’yoeito (人参養栄湯) combined with an erythropoietin (EPO) preparation in preoperative autologous blood donation in cancer patients.

2. Design
Randomized controlled trial (RCT). Intravenous administration of an iron preparation to patients with hemoglobin concentration of ≥14 g/dL. Randomization of patients with hemoglobin concentration of <14 g/dL to receive intravenous iron preparation + Kampo formulation + EPO or intravenous iron preparation + EPO.

3. Setting
Single hospital (Department of Obstetrics and Gynecology, Japanese Red Cross Society Himeji Hospital).

4. Participants
Ninety patients with gynecologic malignant tumors who visited the above institution between January 1992 and the end of November 1997 and preoperatively donated 800 mL or more of autologous blood.

5. Intervention
Arm 1: intravenous administration of an iron preparation (240 mg weekly) from the day of the first donation through the day before the operation.
Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation.
Arm 3: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of TSUMURA Juzentaihoto (十全大補湯) Extract Granules or Ninjin’yoeito (人参養栄湯) Extract Granules 2.5 g t.i.d (before meals), from the day of the first donation through the day before the operation.

6. Main outcome measures
Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).
Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).
Hemoglobin increment: pre-donation hemoglobin concentration × volume of donated blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin volume).

7. Main results
The increase in reticulocyte count from the time of donation to the time of operation was larger in the Kampo group (n=36) and EPO group than in the iron group (n=15). The increase in hemoglobin level was larger in the EPO group (1.73±1.30 g/dL) than the iron group (0.92±0.70 g/dL), and significantly (P<0.05) larger in the Kampo group (2.33±1.11 g/dL) than the EPO group.

8. Conclusions
Combining a Kampo formulation with an iron preparation plus EPO enhances the clinical effectiveness of preoperatively donated autologous blood.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
The finding that adding juzentaihoto or ninjin’yoeito to the preoperative donation management protocol enhances the increase in blood hemoglobin concentration suggests that the hematological profile of donated autologous blood is better after use of the combination than after use of only the iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study is expected including an examination of the possibility that complementary medicines promote cancer cell growth.

12. Abstractor and date
Ushiroyama T, 1 April 2008, 8 August 2009.
Blood Diseases including Anaemia

Reference

1. **Objectives**
To evaluate the efficacy of using juzentaihoto (十全大補湯) to augment preoperative autologous blood donation in cancer patients.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Not identified (but the abstractor infers a Department of Obstetrics and Gynecology in each of the following three facilities: Japanese Red Cross Society Himeji Hospital, Fukuyama City Hospital, and Chugoku Central Hospital).

4. **Participants**
One-hundred and twenty patients who visited the above institutions within the past 5 years and 2 months and donated 800 mL or more autologous blood before undergoing surgery for gynecologic malignant tumors. Patients receiving preoperative chemotherapy and patients with collagen disease were excluded.

5. **Intervention**
Arm 1: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation in patients with pre-donation Hb value of ≤ 14 g/dL, n=52.
Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of a sachet (2.5 g) of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d (before meals), from the day of the first donation through the day before the operation in patients with pre-donation Hb value of ≤ 14 g/dL, n=51.
Arm 3: intravenous administration of an iron preparation (240 mg weekly), n=17.

6. **Main outcome measures**
Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).
Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).
Hemoglobin increment: pre-donation hemoglobin concentration × volume of donation blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin concentration).

7. **Main results**
Decrements in RBC count and hematocrit after donation were significantly smaller in the EPO combination groups than in the iron monotherapy group, and significantly smaller in the juzentaihoto and EPO combination group than in the EPO combination group (P<0.05). There was also a significant difference in hemoglobin increment between arms (P<0.05).

8. **Conclusions**
An iron preparation combined with EPO and additionally with juzentaihoto enhances the clinical efficacy of preoperatively donated autologous blood.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
None.

11. **Abstractor’s comments**
This study demonstrated that adding juzentaihoto to the preoperative donation management protocol successfully suppresses reductions in RBC count and hematocrit after donation and enhances the increase in blood hemoglobin concentration. This suggests that the hematological profile of donated autologous blood is better after use of this combination than after use of only an iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study, including an examination of the possibility that complementary medicines promote cancer cell growth, is expected. Similar papers by the first author include: Aoe H, Matsuo T, Ebisutani M, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation in cancer patients . *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2000; 17: 67-71 (in Japanese); Aoe H, Ota M, Kawahara N, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation. *Rinsho Kensa (Journal of Medical Technology)* 2003; 47: 395-9 (in Japanese). Ichushi Web ID: 2003251978

12. **Abstractor and date**
Blood Diseases including Anaemia

Reference

1. **Objectives**
   To evaluate the efficacy and safety of ninjin’yoeito (人参養栄湯) for ribavirin-induced anemia.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   One university hospital.

4. **Participants**
   Twenty-three chronic hepatitis C patients treated with interferon alpha-2b and ribavirin. Five of them withdrew from the study.

5. **Intervention**
   Arm 1: designated “the control group” and treated with interferon alpha-2b (IFNα-2b) and ribavirin, n=13
   Arm 2: designated “the NY group” and treated with IFNα-2b and ribavirin plus TSUMURA Ninjin’yoeito (人参養栄湯) Extract Granules (9 g, orally), n=10.
   IFNα-2b was administered for a total of 24 weeks at a dose of 10 MU intramuscularly, 6 days per week for the first 2 weeks and 3 days per week for the following 22 weeks. Ribavirin was orally administered for 24 weeks at a dose of 800 mg/day (if the patient’s body weight was ≥ 60 kg) or 600 mg/day (body weight < 60 kg).

6. **Main outcome measures**
   Maximum increase in red blood cell count (maxΔRBC), maximum increase in hemoglobin level (maxΔHb), minimum hemoglobin level (min Hb), white blood cell count (WBC), platelet count (Plt), T-helper 1 cell (Th1) count, T-helper 2 cell (Th2) count, Th1/Th2, and glutathione peroxidase level in peripheral blood.

7. **Main results**
   Peripheral maxΔHb and min Hb were significantly improved in the NY group (P=0.026 and P=0.079, respectively). No between-group differences were observed in maxΔRBC, WBC count, Plt count, Th1 count, Th2 count, Th1/Th2, and glutathione peroxidase level. Antiviral effects were not different, either.

8. **Conclusions**
   Ninjin’yoeito is an effective and safe treatment for ribavirin-induced anemia.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    Adverse reactions specific to ninjin’yoeito were not observed.

11. **Abstractor’s comments**
    This study showed the efficacy of ninjin’yoeito for ribavirin-induced anemia. The authors speculated that the mechanism of action of this drug is the activation of undifferentiated erythroid cells and antioxidation.

12. **Abstractor and date**
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1. **Objectives**
   To evaluate the efficacy of unkeito (温経湯) for reducing high luteinizing hormone (LH) levels and improving ovulation disorder.

2. **Design**
   Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. **Setting**
   One hospital (Osaka Medical College Hospital), although not mentioned.

4. **Participants**
   One-hundred patients with ovulation disorder and an LH level of \( \geq 10 \) mIU/mL, aged 21 to 32 years. Of these 100 patients, 38 were diagnosed with polycystic ovarian syndrome (PCOS).

5. **Intervention**
   **Arm 1:** oral administration of a sachet (2.5 g) of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d, 30 min before meals, for 8 weeks, n=52.
   **Arm 2:** clinical observation (without administration of placebo granules) for 8 weeks, n=48.

6. **Main outcome measures**
   - Comparison of plasma LH level.
   - Comparison of ovarian follicle size evaluated by ultrasonography.

7. **Main results**
   - Of 52 patients receiving unkeito, 34 showed decreased LH level, and 28 showed improved menstrual cycle regularity. In addition, ovulation was confirmed in 11 patients. Decreased LH level was significant in patients without PCOS.

8. **Conclusions**
   - Unkeito improves ovulation disorder by normalizing the high level of LH in patients with ovulation disorder. It also increases E2 hormone level in non-PCOS patients. Control patients remained unchanged. Thus, unkeito is an effective treatment for ovulation disorder.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This study is highly significant in that it demonstrated the ovulation disorder-improving effect of unkeito at the hormonal level. However, the underlying mechanism of this improvement is not explained. Further investigation to determine, for example, why some patients do not respond to unkeito, is awaited. Nevertheless, it can be concluded that unkeito contributes to normalization of the menstrual cycle and stimulation of ovulation.

12. **Abstractor and date**
    Nakata H, 1 April 2008, 8 August 2009.
References
Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. The American Journal of Chinese Medicine 2006; 34: 177-87. CENTRAL ID: CN-00563518, Pubmed ID: 16552830

1. Objectives
To evaluate the efficacy of switching to unkeito (温経湯) from treatment based on the traditional diagnostic criterion “eight-principle pattern identification” in women with polycystic ovary syndrome (PCOS).

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

3. Setting
Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine.

4. Participants
Sixty-four patients who visited the outpatient department and were diagnosed with PCOS between 1993 and 2004.

5. Intervention
Sixty-four patients were randomly assigned to one of 2 groups using the diagnostic criterion “in-yo (陰陽, yin and yang), kyo-jitsu (虛実, excess or deficiency), hyo-ri (表裏, interior and exterior), kan-netsu (寒熱, cold and heat)” to receive 8-week preliminary administration of either “keishibukuryogan (桂枝茯苓丸)” or “tokishakuyakusan (当歸芍薬散).” Then, 54 non-ovulating patients were further assigned via the RCT-envelope method to receive either a continuation of the same treatment (the continuous treatment group; n = 27) or unkeito (温経湯) (the unkeito group; n = 27) for 8 weeks.
Arm 1: continuous administration group (TSUMURA Keishibukuryogan Extract Granules 7.5 g or TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 7.5 g), n = 27.
Arm 2: TSUMURA Unkeito (温経湯) Extract Granules 7.5 g/day group, n = 27.

6. Main outcome measures
Blood follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels and ovulation status.

7. Main results
Switching to unkeito decreased blood LH level and significantly stimulated ovulation.

8. Conclusions
Unkeito has an ovulatory inductive effect, regardless of conventional “sho” (証, pattern/syndrome) identification.

9. From Kampo medicine perspective
Although eight-principle pattern identification is an important criterion for treatment selection, it was not used for the selection unkeito, which was found to stimulate ovulation. Traditional diagnosis based on clinical findings, pathology, and hematology can be an important guide to the selection of Kampo formulae.

10. Safety assessment in the article
No special problems noted.

11. Abstracter’s comments
This paper indicates that switching to unkeito after treatment based on traditional “sho” identification improves outcome. The requirement for more objective criteria to make a Kampo diagnosis is extremely important. Other Kampo formulae beside keishibukuryogan and tokishakuyakusan should be considered to treat PCOS. It is of interest to determine whether monotherapy with unkeito would be more effective than monotherapy with other formulae. Future research is expected.

12. Abstracter and date
Nakata H, 10 January 2009, 8 August 2009.
1. Objectives
To evaluate the efficacy of unkeito (温経湯) for luteal phase deficiency.

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

3. Setting
Not mentioned (the authors belong to a clinic of the Department of Obstetrics and Gynecology, Osaka Medical College)

4. Participants
One-hundred and ninety-seven patients with a luteal phase of <10 days or a luteal-phase blood progesterone concentration of <10 ng/mL, who had not received hormone therapy for the past 12 months.

5. Intervention
Arm 1: oral administration of 2.5 g of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d (daily dose 7.5 g), n=103.
Arm 2: untreated control group, n=94. (88 included for analysis)
(Note) During 2 to 8 days after ovulation, 5,000 IU of human chorionic gonadotropin (hCG) was injected three times in 71 of 103 patients in arm 1 and all 94 patients in arm 2.

6. Main outcome measures
Ovarian follicle size, endometrial thickness, and luteal function improvement rating (prolongation of luteal phase or elevation in progesterone value).

7. Main results
During days 14 to 18 of the menstrual cycle, most of the unkeito group showed significant improvement in both ovarian follicle size and endometrial thickness (83/103 patients in arm 1 vs. 13/88 patients in arm 2). Luteal functions were also significantly improved by unkeito treatment

8. Conclusions
Unkeito improves luteal phase defect.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not mentioned

11. Abstractor’s comments
This paper is a follow-up of “Effects of unkeito, an herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion (The Journal of Reproductive Medicine 2001;46:451-6.) by Ushiroyama T, Ikeda A, Sakai M, et al.” In addition to the previously reported efficacy of unkeito for ovulation disorder, the present paper reports its luteal phase-stabilizing effects including thickening of the endometrium and elevating progesterone value. Although the mechanism of action of unkeito remains unclear, this report provides further details of the effects of unkeito.

12. Abstractor and date
Nakata H, 1 April 2008, 8 August 2009.
Metabolism and Endocrine Diseases

Reference

1. Objectives
To evaluate the anti-obesity effect of bofutsushosan (防風通聖散) extract granules in obese patients and the course of high-sensitivity C-reactive protein (HS-CRP) as an arteriosclerosis-promoting factor.

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

3. Setting
The outpatient department of internal medicine at a general hospital.

4. Participants
Patients who were obese (body mass index [BMI] of 25 or greater), hypertensive (diastolic blood pressure of 90 mmHg or higher and/or a systolic blood pressure of 140 mmHg or higher), treatment-naïve or taking oral antihypertensives, and aged ≥20 to <80 years were included after giving written informed consent. Exclusion criteria were: 1) serious complications (cardiac disease, renal disease, malignancy, etc.); 2) use of medications that might affect the outcome of this trial; 3) pregnant, lactating, or likely to become pregnant; and 4) considered ineligible by the investigator.

5. Intervention
Arm 1: bofu group: conventional therapy plus oral administration of bofutsushosan (防風通聖散) extract granules (manufacturer, not specified) 7.5 mg/day before or between meals for 12 weeks in 25 patients (16 males and 9 females; mean age, 63.3±12.3 years).
Arm 2: control group: continuation of conventional therapy in 30 patients (19 males and 11 females; mean age, 64.2±10.3 years).

6. Main outcome measures
1) Body weight, BMI, blood pressure, pulse; 2) levels of fasting blood glucose, hemoglobin a1c (Hba1c), and insulin; 3) levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride; 4) visceral fat (measured by computed tomography [CT]); and 5) blood biochemistry including HS-CRP level, hepatic and renal functions, and electrolyte levels. 1) to 3) were measured at weeks 0, 4, 12, and 24; 4) at weeks 0 and 24; and 5) at weeks 0, 4, 8, 12, and 24.

7. Main results
Body weight was reduced by 1.16 kg (~1.5%) (from 77.82±17.53 kg at week 0 to 76.63±17.66 kg at week 24) in the bofu group, in contrast to the reduction of 1.49 kg (~2.8%) (from 71.79±10.16 kg at week 0 to 70.30±10.36 kg at week 24) in the control group. But the between-group difference was not significant. BMI was decreased by 1.6% (from 30.62±5.81 at week 0 to 30.14±5.78 at week 24) in the bofu group and 2.1% (from 27.80±2.56 at week 0 to 27.22±2.79 at week 24) in the control group.
HS-CRP was 1199.00±1040.46 μg/dL at week 0, then gradually increased by 914.54 μg/dL to 2113.54±4524.08 μg/dL at week 24 in the control group, while it was 2918.17±4239.03 μg/dL at week 0, transiently increased to 5229.26±11066.85 μg/dL at week 4, then decreased to 2694.92±3606.66 μg/dL at week 24 (decrease of 223.25 μg/dL from the week 0 level) in the bofu group.

8. Conclusions
Although body weight and BMI were higher in the bofu group than in the control group, HS-CRP at week 24 was decreased in the bofu group and increased in the control group.

9. From Kampo medicine perspective
The anti-arteriosclerosis effect of keishibukuryogan is also described in this paper.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study is an RCT that used HS-CRP as an outcome measure to evaluate arteriosclerosis. The study is very interesting in that it used a novel approach to assess a Kampo medicine. Although results on body weight and BMI were negative, further studies are expected to reveal some positive effects.

12. Abstractor and date
1. Objectives
To evaluate the efficacy of hachimijiogan (八味地黄丸) for dementia.

2. Design
Double-blinded randomized controlled trial (DB-RCT).

3. Setting
Single hospital (long-term care facility).

4. Participants
Thirty-three anticholinergic-untreated dementia patients with an MMSE score of 0 – 25.

5. Intervention
Arm 1: oral administration of Uchida Hachimijiogan (八味地黄丸) 2.0g t.i.d. after meals for 8 weeks (n=16).
Arm 2: oral administration of 2.0 g of honey-mixed black rice powder as placebo t.i.d. after meals for 8 weeks (n=17).

6. Main outcome measures
Mini-Mental State Examination (MMSE) score, Barthel Index, and internal carotid artery pulsatility index at baseline, 8 weeks after start of dosing, and 8 weeks after completion of dosing.

7. Main results
After 8 weeks of dosing, in arm 1, a significant improvement over baseline was observed in MMSE score, from 13.5±8.5 to 16.3±7.7, Barthel Index, from 61.8±34.6 to 78.9±21.1, and pulsatility index, from 2.5±1.7 to 1.9±0.5, whereas no changes were noted in these variables in arm 2. At 8 weeks after completion of dosing (16 weeks after start of dosing), MMSE score and Barthel Index of arm 1 returned to control (arm 2) levels.

8. Conclusions
Hachimijiogan improves cognitive function, activities of daily living, and internal carotid arterial blood flow in dementia patients.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
During the study period, no adverse drug reactions occurred in either group. After completion of dosing, a hospital change due for personal reasons, and urinary tract infections and upper respiratory tract infections occurred in 1 and 2 patients in arm 1, respectively.

11. Abstractor’s comments
This study, which investigated the efficacy of hachimijiogan for preserving or restoring cognitive function and activities of daily living in elderly dementia patients in a double-blind RCT, provides high-quality evidence. At week 16, MMSE scores of the hachimijiogan group had a large standard deviation (SD), indicating wide inter-individual variation in dementia severity. Even in the placebo group, MMSE score and Barthel Index did not worsen, though the study population included patients with Alzheimer’s disease, suggesting disease progression may have been slower in these very old patients (aged 83 to 85 years, on average). In addition, whether the hachimijiogan-induced improvement (a mean of 2.8 points) in the dementia score of the MMSE led to clinical improvement will require further investigation. It is recommended that investigation separate patients with cerebrovascular disorders from those with Alzheimer’s disease. To further elucidate the efficacy of hachimijiogan, longer-term observation of a larger sample is expected.

12. Abstractor and date
Psychiatric/Behavioral Disorders

Reference

1. **Objectives**
To evaluate the efficacy of chotosan (釣藤散) for improvement of cognitive function and activities of daily living in dementia patients.

2. **Design**
Double-blinded randomized controlled trial (DB-RCT).

3. **Setting**
Not mentioned (authors belong to Department of Geriatric Medicine, Nippon Medical School Hospital, and another hospital).

4. **Participants**
Thirty patients with mild or moderate dementia: 13, Alzheimer type dementia (MMSE\(^1\) score 14 – 25) and 17, Alzheimer disease (MMSE score 10 – 21) or cerebrovascular disorders (MMSE score not indicated). All were included in the analysis population.

5. **Intervention**
Arm 1: oral administration of 2.5 g of TSUMURA Chotosan (釣藤散) Extract Granules t.i.d. before meals for 8 weeks (n=10).
Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. before meals for 8 weeks (n=10).
Arm 3: oral administration of 2.5 g of placebo t.i.d. before meals for 8 weeks (n = 10).

6. **Main outcome measures**
Cognitive function evaluated by the MMSE; activities of daily living, by Barthel Index (BI); and caregiver burden, by Zarit Caregiver Burden Scale (Z score).

7. **Main results**
In arm 1, a significant improvement over baseline was observed in MMSE score, from 15.5±4.0 to 17.5±4.9, and BI, from 67.5±34.6 to 71.5±35.8, whereas no such improvement was seen in arm 2 or 3. There was no significant difference in Z score among the 3 arms.

8. **Conclusions**
Chotosan improves cognitive function and activities of daily living in dementia patients.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
Not mentioned

11. **Abstractor’s comments**
This study, which investigated the efficacy of chotosan and goshajinkigan for cognitive function and activities of daily living in elderly patients with dementia in a double-blind RCT, provides high-quality evidence. Although the sample size was small and no statistically significant difference between the arms was found, cognitive function and activities of daily living were significantly improved over baseline in the chotosan group. However, no baseline characteristics except for age and sex are indicated, the underlying disease is not mentioned, and MMSE scores of patients with cerebrovascular disorders are not given. Patient characteristics and each score should be provided. Furthermore, MMSE score in the chotosan group was improved over baseline, but the level after 8-week dosing was almost equal to that in the placebo group (presumably because there was a significant difference in MMSE score at baseline between 2 groups). A future investigation of the efficacy of chotosan for improving cognitive function and activities of daily living is expected with a larger sample size and for a longer period.

12. **Abstractor and date**
Psychiatric/Behavioral Disorders

Reference

1. Objectives
To evaluate the efficacy and safety of yokukansan (抑肝散) for treating behavioral disorders and improving activities of daily living in dementia patients.

2. Design
Randomized controlled trial (RCT).

3. Setting
Three hospitals (long-term care facilities).

4. Participants
A total of 60 patients with dementia due to Alzheimer’s disease, cerebrovascular disorder, or Lewy body disease, having a Mini-Mental State Examination (MMSE) score of <24 and a neuropsychiatric inventory (NPI) score of >6; of these, 52 patients were included for analysis.

5. Intervention
Arm 1: oral administration of 7.5 g/day of TSUMURA Yokukansan (抑肝散) Extract Granules in 3 divided doses before meals for 4 weeks (n=27).
Arm 2: untreated control group (n=25).

6. Main outcome measures
MMSE score, Barthel Index, and NPI score.

7. Main results
No changes were found in MMSE score in either group. Significant improvements (compared with baseline) were observed in Barthel Index, from 56.4±34.2 to 62.9±35.2, and NPI score, from 37.9±16.1 to 19.5±15.6, in arm 1. In NPI subscales for hallucination, anxiety/excitement, etc., significant improvements over baseline were noted in arm 1. Additional treatment with tiapride hydrochloride, a dopamine D1 selective neuroleptic, was required in 11 patients in arm 2 but in none in arm 1.

8. Conclusions
Yokukansan is effective for improvement of behavioral disorders and activities of daily living in dementia patients.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Dizziness and impaired postural sway were reported in 6 patients (54.5%) treated with tiapride hydrochloride. Two patients (7.4%) who continued yokukansan after the end of the observation period became oversedated but recovered with a reduced dose.

11. Abstractor’s comments
This study, which investigated the efficacy of yokukansan for cognitive function and activities of daily living in elderly dementia patients in an RCT, provides high-quality evidence. However, the same nurses who rated MMSE and NPI scores, and Barthel Index may also have administered yokukansan, suggesting the possibility of a lack of blinding, which may have affected evaluations. In future, the effects of yokukansan in dementia patients are expected to be studied over a longer term.

12. Abstractor and date
Psychiatric/Behavioral Disorders

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1. **Objectives**
   To determine the efficacy of saiboku-to (柴朴湯) as a potentiator of the anxiolytic and antidepressant effects of diazepam.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   A single clinic (pain clinic).

4. **Participants**
   Fifteen patients with chronic anxiety or depression were included for analysis.

5. **Intervention**
   Arm 1: oral administration of 7.5 g/day of saiboku-to (柴朴湯) extract granules (manufacturer, not specified; frequency, not specified) for 2 weeks followed by 6 mg/day of diazepam for 2 weeks. (n=7)
   Arm 2: oral administration of 6 mg/day of diazepam for 2 weeks. (n=8)

6. **Main outcome measures**
   Hamilton Rating Scale (HS) score, diazepam and desmethyldiazepam blood levels, motor nerve conduction velocity (MCV)

7. **Main results**
   Mean HS scores were 11.0, 7.4, and 4.1 before and after saiboku and after diazepam, respectively, in Arm 1, while 8.9 and 5.5, respectively, before and after diazepam in Arm 2. Significant improvement in HS score was observed after diazepam in both arms. No between-arm difference was seen in diazepam and desmethyldiazepam blood levels or MCV.

8. **Conclusions**
   Administration of saiboku-to followed by diazepam, compared with diazepam monotherapy, has at least an equal anxiolytic and antidepressant effect.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor's comments**
    The study comparing diazepam monotherapy with saiboku-to and subsequent diazepam for anxiolytic and antidepressant treatment in patients with anxiety neurosis in a randomized controlled trial provides a high quality of evidence. The statement concluding that administration of saiboku-to was likely to be associated with clinical improvement of symptoms was in the Discussion, although not in the Results. Despite the small sample size, it is likely that the effect of diazepam was enhanced by prior saiboku-to treatment, so studies with larger sample size are needed. A trend towards clinical improvement of symptoms in the saiboku-to arm was presented as a conclusion in the Discussion, but the measures of clinical symptoms are not mentioned. Providing details of these measures would improve the quality of this study.

12. **Abstractor and date**
Psychiatric/Behavioral Disorders

Reference

1. Objectives
To determine the efficacy of lansoprazole in patients with pharyngolaryngeal paresthesia and acid reflux symptoms (compared with rikkunshito (六君子湯) as a control).

2. Design
Quasi-randomized controlled trial (quasi-RCT).

3. Setting
Two institutions including Matsusaka Chuo General Hospital.

4. Participants
Eighty-six patients with pharyngolaryngeal paresthesia and acid reflux symptoms who presented to the participating institutions between May 2003 and November 2005.

5. Intervention
Arm 1: administration of TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 2 weeks in 38 patients who started treatment on odd-numbered days.
Arm 2: administration of lansoprazole 15 mg/day for 2 weeks in 48 patients who started treatment on even-numbered days.

6. Main outcome measures
Pharyngolaryngeal discomfort and reflux symptoms.

7. Main results
Rates of excellent, moderate, mild, and no improvement in pharyngolaryngeal discomfort after 2 weeks of treatment were 29, 34, 11, and 26%, respectively, in arm 1 and 33, 27, 19, and 21%, respectively, in arm 2. The respective rates of improvement in heartburn/acid reflux symptoms were 57, 30, 3, and 10% in arm 1 and 89, 9, 0, and 2% in arm 2.

8. Conclusions
No conclusions were drawn from this data (the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients).

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This paper describes the efficacy of lansoprazole (compared with rikkunshito as a control) in patients with pharyngolaryngeal paresthesia and acid reflux symptoms. But, since the two treatment arms were not compared, the analysis seems to be incomplete. As the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients, a follow-up report is anticipated.

12. Abstractor and date
Nervous System Diseases (including Alzheimer's Disease)

Reference

1. **Objectives**
To evaluate the efficacy and safety of kihito (帰脾湯) for Alzheimer-type dementia.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Hanwa Daini Senboku Hospital.

4. **Participants**
Seventy-five elderly patients diagnosed with Alzheimer’s disease according to DSM-IV criteria, with Hachinski ischemic score of ≤4 points and Mini-Mental State Examination (MMSE) score of 10–26 points. Patients with marked hypertension, diabetes, hypercholesterolemia, heart disease, renal failure, or depression, or MRI findings of marked cerebral infarction were excluded.

5. **Intervention**
Arm 1: no treatment, n=20.
Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. after meals for 3 months, n=24.
Arm 3: Oral administration of 2.5 g of TSUMURA Kihito (帰脾湯) Extract Granules t.i.d. after meals for 3 months, n=20.

6. **Main outcome measures**
MMSE score, activities of daily living (ADL) evaluated in all patients at baseline and 3 months. Brain blood flow measured by single photon emission computed tomography (SPECT) in 6 patients in arm 2 and 4 patients in arm 3 at baseline and 3 months (selection criteria for performing SPECT not indicated).

7. **Main results**
Of 75 participants, 64 were included in the analysis population. MMSE score in arm 3 was significantly improved from baseline at 3 months and was also significantly improved compared with arm 1 and arm 2. In particular, disorientation and attentiveness were markedly improved. There were no among-arm differences in ADL and between baseline and 3 months. SPECT revealed no obvious changes in brain blood flow.

8. **Conclusions**
Kihito is an effective treatment for Alzheimer-type dementia.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
One patient in arm 2 experienced diarrhea and 1 patient in arm 3 increased blood pressure, leading to discontinuation of treatment.

11. **Abstractor’s comments**
This excellent clinical study investigated and demonstrated the efficacy of kihito for Alzheimer’s dementia using a non-Kampo-treatment and goshajinkigan as controls. The authors selected goshajinkigan as a control because of its onji-free composition and the lack of reports showing an effect on cognitive function. However, since the efficacy of hachimijiogan, containing goshajinkigan ingredients other than gohisu and shazenshi, for elderly dementia has already been reported (Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine “Ba wei di huang wan” in the treatment of dementia. Journal of the American Geriatrics Society 2004; 52: 1518-21.), goshajinkigan was considered inappropriate for a control, although the results showed significantly improved MMSE score only with kihito. Furthermore, although they attribute, in the discussion, the absence of a difference in brain blood flow to the small sample size, information on selection criteria for performing SPECT would be necessary. The number of dropouts in arm 1 should be indicated. Although these details were omitted, this clinical research demonstrated the efficacy of kihito for treatment of dementia, and investigation of the mechanism of action and long-term effect using a larger sample size is expected.

12. **Abstractor and date**
### Nervous System Diseases (including Alzheimer's Disease)

#### Reference

1. **Objectives**
   
   To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for treatment of migraine.

2. **Design**
   
   A crossover randomized controlled trial (RCT-crossover).

3. **Setting**
   
   No description of the setting is available; the authors belong to the Department of General Medicine, Iida Municipal Hospital.

4. **Participants**
   
   Fourteen patients with at least a 1-year history of migraine and suffering a mean of 3 or more migraine attack events monthly.

5. **Intervention**
   
   Arm 1: oral administration of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g t.i.d. for 28 days (n=14).
   
   Arm 2: oral administration of lomerizine hydrochloride 5 mg b.i.d. for 28 days (n=14).
   
   With 2-week withdrawal between courses. Oral triptans to treat migraine attacks were allowed.

6. **Main outcome measures**
   
   Frequency of migraine attacks, visual analogue scale (VAS) score, number of triptan oral tablets used, response to a triptan (time to relieve attacks), evaluated in the pretreatment period (28 days), course 1 (28 days), withdrawal period (14 days), course 2 (28 days), and final period (28 days).

7. **Main results**
   
   Differences in measures of drug efficacy (i.e., frequency of migraine attacks, VAS peak value, and number of triptan oral tablets used) were greater in goshuyuto group than in lomerizine hydrochloride group.

8. **Conclusions**
   
   Goshuyuto is more effective for migraine attacks than lomerizine hydrochloride.

9. **From Kampo medicine perspective**
   
   As indications of goshuyuto, the following *shoes* were identified: *genchimyaku* (弦遅脈, string-like, slow pulse), *katsuhakutai* (滑白苔, slippy white tongue coating), *shinsuion* (振水音, splashing sounds in the stomach), *shinkahikou* (心下痞鞕, stuffiness and rigidity below the heart), *shishikanrei* (四肢厥冷, reversal cold of the limbs) in 71.4, 57.1, 64.3, 85.7, and 100% of patients.

10. **Safety assessment in the article**
    
    While 2 patients receiving lomerizine hydrochloride experienced sleepiness, none receiving goshuyuto experienced any adverse drug reactions.

11. **Abstractor's comments**
    
    This excellent clinical study investigated the effect of goshuyuto on migraine using lomerizine hydrochloride as the control and demonstrated that it prevented migraine attacks. However, the author stated in the discussion of his paper that lomerizine hydrochloride used as the control was weaker than reported in previous clinical research. Therefore, it would be necessary to determine whether migraine was correctly diagnosed in participants and whether response to previous oral treatment with lomerizine hydrochloride was poor. Furthermore, in arm 2, goshuyuto was received in course 1, and the frequency and severity of migraine attack had not returned to baseline levels by the start of lomerizine in course 2, suggesting that the pace of withdrawal was too rapid. This may explain the stronger effect of goshuyuto in arm 1 (patients who received goshuyuto in course 2). Moreover, compliance with goshuyuto treatment (74%) was significantly lower than compliance with lomerizine hydrochloride treatment (93%), warranting improvement in future compliance. Nevertheless, this research demonstrated that goshuyuto prevented migraine, and further investigation of its efficacy is expected with various prescriptions.

12. **Abstractor and date**
    
Nervous System Diseases (including Alzheimer's Disease)

Reference

1. Objectives
To evaluate the efficacy of yokukansankachimpihange (抑肝散加陳皮半夏) for sleep disorders.

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

3. Setting
Not mentioned (probably the Akita Red Cross Hospital)

4. Participants
Of 20 normal healthy men receiving yokukansankachimpihange before the start of the study, 7 with sleep disorders favorably affected were selected for the study.

5. Intervention
Arm 1: oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of anchusan (安中散) extract for 3 days.
Arm 2: oral administration of anchusan (安中散) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract product for 3 days.
(The grouping method for the 7 subjects is not indicated).

6. Main outcome measures
Sleep time, sleep latency, sleep depth, and rapid eye movement (REM) sleep time.

7. Main results
Total sleep time was significantly prolonged in arm 1 (438±13 min vs 371±19 min in arm 2).

8. Conclusions
Yokukansankachimpihange increases sleep time.

9. From Kampo medicine perspective
Seven subjects responding to yokukansankachimpihange were selected for the double-blind study.

10. Safety assessment in the article
No adverse drug reactions occurred in either group.

11. Abstractor's comments
This study, which investigated the efficacy of yokukansankachimpihange for sleep in a double-blind RCT, provides high-quality evidence. However, giving participants yokukansankachimpihange as pretreatment and using anchusan (which has a similar taste) as the control may have compromised blinding. Nevertheless, the research content is advantageous in that it involved objective evaluation of sleep using all-night polysomnography. Investigation with a larger sample size is expected.

12. Abstractor and date
**Reference**


1. **Objectives**

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for treatment of lumbar (low back) and leg pain.

2. **Design**

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

3. **Setting**

One general hospital and one university hospital.

4. **Participants**

Twenty patients with lumbar degeneration (aged 60 years or older) with a chief complaint of low back and leg pain persisting over 6 months.

5. **Intervention**

Arm 1: oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks, followed by oral administration of 75 mg/day of benfotiamine for 4 weeks (n=10).

Arm 2: oral administration of 75 mg/day of benfotiamine for 4 weeks, followed by oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks (n=10).

In each group, one patient experienced gastrointestinal symptoms following administration of goshajinkigan (牛車腎気丸) and was excluded from the statistical analysis.

6. **Main outcome measures**

Subjective symptoms (low back pain at rest, low back pain with motion, leg pain at rest, leg pain with motion, leg numbness, and leg fatigue), and clinical laboratory tests (hematology, blood biochemistry, and urinalysis).

7. **Main results**

Subjective symptoms – low back pain at rest, low back pain with motion, and leg numbness – were significantly improved after administration of goshajinkigan, compared with benfotiamine.

8. **Conclusions**

Goshajinkigan is more effective than benfotiamine, a vitamin B1 derivative, in the treatment of lumbar (low back) and leg pain.

9. **From Kampo medicine perspective**

In each arm, 6 patients with jinkyo (腎虚, kidney deficiency) were included. No difference was observed in the efficacy between patients with and without jinkyo.

10. **Safety assessment in the article**

Of 20 patients receiving goshajinkigan, 2 experienced gastrointestinal symptoms, which led to discontinuation of treatment. Hematology/biochemistry tests and urinalysis revealed no abnormalities in either arm.

11. **Abstractor’s comments**

This study suggests the efficacy of goshajinkigan for low back and leg pain. To confirm that efficacy is not influenced by the presence of jinkyo, a clinical trial with a larger sample size is recommended.

12. **Abstractor and date**

Nervous System Diseases (including Alzheimer's Disease)

Reference

1. Objectives
To evaluate the potential use of sokeikakketsuto (疏經活血湯) and shakuyakukanzoto (芍薬甘草湯) in preventing peripheral nerve disorder in patients receiving taxol.

2. Design
A randomized crossover controlled trial (RCT-crossover).

3. Setting
Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, University Hospital.

4. Participants
Seven patients who received monthly paclitaxel–carboplatin (TJ) as the initial anticancer therapy (18 cycles) for gynecological malignant tumors (ovarian cancer, uterine cervical cancer, and endometrial cancer) at the above facility between April 2002 and March 2005.

5. Intervention
Arm 1: monthly TJ + oral administration of Kampo medicines (sokeikakketsuto (疏經活血湯), shakuyakukanzoto (芍薬甘草湯)) (manufacturer unknown) before meals for 14 days before and after TJ therapy.
Arm 2: monthly TJ.

6. Main outcome measures
Current perception threshold (CPT) measured by Neurometer® (2000 Hz, 250 Hz, and 5 Hz) 7 days before and 7 days after the start of TJ therapy: CPT value.

7. Main results
The value (predose CPT – postdose CPT)/predose CPT × 100 (%) decreased after TJ therapy, indicating deteriorating perception without Kampo treatment but remained unchanged with Kampo treatment.

8. Conclusions
TJ therapy when combined with Kampo medicines (sokeikakketsuto, shakuyakukanzoto), but not TJ therapy alone, reduces the severity of peripheral nerve disorder.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Administration of medicines caused no adverse drug reactions.

11. Abstractor’s comments
This is a valuable study verifying the efficacy of sokeikakketsuto and shakuyakukanzoto for peripheral nerve disorder, an occasional adverse reaction to anticancer drug treatment that is evaluated by current perception threshold measurement. However, considering the small sample size (7 subjects), individual characteristics may greatly affect and bias the results; thus, increased number of cases may change the results. It is also important to ensure symptoms are consistent and relief of actual symptoms is documented by measured values, warranting continued research efforts. Furthermore, logically, the effect of a Kampo medicine is not constant but depends on the physical status of the host in each cycle of anticancer therapy. Therefore, identification of the “sho” (証, pattern/syndrome) of each individual in each cycle is recommended to investigate the correlation between pathological analysis in Kampo medicine and the objective evaluation by current perception threshold used in this study. This may lead to proper usage of Kampo medicines and establishment of highly effective regimens in cancer treatment.

12. Abstractor and date
Eye Diseases

Reference

1. **Objectives**
To evaluate the efficacy of hainosankyuto (排膿散及湯) for internal hordeolum in the acute phase.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Two hospitals.

4. **Participants**
Twenty-six patients with internal hordeolum not complicated with other ophthalmopathy or diabetes who received basic treatment with 4 doses of antibiotic eye-drops (0.3% ofloxacin) + steroid eye-drops (0.1% fluorometholone) per day.

5. **Intervention**
Arm 1: basic treatment + oral administration of 2.5 g of TSUMURA Hainosankyuto (排膿散及湯) Extract Granules t.i.d. before meals (n=16).
Arm 2: basic treatment alone (n=10).

6. **Main outcome measures**
Duration of treatment (in days) required to achieve improvement in subjective symptoms, need for adjunctive treatment.

7. **Main results**
Duration of treatment in days required to achieve symptom improvement was significantly shorter in arm 1 (2.2±0.9) than in arm 2 (5.5±4.1) (P<0.001). The number of subjects requiring adjunctive treatment was not significantly different in arm 1 (1/16; 6.3%) and arm 2 (3/10; 30%). One patient in arm 1 healed 3 days after the start of treatment but had a recurrence 4 days after treatment discontinuation.

8. **Conclusions**
TSUMURA Hainosankyuto Extract Granules induced proliferation and differentiation of pluripotent stem cells and activity of granulocyte colony stimulating factor, strongly suggesting its suppressive effect on neutropenia.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
No adverse events were observed in either arm.

11. **Abstractor’s comments**
In western medicine, antibiotics are concomitantly used with anti-inflammatory drugs. Kampo medicine, which preceded the discovery of the antibiotics used in the modern medicine, targets pathogenic microorganisms by an entirely different mechanism.

12. **Abstractor and date**
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Eye Diseases

Reference

1. Objectives
To determine the efficacy of goshajinkigan (牛車腎気丸) for corneal sensitivity, superficial keratitis, and tear secretion in patients with insulin-dependent (type 1) diabetes mellitus.

2. Design
Double-blinded randomized controlled trial (DB-RCT).

3. Setting
Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital), Department of Ophthalmology.

4. Participants
Fifty patients with insulin-dependent diabetes mellitus complicated with keratopathy. Participants met the following selection criteria: (1) 5 years or longer duration of insulin dependence; (2) simple or preproliferative diabetic retinopathy; (3) diffuse superficial keratitis revealed by fluorescein staining; (4) no history of eye disease other than diabetic retinopathy; and (5) no treatment with eye drops in the past 3 months.

5. Intervention
Arm 1: treatment with TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 25.5±6.9 years; male:female = 10:15; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group A).
Arm 2: treatment with placebo granules (lactose granules not containing extract powder) 2.0 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 26.6±5.2 years; male:female = 13:12; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group B).
Arm 3: treatment with goshajinkigan (牛車腎気丸) for 3 months in 25 healthy volunteers (age 26.2±5.4 years; male:female = 11:14; group C).

6. Main outcome measures
Corneal sensitivity, fluorescein staining score, and Schirmer score were evaluated before and after the treatment.

7. Main results
Corneal sensitivity significantly improved from the pre-treatment value of 2.47±1.1 to the post-treatment value of 2.03±0.63 in group A (P<0.05) but not in group B (2.36±1.35 and 2.33±1.02, respectively). Schirmer score markedly improved from the pre-treatment value of 9.3±3.5 to the post-treatment value of 11.0±3.3 in group A (P<0.01) but not in group B (9.0±3.8 and 9.0±4.0, respectively). Fluorescein staining score markedly improved from the pre-treatment value of 1.32±0.56 to the post-treatment value of 0.64±0.49 in group A (P<0.01) but not in group B (1.40±0.64 and 1.36±0.68, respectively). Corneal sensitivity, Schirmer score, and fluorescein staining score all remained within their normal ranges in group C.

8. Conclusions
Goshajinkigan improves reduced corneal sensitivity, increases tear secretion, and markedly repairs damage to the corneal surface, thereby improving keratopathy without affecting the progression of diabetes mellitus.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No adverse drug reactions were observed.

11. Abstractor's comments
This study was a double-blind RCT involving 50 diabetic patients (groups A and B). It is a well-designed clinical trial in which both prescribing physician and patients were blinded. I would include a comment on a similar article (Nagaki Y. Effects of goshajinkigan on diabetic keratopathy. Kampo Igaku (Kampo Medicine) 2004; 28: 63-5 [in Japanese]) in the present study. If more details, such as data on withdrawals, had been described, intention-to-treat (ITT) analysis data and more reliable results could have been obtained. Further studies are expected to determine effects of goshajinkigan on ocular complications of type 2 diabetes mellitus as a lifestyle-related disease.

12. Abstractor and date
Eye Diseases

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1. **Objectives**
   To determine the efficacy of Kampo medicines for aqueous flare elevation after small-incision cataract surgery.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital) and an affiliated hospital.

4. **Participants**
   Fifty-four patients undergoing surgery for age-related cataract. Patients with complications (such as diabetes mellitus and autoimmune disease), a history of uveitis, or use of anti-inflammatory drugs were excluded.

5. **Intervention**
   Arm 1: no medication in 20 patients (8 males and 12 females; 9 right eyes and 11 left eyes; mean age, 73.1 years [48-85 years]) as a control group.
   Arm 2: treatment with TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 7.5 g/day for 3 days before surgery, on the day of surgery, and for 7 days after surgery in 14 patients (5 males and 9 females; 8 right eyes and 6 left eyes; mean age, 74.5 years [56-90 years]).
   Arm 3: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules 7.5 g/day on the same schedule as arm 2 in 10 patients (3 males and 7 females; 6 right eyes and 4 left eyes; mean age, 75.5 years [68-83 years]).
   Arm 4: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 9.0 g/day on the same schedule as arm 2 in 10 patients (5 males and 5 females; 4 right eyes and 6 left eyes; mean age, 73.8 years [61-84 years]).

Cataract surgery in all patients was performed by a single surgeon according to a standard small-incision procedure.

6. **Main outcome measures**
   Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. **Main results**
   Preoperatively, no differences were observed in aqueous flare intensity among the groups. Aqueous flare intensity on postoperative days 1, 3, and 5 was significantly lower in the orengedokuto group ($P<0.05$) and kakkonto group ($P<0.01$) than in the control group. There was no difference between the saireito and control groups.

8. **Conclusions**
   Orengedokuto and kakkonto reduce aqueous flare elevation after small-incision cataract surgery.

9. **From Kampo medicine perspective**
   Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.

10. **Safety assessment in the article**
    No adverse drug reactions were observed.

11. **Abstractor’s comments**
    Aqueous flare intensity was used in this RCT as a measure of intraocular inflammation after cataract surgery. Since aqueous flare is a surrogate outcome, results from clinical trials examining other outcomes such as reduction of treatment duration and dosage of commonly used postoperative medication are anticipated. See the article “Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of Kakkon-to and Sairei-to on aqueous flare elevation after complicated cataract surgery. *The American Journal of Chinese Medicine* 2002; 30: 347-53”, as a follow-up of the present study.

12. **Abstractor and date**
Eye Diseases

Reference

1. Objectives
To determine the efficacy of Kampo medicines for aqueous flare elevation after complicated cataract surgery.

2. Design
Randomized controlled trial (RCT).

3. Setting
One hospital (one department of ophthalmology).

4. Participants
Twenty-seven patients with bilateral cataracts (54 eyes were eligible) associated with idiopathic or sarcoid uveitis. Of these patients, 5 were excluded from analysis.

5. Intervention
No Kampo formulation was administered in right eye surgeries. In left eye surgeries, one of the following Kampo formulations was administered for 3 days before surgery, on the day of surgery, and for 7 days after surgery.

Arm 1: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. in 12 patients (mean age, 64.2 years [48-75 years]; 6 males and 6 females; 9 with idiopathic uveitis and 3 with sarcoid uveitis).

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. in 10 patients (mean age, 73.8 years [61-84 years]; 7 males and 8 females; 12 with idiopathic uveitis and 3 with sarcoid uveitis).

Cataract surgery in all patients was performed by a single surgeon following a standard procedure.

6. Main outcome measures
Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. Main results
Preoperatively, aqueous flare intensity was not different between the two groups. For right eyes, flare intensity was 99.1 in the kakkonto group and 89.6 in the saireito group on postoperative day 1, and then gradually decreased in both groups. For left eyes, compared with the untreated right eyes, aqueous flare intensity was significantly decreased in the kakkonto group on postoperative days 1, 3, and 5 (P<0.001 for each). In contrast, there was no difference between left and right eyes in the saireito group.

8. Conclusions
Kakkonto inhibits the elevation in aqueous flare intensity after complicated cataract surgery.

9. From Kampo medicine perspective
Evaluation of sho and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.

10. Safety assessment in the article
No adverse drug reactions were observed.

11. Abstractor’s comments
This study was conducted as a follow-up to the preceding study “Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. Journal of Ocular Pharmacology and Therapeutics 2001; 17: 59-65”. Participants in the present study were different from those in the preceding study, and patients with both cataracts and uveitis were examined. Also, kakkonto, which had been more effective than orengedokuto in the preceding study, was used as a test Kampo drug. These studies were conducted by the same investigators and the blinding was not described in either article; suggesting that these might have been single-blind studies.

12. Abstractor and date
Ear Diseases

Reference

1. Objectives
To determine the efficacy of shoseiryuto (小青竜湯) combined with eppikajutsuto (越婢加朮湯) for otitis media with effusion (OME) in adults.

2. Design
A quasi-randomized controlled trial (quasi-RCT).

3. Setting
A clinic (otorhinolaryngology).

4. Participants
Thirty-four patients aged 16 years or older with acute OME.
Diagnostic criteria: eligible patients were those who complained chiefly of aural fullness, hearing loss, and autophony in the preceding three weeks at interview, and who had tympanic effusion evident under a binocular microscope.

5. Intervention
Arm 1: treatment with carbocisteine 500 mg t.i.d. and clarithromycin 200 mg b.i.d. (after meals).
(a total of 18 ears of 14 patients; 10 males and 4 females; aged 37.9±11.5 years).
Arm 2: treatment with shoseiryuto (小青竜湯) extract 1 pack t.i.d. and eppikajutsuto (越婢加朮湯) 1 pack t.i.d. (after meals).
(a total of 28 ears of 20 patients; 11 males and 9 females; aged 38.1±16.9 years).
Patients in both arms were treated for 7 days. If excellent or good response was obtained and subjective symptoms disappeared at 4 days, treatment was stopped at 4 days.

6. Main outcome measures
Main variables were symptoms (assessed on interview) and eardrum findings (under a microscope) at 4 and 7 days after the first visit. Symptoms were evaluated on a 4-point scale as follows: ‘excellent response,’ ‘good response,’ ‘minimal response,’ and ‘no response.’ Eardrums were checked primarily for tympanic effusion. Tympanogram was recorded at the first visit and 7 days later (or at 4 days in patients who showed improvement at that point).

7. Main results
‘Excellent or good response’ with normalization or improvement of the tympanogram and with disappearance of tympanic effusion was achieved in 38.9% of the control group (arm 1) vs 75.0% of the Kampo group (arm 2); the outcome was significantly better in the Kampo group ($P=0.02$, Wilcoxon rank sum test). In patients with abnormal tympanogram at the first visit, therapeutic response tended to be more pronounced in the Kampo group. Time to the onset of improvement of subjective ear symptoms was significantly shorter in arm 2 than arm 1 ($P=0.05$).

8. Conclusions
In acute OME in adults, combination therapy with shoseiryuto extract and eppikajutsuto extract results in rapid disappearance of the effusion and improvement of ear symptoms.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Nausea was observed in one patient in arm 2, while no adverse drug reactions occurred in arm 1.

11. Abstracter’s comments
This report is clinically relevant. Since patients were randomly assigned to each arm, based on odd- or even chart number, this study was strictly a randomized clinical controlled trial (CCT), not an RCT, and is classified as a quasi-randomized trial. Results from larger rigorously-designed trials are awaited.

12. Abstracter and date
### Ear Diseases

#### Reference

1. **Objectives**
   To determine the efficacy of chotosan (釣藤散) for tinnitus.

2. **Design**
   A crossover randomized controlled trial (RCT-crossover).

3. **Setting**
   A community hospital (department of otorhinolaryngology).

4. **Participants**
   Fifty-eight patients with tinnitus.

5. **Intervention**
   Arm 1: oral administration of TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks, followed by mecobalamin 0.5 mg, t.i.d. for 4 weeks (n=29).
   Arm 2: oral administration of mecobalamin 0.5 mg, t.i.d. for 4 weeks, followed by TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks (n=29).

6. **Main outcome measures**
   The intensity (loudness level) and duration of tinnitus, and tinnitus-associated annoyance was evaluated on a 6-point scale (from 0 = disappearance to 5 = maximum) according to the diagnosis criteria established by a study group of the Japan Audiological Society. Scores of these three measures were summed before and after each treatment, and the degree of improvement was measured by reduction in the summed score from the pre-treatment value. ‘Disappearance’ was defined as reduction to zero, ‘marked improvement’ as reduction of 8 or more points, ‘moderate improvement’ as reduction of 4 to 7 points, ‘mild improvement’ as reduction of 1 to 3 points, ‘no improvement’ as no change in score, and ‘worsening’ as increase in score.

7. **Main results**
   In the chotosan-first group (arm 1), scores were significantly reduced after 4 weeks of chotosan treatment, but significantly increased after the switch to mecobalamin treatment. In mecobalamin-first group (arm 2), scores did not change at 4 weeks, and significantly increased after the switch to chotosan treatment. The degree of improvement in tinnitus was significantly different between groups at 4 weeks, then similar at 8 weeks. Improvements were significant, as compared with the pre-treatment baseline values, in both groups. Tinnitus had disappeared in 5 ears, was markedly improved in 8 ears, and was moderately improved in 14 ears. Moderate-to-marked improvement was seen in 39.8% of ears and mild-to-marked improvement in 80.9%. There was no case of ‘worsening’ tinnitus. Regarding background factors, there were no between-group differences in sex, age, diagnosis, disease duration, side of diseased ear, and medical history. Chotosan showed significant efficacy for tinnitus with heaviness of head/ headache or shoulder stiffness, compared with other accompanying symptoms.

8. **Conclusions**
   Chotosan is more effective than mecobalamin in improving tinnitus.

9. **From Kampo medicine perspective**
   Although specific results were not provided, the author concluded that the treatment would be more effective when they took into account on the patient’s condition.

10. **Safety assessment in the article**
    Serious adverse drug reactions were not reported in either group.

11. **Abstractor’s comments**
    This study provided high-quality evidence that chotosan is efficacious for tinnitus, which is often difficult to treat. Chotosan tended to improve, though not significantly, Meniere’s disease and tinnitus without hearing loss, but not C5dip-type sensorineural hearing loss. These points are helpful when the efficacy of chotosan is determined, and also provide useful insights in its mechanism. In addition, unlike previous reports showing that patients with shorter disease duration were more likely to respond, this study described striking improvement in some cases, such as ‘marked improvement’ in a patient with disease for 30–40 years and complete recovery in several patients with disease for 4–5 years. The problems of this study are as follows: 1) The presentation of the results is inconsistent. For example, results are presented on a patient basis at first, and then on an affected-ear basis. 2) The report is incomplete because results from a Kampo medicine perspective are not presented. And 3) there is no description of the randomization step or the method of assignment to arm 1 and arm 2. The randomization step may have been omitted because of the crossover design. Nevertheless, an accurate description is desired. However, the article presents future challenges, and further developments are expected.

12. **Abstractor and date**
Cardiovascular Diseases

Reference


1. Objectives
To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in patients with hypertension symptoms.

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

3. Setting
A total of 116 university hospitals and community hospitals.

4. Participants
A total of 265 patients with hypertension who met the inclusion and exclusion criteria; 204 included and 61 not included for analysis.

5. Intervention
Arm 1: administration of TJ-15 (containing 0.25 g of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules) capsules, 2 cap, t.i.d. (n=103).
Arm 2: administration of placebo capsules, 2 cap, t.i.d. (n=101).
Oral administration before each meal. Duration of treatment: 8 weeks.

6. Main outcome measures
Reduction in blood pressure was evaluated by comparing blood pressure measurements (systolic, diastolic, and mean) obtained after the run-in period and after the treatment period, and the antihypertensive effect was classified into 5 grades. Improvement in five major accessory symptoms – irritability (feeling irritated), anxiety, sleep disorder, hot flushes, and facial flushing – and other subjective symptoms – headache/heavy-headedness, shoulder stiffness, dizziness, and malaise – were graded from –3 to 3.

7. Main results
There was no significant difference in blood pressure decrease, or antihypertensive effect, between the TJ-15 group and placebo group. Significant efficacy against hot flushes and facial flushing was observed in the treatment group. Irritability, anxiety, and sleep disorder were also improved in the treatment group as compared with the placebo group. Scores of the other subjective symptoms improved significantly. There was no significant between-group difference in the overall safety rating.

8. Conclusions
This study demonstrated the efficacy and safety of orengedokuto for the treatment of hypertension symptoms.

9. From Kampo medicine perspective
The inclusion criteria were high blood pressure and presence of hypertension symptoms (irritability, anxiety, sleep disorder, hot flushes, and facial flushing) indicating orengedokuto “sho” (pattern/syndrome). Also, ‘patients with “kan-sho” (寒証, cold/yin pattern) or “kyo-sho” (虚証, deficiency pattern)” in Kampo medicine’ were excluded. Although “sho” is not fully equivalent to body-mass index (BMI), patients with thin physique were excluded from this study, resulting in the mean BMI of 24.3. Thus, the focus of this study was on the patients who were most likely to respond to and benefit from orengedokuto.

10. Safety assessment in the article
Adverse effects were observed in eight patients (6.3%) in the placebo group and 15 patients (11.5%) in the TJ-15 group. Nausea (n=2), abnormal laboratory data such as liver dysfunction (elevated liver enzymes) (n=7), and generalized rash (n=1) might be associated with orengedokuto.

11. Abstractor’s comments
Orengedokuto, a typical Kampo medicine for hypertension, was reevaluated in this original article. This study targets the symptoms related to stress or hyper-activation of sympathetic nervous system such as anger, stress, anxiety, and fear. In this multicenter double-blind clinical trial, blood pressure tended to decrease, but did not significantly decrease, in response to treatment. However, significant improvement in some accessory symptoms is a milestone. Compared with benzodiazepine anxiolytics in a study of essential hypertension, Orengedokuto seemed to show more efficacy. However, simple comparison cannot be done owing to different criteria used in selecting study participants. This study suggests that treatment based on “sho” may be effective. Related article: “Arakawa K, Saruta T, Abe K, et al. Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: a double-blind, placebo-controlled study. *Phytomedicine* 2006; 13: 1-10. [CENTRAL ID: CN-00553637, Pubmed ID: 16360926]” This study is published in an English-language journal and has the same content.

12. Abstractor and date
Cardiovascular Diseases

Reference

1. Objectives
To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for treatment of hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder.

2. Design
Randomized controlled trial (RCT) (assigned by randomized allocation in 20 cases and chosen by the patient in 6 cases).

3. Setting
University hospital and community hospital.

4. Participants
Thirty-one patients with sequelae of cerebrovascular disorder.

5. Intervention
Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules between meals (n=16) (for 12 months).
Arm 2: no administration of Kampo medicines (n=15).

6. Main outcome measures
The Stroke Impairment Assessment Set (SIAS), Functional Independence Measure (FIM), body weight and *oketsu* (瘀血, static blood), *qikyo* (気虚, qi deficiency), *qiutsu* (気鬱, qi movement stagnation) and *jinkyo* (腎虚, kidney deficiency), evaluated on a 5-point scale at baseline and every 3 months thereafter.

7. Main results
Both SIAS and FIM scores remained at baseline levels in arm 1 but increased significantly in arm 2 at 12 months, resulting in a significant between-arm difference. In arm 2, stroke recurred at 9 or 12 months.

8. Conclusions
Tokishakuyakusan suppresses hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder requiring an intermediate level of care.

9. From Kampo medicine perspective
At 12 months, *oketsu* and *jinkyo* significantly improved in arm 1, but *oketsu* remained unchanged and *jinkyo* worsened in arm 2, resulting in a significant between-arm difference. In contrast, there was no significant difference in *qikyo* and *qiutsu* between arms.

10. Safety assessment in the article
One patient in arm 1 felt numbness in hands and feet. Since the cause (tokishakuyakusan, amantadine hydrochloride, or captopril) was unclear, all these drugs were discontinued in this patient.

11. Abstractor’s comments
In this valuable report about the 1-year follow-up of patients with sequelae of cerebrovascular disorder, tokishakuyakusan was shown to suppress the hypofunction and decreased independence observable in the control group at 12 months. Since the sample size is small (15 or 16 patients), a study with a larger sample size is expected in the future. Further exploration of Kampo medicines potentially able to improve this condition is also expected.

12. Abstractor and date
Cardiovascular Diseases

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1. **Objectives**
   To evaluate the effectiveness of orengedoku (黄連解毒湯) in improving peripheral circulation in Raynaud’s phenomenon.

2. **Design**
   Quasi-RCT.

3. **Setting**
   Two departments (Department of Rheumatology and Department of Oriental Medicine) in Saitama Medical School.

4. **Participants**
   Twenty patients with Raynaud’s phenomenon who consulted at the above two departments between October and March from 1994 to 1997 (3 men and 17 women).

5. **Intervention**
   Arm 1: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals.
   Arm 2: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals, and orengedoku (黄連解毒湯) 2.5 g t.i.d. before meals.
   Arm 3: oral administration of sarpogrelate hydrochloride (100 mg) in three divided doses after meals, and tokishakuyakusan (当帰芍薬散) 2.5 g t.i.d. before meals.

6. **Main outcome measures**
   Raynaud’s phenomenon – subjective symptoms (cold sensation, numbness, pain) and increase in skin temperature assessed by thermography (increase of more than 0.6°C in the mean temperature of all 10 fingertips of both hands) – were evaluated before and after 12-week treatment. The efficacy was compared among subjects with different “sho” (証, pattern/syndrome) (jitsu-sho [実証, excess pattern], chukan-sho [中間証, intermediate pattern], and kyo-sho [虚証, deficiency pattern]) in Kampo medicine.

7. **Main results**
   After 12-week treatment, the combination with orengedokuto had significantly higher efficacy than sarpogrelate hydrochloride alone (90% vs. 52.5%; P<0.02), while the combination with tokishakuyakusan had similar efficacy to sarpogrelate hydrochloride alone. Skin temperature at the fingertips was significantly increased in arm 3 (1.8±1.9°C; P<0.02) compared with arm 1 (0.6±0.8°C), and also significantly elevated in arm 2 (4.1±2.1°C; P<0.005) compared with arm 3. Combination therapy with Kampo formulations was effective in patients with jitsu-sho, but not in patients with kyo-sho.

8. **Conclusions**
   Orengedokuto combined with sarpogrelate hydrochloride has higher efficacy in the treatment of Raynaud’s phenomenon. However, kyo-sho patients did not respond to this combination therapy and had higher incidence of adverse drug reactions (ADRs), suggesting the importance of prescriptions according to the patient’s “sho.”

9. From Kampo medicine perspective
   In this study, 72.7% of the subjects were regarded as kyo-sho type. No subject was identified as the so-called orengedokuto-sho type – having conditions that are expected to respond to orengedokuto therapy. In kyo-sho subjects, the efficacy of the orengedokuto combination therapy was similar to that of sarpogrelate hydrochloride monotherapy, and a higher dropout rate was observed because of ADRs from the bitherapy. Therefore we suggest that administration of sarpogrelate hydrochloride plus orengedokuto should be withheld from kyo-sho subjects.

10. Safety assessment in the article
    ADRs of the orengedokuto combination occurred in kyo-sho patients, including nausea (n=2) and diarrhea (n=2), neither of which was serious. No serious ADRs due to the tokishakuyakusan combination were noted.

11. Abstrator’s comments
    Sarpogrelate hydrochloride in combination with orengedokuto, which has been reported to improve peripheral circulation, improved more efficiently peripheral circulation in Raynaud’s phenomenon when compared with sarpogrelate hydrochloride monotherapy as positive control in this study. It is interesting that improvement was greater with this combination than with the tokishakuyakusan combination, even when more than 70% of subjects were kyo-sho. Further scientific evaluation with a larger number of subjects is awaited.

12. Abstrator and date
    Ushiroyama T. 1 April 2008, 8 August 2009.
Cardiovascular Diseases

Reference

1. Objectives
To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of lymphedema.

2. Design
Randomized controlled trial (RCT).

3. Setting
One hospital (department of cardiovascular surgery).

4. Participants
A total of 80 patients with lymphedema of the upper limbs (n=40) and lower limbs (n=40).

5. Intervention
Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (TJ-107) 2.5g t.i.d for 1 month in combination with compression therapy (n=40).
Arm 2: compression therapy without administration for 1 month (n=40).

6. Main outcome measures
Percentage reduction in edema: reduction in limb circumference assessed between the first visit (baseline) and after 1-month treatment was divided by baseline limb circumference, and expressed in percentage.

7. Main results
For lymphedema of the upper limbs, there was significant percentage reduction in arm 1 (15±3.4%) compared with arm 2 (5.7±1.2%; \( P < 0.05 \)). For lymphedema of the lower limbs, the percentage reduction was also significant in arm 1 (17.5±2.8% vs 6.7±0.8% in Arm 2; \( P < 0.05 \)).

8. Conclusions
Edema was significantly reduced in both patients with lymphedema of the upper limbs and those with lymphedema of the lower limbs by TSUMURA Goshajinkigan Extract Granules (TJ-107).

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
The indications for goshajinkigan are chronic nephritis, nephritic syndrome, low back pain, edema in the lower extremity, and oliguria. This RCT assessed the efficacy of goshajinkigan for the treatment of lymphedema secondary to surgical procedures. Secondary lymphedema is generally intractable in many cases despite combined treatments including lymph drainage massage, compression skin care, exercise therapy under compression, and administration of anticoagulants. It is very meaningful that goshajinkigan was shown to be efficacious. The problem is that this paper is published in a business periodical without peer review, and information on patients’ background and so on is therefore insufficient. Also, since the efficacy of goshajinkigan plus compression was assessed, the effect of goshajinkigan alone will need to be evaluated by comparison with placebo and positive control drugs in the future.

Article related to this paper:
A report on the same result is shown.

12. Abstractor and date
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Cardiovascular Diseases

Reference

1. Objectives
To examine the safety and efficacy of goreisan (五苓散) in the treatment of orthostatic hypotension in patients with diabetes mellitus.

2. Design
Randomized controlled trial (crossover design) (RCT- crossover).

3. Setting
One internal medicine clinic.

4. Participants
Ten patients with diabetes mellitus (type 1, 2; type 2, 8) associated with orthostatic hypotension diagnosed according to McDowell’s criteria.

5. Intervention
Arm 1: Kanebo Goreisan (五苓散) Extract Tablets (EKT-17) 18 tablets/day, for 1 month, n=10.
Arm 2: placebo 18 tablets/day, for 1 month, n=10.

6. Main outcome measures
Body weight, subjective symptoms, and response to orthostatic challenge (change in blood pressure, plasma adrenaline noradrenaline, and aldosterone concentrations, and plasma renin activity) were evaluated at baseline, and 1 and 2 months after the start of treatment; adverse drug reactions (ADRs) were checked during the study.

7. Main results
There was no difference in body weight between the goreisan and placebo groups. The subjective symptom of orthostatic dizziness improved in 9 of 10 patients in the goreisan group, whereas no change was reported in all 10 subjects in the placebo group. Results of orthostatic challenge: Before standing, no significant difference was found in blood pressure between at baseline and after administration of goreisan or placebo. After standing, systolic and diastolic pressures increased significantly in the goreisan group (P<0.05), while no significant change was observed in the placebo group. There were no changes in the concentration of adrenaline, noradrenaline, or aldosterone, nor in plasma renin activity at orthostatic challenge after administration of goreisan or placebo.

8. Conclusions
In diabetic patients with orthostatic hypotension, goreisan improved subjective symptoms and normalized the decrease in blood pressure on standing.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were no observed adverse drug reactions.

11. Abstractor’s comments
General indications for goreisan are edema, nausea, vomiting, dizziness in subjects with thirst and decreased urine output. Authors applied this to diabetic orthostatic hypotension, which is neuropathic and intractable/ resistant to therapies in most cases. Modern medicine can prevent the decline in blood pressure on standing; however, problems such as adverse increase in supine blood pressure remain. In contrast, goreisan causes no increase in supine blood pressure, suggesting this Kampo formulation as an ideal therapeutic agent for orthostatic hypotension in diabetic patients. It is very meaningful that this randomized controlled trial demonstrated that goreisan has efficacy. It is thought that further investigation with increased case numbers and multicenter trials will improve the reliability of data.

12. Abstractor and date
### Respiratory Diseases (including Influenza and Rhinitis)

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1. **Objectives**
   To assess the efficacy and safety of shosaikoto (小柴胡湯) in patients with common cold.

2. **Design**
   Double-blind randomized controlled trial (DB-RCT)

3. **Setting**
   Ten university hospitals, 42 community and other hospitals, and 2 clinics.

4. **Participants**
   Patients with persistent symptoms for more than 5 days after the onset of common cold, age from 25 to 75 years, and complaints of at least one of the following symptoms: oral discomfort (bitter taste, sticky sensation, dysgeusia), anorexia, or malaise.

5. **Intervention**
   The placebo had similar appearance and properties. Concomitant drug use was basically prohibited, except for dimenhydrinate phosphate (Astomin tablets) after day 3.
   - Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules (TJ-9) 2.5g t.i.d., n=131.
   - Arm 2: placebo 2.5 g t.i.d., n=119.
   - Duration of administration: 1 week or less

6. **Main outcome measures**
   Global improvement rating (comprehensive evaluation based on improvement rating of each symptom and patient’s impression), improvement rating of each symptom, and safety evaluation.

7. **Main results**
   At baseline, the patients allotted to arm 1 were not matched to those allotted to arm 2 in the severity of headache, and the amount and viscosity of sputum. General improvement was significantly better in arm 1 than in arm 2, with the percentage of patients rated 4 (improved) or 5 (markedly improved) on a 5-point scale being 64.1% and 43.7% in arm 1 and arm 2, respectively. Individual symptoms (throat pain and malaise at day 3-4, clearance of sputum, appetite, joint pain and muscular pain at the end of study) all were significantly better in arm 1.

8. **Conclusions**
   For patients with persistent common cold associated with oral discomfort (bitter taste, sticky sensation, dysgeusia), decreased appetite, and/or malaise, shosaikoto is effective and useful.

9. **From Kampo medicine perspective**
   Subject selection was made on the basis of persistent symptoms and discomfort in the mouth, which indicate “shosaikoto-sho”

10. **Safety assessment in the article**
    Ten (7.4%) of 136 subjects in arm 1 and 15 (11.4%) of 132 subjects in arm 2) experienced adverse effects. However, there were no serious adverse drug reactions.

11. **Abstractor’s comments**
    This study is a large-scale DB-RCT on Kampo therapy fitted to “sho” in Kampo medicine.

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. **Objectives**
To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for postinfectious cough.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Department of Medicine, Niigata University Medical and Dental Hospital, and a general hospital (internal medicine department).

4. **Participants**
Non-smoking patients with postinfectious cough for whom other causes for cough were ruled out, n=25.

5. **Intervention**
Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9g/day for 7 days, n=13.
Arm 2: administration of dextromethorphan hydrobromide 60mg/day for 7 days, n=12.

6. **Main outcome measures**
Cough scores (cough frequency and intensity) were self-assessed everyday on a scale ranging from 0 to 9.

7. **Main results**
Arm 1: the cough score of 5.4±1.7 at baseline decreased significantly to 1.5±1.3 on day 7.
Arm 2: the cough score of 4.1±2.0 at baseline decreased significantly to 1.8±1.3 on day 7.
The antitussive effect developed more rapidly in arm 1 than in arm 2.

8. **Conclusions**
Bakumondoto is effective for postinfectious cough in non-smoking patients, and the antitussive effect is prompt.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
No serious adverse drug reactions were observed in either group.

11. **Abstractor’s comments**
The cough in all patients resolved within 4 weeks. Dextromethorphan hydrobromide suppresses cough; however, it may adversely lead to delay in the healing process. Therefore, whether bakumondoto is effective for postinfectious cough in non-smoking patients should be studied by comparing arm 1 with an untreated/placebo control group (postinfectious cough in a natural course). As cough score is a subjective measure, assessment with objective measures is also necessary. In terms of Kampo medicine, postinfectious cough can be caused in a variety of pathologies ("Shokanron” [傷寒論]). There are different formulae for different pathologies. For some of these, bakumondoto is not effective.

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To compare the cough-improvement effect of maobushisaishinto (麻黃附子細辛湯) and western drugs in patients with the common cold.

2. Design
Randomized controlled trial (RCT).

3. Setting
Two hospitals and four clinics.

4. Participants
Patients with the common cold.

5. Intervention
The study duration was 15 years.
Arm 1: Tsumura Maobushisaishinto (麻黃附子細辛湯) Extract Granules (TJ-127), n=879.
Arm 2: Western drugs for the common cold, n=879.

6. Main outcome measures
Various subjective symptoms (i.e. fever, headache, chill etc.).

7. Main results
In various assessments, maobushisaishinto was more effective than western drugs.

8. Conclusions
Administration of maobushisaishinto was efficacious for the common cold syndrome.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not documented.

11. Abstractor's comments
The methodology and the subjects in this randomized controlled trial were not described. “Cough-improvement effect” is mentioned only in the title, but not in the text. Considering the short time course of the common cold syndrome, it is unclear why the randomized controlled study has been conducted for the past 15 years and continues even now.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To determine the effect of maoto (麻黄湯) in combination with oseltamivir on the duration of fever.

2. Design
Randomized controlled trial (RCT) (partly).

3. Setting
A hospital screening patients from January to May 2004.

4. Participants
Children (aged 0–13 years; n=60) suffering from influenza-like illness with fever of ≥38°C.

5. Intervention
Oseltamivir 2 mg/kg b.i.d., TSUMURA Maoto (麻黄湯) Extract Granules 0.06 g/kg t.i.d
Influenza infection was screened with a rapid diagnosis test, and diagnosis was confirmed by isolation of the virus or viral detection using RT-PCR
Arm 1: oseltamivir; influenza A; n=18.
Arm 2: oseltamivir and maoto (麻黄湯); influenza A; n=14.
Arm 3: maoto (麻黄湯); influenza A; n=17.
(Influenza-positive patients [by the rapid test] were randomly assigned to arm 1 and arm 2. Arm 3 included influenza-positive patients under the age of 1 year, who did not meet the criteria for oseltamivir treatment, and influenza-negative patients aged 1 year or older. Patients [n=11] without confirmed influenza virus infections were excluded.)

6. Main outcome measures
Time to becoming afebrile after initiation of the treatment.

7. Main results
The median duration of fever was 24 h, 18 h, and 15 h in arm 1, 2, and 3, respectively. Using the Wilcoxon rank sum test, significant differences were observed in arm 2 (P<0.05) and 3 (P<0.01) when compared with arm 1.

8. Conclusions
Maoto effectively reduces the duration of fever in children with influenza. A future large-scale trial is expected to investigate the efficacy of maoto in treating influenza, with a double-blinded, randomized controlled manner.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were no adverse events in any group.

11. Abstractor’s comments
Comparison between arms 1 and 2 was performed in an RCT. The result of this trial is also reported in “Kubo T. The effect of maoto for treatment of influenza infection in children. (from Presentation C-41 of the Japan Society for Oriental Medicine, 56th Annual Meeting) *Medicament News* 2005 Sep 5; 1846: 15 (in Japanese),” in which mean values are used as representative values for each arm.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. **Objectives**
To evaluate the efficacy of maoto (麻黃湯) in combination with oseltamivir phosphate in treating influenza.

2. **Design**
Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
An internal medicine clinic screening patients from January to March 2004.

4. **Participants**
Adult patients (n=37) positive for influenza (rapid diagnostic test), and having fever (≥38°C) within 48 hours of onset.

5. **Intervention**
Oseltamivir phosphate (75 mg b.i.d. for 5 days), TSUMURA Maoto (麻黃湯) Extract Granules 2.5 g t.i.d. for 3 days), and Western medicines (an antihistamine [cyproheptadine hydrochloride] with either a bronchodilator [clobuterol hydrochloride] or expectorant [carbocysteine]) were administered for 3 days.
Arm 1: oseltamivir phosphate and maoto (麻黃湯), n=10.
Arm 2: oseltamivir phosphate and Western medicines, n=9.

6. **Main outcome measures**
Body temperature.
The magnitude and time course of symptoms such as appetite, fatigue, and dizziness/light-headedness.

7. **Main results**
All subjects studied were infected with influenza A. Patients in arm 1 tended to become afebrile 12 hours earlier than patients in arm 2. There were no significant between-group differences in anorexia, fatigue, and dizziness/light-headedness, though patients in arm 1 tended to improve more rapidly than patients in arm 2.

8. **Conclusions**
Compared with oseltamivir plus Western formulations, oseltamivir plus Kampo formulation (maoto) tended to shorten the duration of fever and allowed patients to maintain normal activity.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
There were no adverse events in any group.

11. **Abstractor’s comments**
From the evidence presented, efficacy against symptoms other than fever remains unclear. This report seems to be an interim report. In the following paper “Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and Ma-to for influenza – 3rd report. Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy) 2006; 19: 17-25 (text in Japanese with English abstract),” the number of participants was increased to 91 subjects, and the duration of fever above 38°C tended to be shorter in arm 1 (after combined treatment with maoto) compared to arm 2 (after combined treatment with Western formulations).

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

1. **Objectives**
   To determine the efficacy of combined oseltamivir phosphate and maoto (麻黃湯) for the treatment of influenza.

2. **Design**
   Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
   February to March 2005.
   One hospital and one clinic.

4. **Participants**
   One hundred and seven children who presented within 48 hours of symptom onset, were febrile (body temperature, 38°C or higher), and were positive for influenza by the rapid diagnostic test.

5. **Intervention**
   Oseltamivir phosphate was administered at a dose of 75 mg, b.i.d. for 5 days. TSUMURA Maoto (麻黃湯) Extract Granules were administered at a dose of 2.5 g, t.i.d. for 3 days.
   Arm 1: treatment with oseltamivir phosphate + maoto (麻黃湯) (n=52).
   Arm 2: treatment with oseltamivir phosphate alone (n=55).

6. **Main outcome measures**
   Body temperature.
   Time-course changes in each of the following symptoms such as anorexia, cough, rhinorrhea, and insomnia was evaluated on a 3-point scale.

7. **Main results**
   Fever tended to resolve more rapidly in arm 1 than in arm 2. Scores for anorexia, cough, rhinorrhea, and insomnia tended to be lower in arm 1 than in arm 2.

8. **Conclusions**
   Maoto could be administered safely and its combination with western medicine seemed to improve symptoms further. Maoto seems to be a viable treatment for influenza in children.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    No adverse drug reactions occurred.

11. **Abstractor’s comments**
    This study follows up a comparative study of oseltamivir + maoto vs. oseltamivir + western medicine, which found a trend toward earlier resolution of fever in the oseltamivir + maoto group (“Kimoto H, Kuroki H. The efficacy of combined oseltamivir phosphate and maoto for the treatment of influenza”. *Kampo Igaku [Kampo Medicine]* 2005; 29:166-9 [in Japanese].[Ichushi Web ID: 2005292428]).

12. **Abstractor and date**
    Fujisawa M, 8 March 2009, 8 August 2009.
**Respiratory Diseases (including Influenza and Rhinitis)**

**Reference**


1. **Objectives**
   
   To evaluate the efficacy and safety of maobushi-saishin (麻黄附子細辛湯) as an adjuvant for influenza vaccination in the elderly.

2. **Design**

   Randomized controlled trial (RCT).

3. **Setting**

   Not documented.

4. **Participants**

   Eighteen patients with antibody titers of <1:10 to two types of influenza A antigens (H1N1, H3N2) as measured using an hemagglutination inhibition (HI) assay.

5. **Intervention**

   Arm 1: oral administration of TSUMURA Maobushi-saishin (麻黄附子細辛湯) Extract Granules ([TJ-127]), 7.5 g/day, from 7 days before influenza vaccination until 14 days after vaccination; n=10.
   
   Arm 2: no administration of TJ-127; influenza vaccination only; n=8.

6. **Main outcome measures**

   Rise in antibody titer from baseline was measured at 4 weeks after vaccination and the rate of rise was compared between arms.

7. **Main results**

   There was no significant between-arm difference in anti-H1N1 antibody titer. Anti-H3N2 antibody titer increased on average 4.9-fold in arm 2 (when compared with baseline) and 57.3-fold in arm 1 which was significant ($P<0.04$) when compared with arm 2. During the observation period, 2 patients in arm 2 but none in arm 1 became infected with influenza A virus.

8. **Conclusions**

   The rise in anti-H3N2 antibody titer (but not anti-H1N1 antibody titer) was significantly greater in arm 1 than arm 2, suggesting that maobushi-saishin enhances the anti-H3N2 antibody titer induced by influenza vaccination and enhances specific immunity.

9. **From Kampo medicine perspective**

   None.

10. **Safety assessment in the article**

    Not documented.

11. **Abstractor's comments**

    Influenza infection complicated with infections such as pneumonia contributes substantially to mortality in the elderly. Therefore, boosting the production of anti-influenza virus antibody would have an important preventive effect and reduce the cost of influenza treatment. From these points of view, this study investigated whether administration of maobushi-saishin can increase antibody level, with the expectation that maobushi-saishin acts as an adjuvant of the humoral immune response in the elderly with low influenza-antibody level. This report focuses on strategies for the prevention of influenza in the elderly with low response to influenza vaccine. Further studies are needed to determine why only anti-H3N2 antibody titer is significantly increased compared with control group whereas no significant difference was observed in anti-H1N1 antibody, and whether maobushi-saishin can promote production of specific antibodies.

    The small number of patients was a problem in this study. Further analyses with an increased number of cases are necessary. Also studies on other Kampo medicines with adjuvant effects in subjects with low antibody production against influenza virus, and on methods of administration, are awaited.


    The number of the participants is higher, i.e., 18 in arm 1 (the maobushi-saishin group) and 15 in arm 2 (the control group). The results were almost the same, revealing elevated anti-H3N2 antibody titer in arm 1.

12. **Abstractor and date**

Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To compare the efficacy of bakumondoto (麦門冬湯) and tipepidine hibenzate as antitussive agents in patients with mycoplasmal bronchitis.

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

3. Setting
An internal medicine department in a hospital (the authors belong to the Division of Respiratory and Infectious Diseases, Department of Internal Medicine, St. Marianna University School of Medicine).

4. Participants
Female patients with mycoplasmal bronchitis who exhibited no signs of pneumonia on chest radiographs, n=14.

5. Intervention
Arm 1: administration of azithromycin 500 mg for 3 days, Tsumura Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 3.0 g t.i.d. for 2 weeks, n=6.
Arm 2: administration of azithromycin 500 mg for 3 days, tipepidine hibenzate 60 mg for 2 weeks, n=8.

6. Main outcome measures
Cough score, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) level.

7. Main results
In arm 1, cough score was significantly decreased on day 5 compared to day 1 after the first visit ($P<0.05$). In arm 2, cough score was significantly decreased on day 7 ($P>0.05$). The rate of cough score decline was significant on day 5 in arm 1 ($P<0.05$) and on day 11 in arm 2 ($P<0.05$). There were no significant differences in white blood cell count, erythrocyte sedimentation rate, and CRP level.

8. Conclusions
Combination therapy with azithromycin and bakumondoto or tipepidine hibenzate appears to be effective in the treatment of cough in patients with mycoplasmal bronchitis.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not documented.

11. Abstractor’s comments
Persistent cough in mycoplasmal bronchitis is often difficult to treat. This interesting study evaluates the efficacy of bakumondoto in a randomized controlled trial. It is likely that allocation by the envelope method leads to difficulty in preserving randomization. This clinical trial investigates the efficacy of azithromycin combined with bakumondoto or tipepidine hibenzate in treating cough in mycoplasmal bronchitis, but the investigation lacks a placebo-group as control. Furthermore, to determine the difference in efficacy between the two arms, post-administration cough scores must be compared between the two arms. In addition, some participants have persistent cough even after 2 weeks in both arms. Consideration of Kampo “sho” (証, pattern/syndrome) for bakumondoto is required for further studies. Future studies regarding these points, and also inclusion of male patients, are awaited.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

1. Objectives
To compare the efficacy of shoseiryuto (小青竜湯), and keimakakuhanto (桂麻各半湯) in treating springtime nasal allergy and allergic conjunctivitis.

2. Design
Quasi-randomized controlled trial (quasi-RCT).

3. Setting
One hospital and three clinics of internal medicine.

4. Participants
Eighty eight patients with springtime nasal allergy and allergic conjunctivitis. Of these patients, 65 were included for analysis.

5. Intervention
Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g, t.i.d. for 2 weeks, n=32.
Arm 2: keimakakuhanto (桂麻各半湯) 8.0 g/day in three divided doses (4.0 g of TSUMURA Keishito (桂枝湯) Extract Granules [TJ-45] + 4.0 g of TSUMURA Maoto (麻黄湯) Extract Granules [TJ-27]) for 2 weeks, n=33.

6. Main outcome measures
Improvement in each symptom and global improvement.

7. Main results
Efficacy (percent improvement in arm 1 and arm 2, respectively) was observed against sneezing (68.8% and 66.7%), rhinorhea (56.3% and 63.6%), nasal sinus obstruction (40.6% and 30.3%), and periocular pruritus (46.9% and 54.5%); there was no significant difference in between-arm improvements. As for global improvement, 62.5% and 60.6% of patients in arm 1 and arm 2, respectively, were rated “moderately-to-markedly improved,” demonstrating no significant between-arm difference in efficacy.

8. Conclusions
Keimakakuhanto is as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
In the shoseiryuto arm, two subjects reported dry mouth, one reported gastric distension, and one reported stomach discomfort leading to discontinued administration; and in the keimakakuhanto arm, one reported dry mouth and one discontinued administration because of nausea.

11. Abstractor’s comments
As of 1999, no definite evidence-based medicine (EBM) approach had been used to study the efficacy of Kampo formulations in treating springtime nasal allergy and allergic conjunctivitis. This paper presents a comparative study of the efficacies of two Kampo medicines, and further placebo-controlled analysis is awaited.

12. Abstractor and date

Reference
### 1. Objectives
To compare the effects of shoseiryuto (小青竜湯) and maobushisaishinto (麻黄附子細辛湯) in treating springtime nasal allergy and allergic conjunctivitis.

### 2. Design
Quasi-randomized controlled trial (quasi-RCT).

### 3. Setting
Five clinics of internal medicine.

### 4. Participants
Of the patients who visited the above-mentioned clinics for the first time with springtime nasal allergy and allergic conjunctivitis (allergic rhinitis), 66 having previously diagnosed pollen hypersensitivity/pollinosis or newly diagnosed rhinitis with increased eosinophils in nasal discharge and elevated IgE level were enrolled. Exclusion criteria were: “kyo-sho (虚証, deficiency pattern),” sinusitis, nose disorders such as nasal septal deviation, conjunctivitis other than allergic conjunctivitis, pregnancy, and refusal to take Kampo medicines.

### 5. Intervention
Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-019) 3.0 g t.i.d., n=34.
Arm 2: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules (TJ-127) 2.5 g t.i.d., n=32.

Concomitant drug use was prohibited, with the exception of Intal eye drops or nasal spray for severe and intolerable symptoms.

### 6. Main outcome measures
- **Symptom improvement:** Each of nose and eye symptoms after 2-week administration was rated on a 5-point scale (markedly improved, moderately improved, slightly improved, unchanged, and aggravated).
- **Global improvement:** The severity of illness (nose and eye symptoms) after 2-week administration, compared with that before treatment, was rated on a 5-point scale (as maobushisaishinto acts rapidly, change in the symptoms was recorded beginning one week after the initiation of treatment.).
- **Overall safety:** Adverse drug reactions after 2-week administration were evaluated on a 5-point scale.
- **Usefulness:** The global improvement combined with overall safety was assessed on a 5-point scale (very useful, useful, slightly useful, indiscernible, and useless).

### 7. Main results
Slight-to-marked (or moderate-to-marked) improvement was seen in each of the following symptoms: sneezing (41.2% and 59.4% in arms 1 and 2, respectively), rhinorrhea (47.1% and 53.1%), nasal obstruction (58.8% and 37.5%), periorcular pruritus (35.3% and 45.2%), lacrimation (23.5% and 19.4%), and ocular discharge (11.8% and 9.7%). The chi-square test and Mann-Whitney U test revealed no significant differences in improvement of any symptoms between the two arms. Also, there was no significant difference between the arms in global improvement (slight-to-marked global improvement in 67.6% and 71.9% for arms 1 and 2, respectively, and moderate-to-marked global improvement, 52.9% and 53.1%). As for usefulness, interventions were assessed to be “useful or very useful” in 50% for arm 1 and 50% for arm 2, with no significant between-arm difference.

### 8. Conclusions
Maobushisaishinto is suggested to be as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

### 9. From Kampo medicine perspective
Maobushisaishinto is more suitable than shoseiryuto for treating subjects with “kyo-sho,” who are frail or elderly.

### 10. Safety assessment in the article
No adverse drug reactions were observed in either arm.

### 11. Abstractor’s comments
This study followed a RCT of shoseiryuto for nasal allergy and allergic conjunctivitis in spring (Jibiinkoka Rinsyo [Practica otologica] 1995; 88: 389-405 [in Japanese]), and uses the same outcome measures. However, patients were allocated sequentially and not properly randomized, making this study a clinical controlled trial (CCT: quasi-RCT). Results with no significant differences in this study provide a new therapeutic option for springtime nasal allergy and allergic conjunctivitis, and can be regarded as clinically meaningful.

### 12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. **Objectives**
   To compare the effects of shoseiryuto (小青竜湯) and gokoto (五虎湯) in subjects with nasal allergy and allergic conjunctivitis in spring.

2. **Design**
   Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
   One hospital and four clinics.

4. **Participants**
   Patients with nasal allergy and allergic conjunctivitis in spring who had increased nasal eosinophil count and high IgE level, n=116.

5. **Intervention**
   Patients who visited the setting of this study for the first time between 31 January 2000 and 10 April 2000 were recruited. Patients with severe symptoms were treated with Intal (sodium cromoglicate) nasal drops and eye drops. Assessments were done after two weeks of administration of one of the following.
   - Arm 1: Tsumura Gokoto (五虎湯) Extraction Granules 2.5 g, t.i.d., n=58.
   - Arm 2: Tsumura Shoseiryuto (小青竜湯) Extraction Granules 3.0 g, t.i.d., n=58.

6. **Main outcome measures**

7. **Main results**
   Ten subjects in arm 1 and 17 in arm 2 who stopped visiting hospital/clinic and 1 subject in arm 1 who discontinued drug administration because of adverse effect were excluded. Though not significantly different between arms, the efficacy rates were higher in arm 2 for all outcome measures except eye discharge and orbital pain, which were higher in arm 1.

8. **Conclusions**
   There was no significant between-arm difference in treatment usefulness, with usefulness in 70.8% of arm 1 and 80.5% of arm 2 was characterized as moderate or more than moderate.

9. **From Kampo medicine perspective**
   Subjects with kyosho (虚証, deficiency pattern) were excluded because shoseiryuto and gokoto are used to treat subjects with jitsusho (実証, excess pattern) or chukansho (中間証).

10. **Safety assessment in the article**
    Adverse effects included dry mouth (n=5), abdominal pain (n=1), hard stool (n=1), palpitation (n=1, excluded from analysis) in arm 1, and dry mouth (n=1) and constipation (n=1) in arm 2.

11. **Abstractor’s comments**
    The authors also compare Kampo drugs for allergic rhinitis or nasal allergy and allergic conjunctivitis in spring in several previous papers, which should be read together.

12. **Abstractor and date**
1. **Objectives**
To evaluate the efficacy and safety of shoseiryuto (小青竜湯) in the treatment of bronchitis.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Seventeen university hospitals, forty-two hospitals, and three clinics.

4. **Participants**
Patients aged 16 to <65 years with mild to moderate bronchitis, and evaluable symptoms (any of watery sputum, rales/rhonchi, and cough).

5. **Intervention**
The concomitant use of other drugs was prohibited with the exception of dimenhydrinate (Astomin) after day 4.
Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g t.i.d. for 7 days, n=101.
Arm 2: placebo 3.0 g t.i.d. for 7 days, n=91.

6. **Main outcome measures**
Global improvement (rate), improvement of bronchitis symptoms (such as cough and sputum), and safety.

7. **Main results**
At the end of treatment, there was a trend toward higher percentage of patients with moderate-to-marked global improvement in arm 1, compared with arm 2 (57.4% in arm 1 vs 42.9% in arm 2; *P*=0.06. No significant difference was observed at day 3 or 4. As for improvement of each symptom, ease of raising sputum, properties of sputum (purulent, viscous, etc.), and disturbance in activities of daily living, was significantly better in arm 1 at days 3-4. At the end of treatment, there was significant improvement in frequency of coughing, intensity of coughing, ease of raising sputum, and activities of daily living, and a tendency toward improvement in sneezing and nasal obstruction in arm 1.

8. **Conclusions**
Shoseiryuto was effective for bronchitis with mild symptoms.

9. **From Kampo medicine perspective**
Inclusion criteria of patients with watery sputum, rales/rhonchi, and/or cough were chosen to adopt the “sho (証, pattern/syndrome)” for shoseiryuto in Kampo medicine. Further subgroup analyses in patients without physical frailty and those with cough and watery sputum showed a significantly higher rate of global improvement in arm 1 than arm 2.

10. **Safety assessment in the article**
The incidence of adverse effects was 6.7% (7 cases) in arm 1 and 9.9% (9 cases) in arm 2, with no significant difference. No serious adverse effects were found.

11. **Abstractor’s comments**
This is a large-scale double-blind RCT involving the subjects with shoseiryuto-sho in Kampo medicine. Also, in another article "Miyamoto T. Clinical effectiveness of Shosei-ryuto in bronchitis. Pharma Medica 2007; 25: 23-5 (in Japanese). [Ichushi Web ID: 2008035989]", the efficacy of shoseiryuto is shown for mild to moderate bronchitis in patients who have watery sputum, rales/rhonchi, and/or cough.

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
   To assess the efficacy of smoking cessation combined with administration of seihaito (清肺湯) for chronic obstructive pulmonary disease (COPD).

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

3. Setting
   Two university hospitals.

4. Participants
   Patients with GOLD stage 0, 1, or 2 COPD who had stopped smoking, but whose respiratory symptoms (cough, sputum, and dyspnea) were still present one month after smoking cessation, n=31.

5. Intervention
   Arm 1: smoking cessation and administration of TSUMURA Seihaito (清肺湯) Extract Granules 9.0 g/day, for 24 months, n=16.
   Arm 2: smoking cessation only, for 24 months, n=15.

6. Main outcome measures
   Respiratory symptoms.
   Chest radiography and chest CT findings (emphysema, organizing pneumonia, bronchial obstruction by sputum).

7. Main results
   Respiratory symptoms were significantly improved in arm 1 compared with arm 2 for 1 to 6 months; however, no significant difference was found after 12 months. The imaging findings were significantly improved in arm 1 at 24 months.

8. Conclusions
   Administration of seihaito for 6 months improves clinical symptoms, and administration for 24 months is necessary for improvement in imaging findings.

9. From Kampo medicine perspective
   None.

10. Safety assessment in the article
    Not documented.

11. Abstractor’s comments
    Dyspnea can be evaluated objectively by respiratory function testing and measurement of blood oxygen saturation, therefore use of these tests in the follow up period is desired.

12. Abstractor and date
Respiratory Diseases (including influenza and rhinitis)

Reference


1. Objectives

To investigate the effect of hochuekkito (補中益気湯) on systemic inflammation in subjects with chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

Twelve university hospitals and thirteen hospitals.

4. Participants

Clinically stable patients who fulfilled the diagnostic criteria of the Japan Respiratory Society Guidelines for COPD, n=71.

5. Intervention

Assessments were done after 6 months of treatment.

Arm 1: conventional treatments with Tsumura Hochuekkito (補中益気湯) Extract Granules (TJ-41), 2.5 g, b.i.d or t.i.d., n=34.

Arm 2: control: continued conventional treatments, n=37.

6. Main outcome measures

Subjective symptoms: SGRQ (St. George’s Respiratory Questionnaire), symptoms related to ki-kyo, incidence of common cold (assessed using patients’ diaries), and frequency of exacerbations (defined on the basis of Anthonisen's criteria and requirement for systemic administration of steroids).

Objective measurements: body mass index (BMI), change in body weight, respiratory function, blood gas analysis, markers of nutrition status (prealbumin, leptin, and adiponectin), and markers of inflammation (high sensitivity C-reactive protein [hsCRP], TNF-α, and IL-6).

7. Main results

SGRQ subjective symptom score was significantly improved in arm 1. Also, incidence of the common cold and frequency of exacerbation were significantly less in arm 1 than in arm 2. There was no significant change in body weight in both arms during 6 months of observation. Prealbumin, a marker of nutritional status, increased significantly only in arm 1. Leptin level remained unchanged after administration of hochuekkito. The markers of systemic inflammation (hsCRP, TNF-α, and IL-6) were negatively correlated with severity of COPD (represented by FEV1% predicted). In arm 1, hsCRP and TNF-α decreased significantly, but IL-6 remained unchanged. Concentration of adiponectin, secreted by adipocytes and suggested to be involved in the development of arteriosclerosis, was negatively correlated with BMI and significantly increased after treatment with hochuekkito.

8. Conclusions

Administration of hochuekkito improved systemic inflammation and nutritional status in subjects with COPD, and decreased COPD exacerbation and incidence of the common cold.

9. From Kampo medicine perspective

Among the symptoms related to qikyo (気虚, qi deficiency), physical lassitude, morale, fatigability, susceptibility to the common cold, and appetite improved.

10. Safety assessment in the article

There were no safety issues.

11. Abstractor’s comments


12. Abstractor and date

Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
Development of saibokuto (柴朴湯) inhalation therapy, and to evaluate its efficacy in preventing attacks of aspirin-induced asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
Two clinics.

4. Participants
Patients with aspirin-induced asthma in whom the threshold dose of L-lysine-aspirin for provoking an asthma attack was determined by inhalation, n=74.

5. Intervention
Saibokuto inhalant: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96) were dissolved in injectable saline, sonicated for 90 minutes, and filtered through a Millipore sterile 0.22-micron filter. After adjustment to a concentration of 100 \( \mu \)g/mL, 5 mL of the inhalant was inhaled three times a day.
Arm 1: inhalation of saibokuto (柴朴湯) inhalant for 6 months, n=35.
Arm 2: inhalation of saline for 6 months, n=39.

6. Main outcome measures
The efficacy and safety of inhaled saibokuto for reducing the frequency of asthma attacks.

7. Main results
Saibokuto inhalant was newly developed. Prolonged inhalant usage significantly reduced the frequency of asthma attacks (0.004 times/person/6 months in arm 1 vs 0.120 times/person/6 months in arm 2).

8. Conclusions
Inhalation, compared with oral administration, can increase the concentration of saibokuto in the lung to the same level as achieved in experiments *in vivo* and *in vitro*, resulting in suppression of the production and release of biologically active substances in bronchoalveolar lavage fluid, and thereby of asthma attacks.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse effects were observed in 7 cases (20.0%) in arm 1 and 7 cases (17.9%) in arm 2, none of which led to withdrawal from the study.

11. Abstractor’s comments
The preparation of saibokuto inhalant (as described above) involved more than simply dissolving the extract granules in saline.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To evaluate the efficacy of short-term inhaled saibokuto (柴朴湯) in suppressing airway constriction, and long-term inhaled saibokuto (柴朴湯) in alleviating psychological suffering.

2. Design
Randomized controlled trial (RCT).

3. Setting
One hospital and three clinics.

4. Participants
Thirty-two patients with aspirin-induced asthma.

5. Intervention
1) Suppression of airway constriction (assessed by inhaling lysine-aspirin after inhaling the following):
   Arm 1: saibokuto (柴朴湯) inhalant.
   Arm 2: injectable distilled water.
2) Alleviation of mental suffering by inhalation for a long period (cross-over design with 6 months on saibokuto (柴朴湯) and 6 months on distilled water), n=32.

6. Main outcome measures
Suppression of airway constriction (forced expiratory volume in one second; FEV$_{1.0}$), biologically active substances in bronchoalveolar lavage fluid (BALF) at 30 minutes after inhaling lysine-aspirin, chronic pain.

7. Main results
In the trial of long-term inhalation, significant improvements were observed in each QOL domain and also in global QOL scores (this global QOL assessment method was developed by the authors using a visual analog scale [VAS] to assess physical [QOL-P], mental/psychological [QOL-M], social activity [QOL-S], medical economics [QOL-E], therapeutic drug [QOL-D], and individual QOL [QOL-I] incorporated items measuring the perspectives of individuals [including his/her perspectives on philosophy, thoughts, ethics, generation, policy, religion, and so on], as well as face scale and modified health assessment questionnaires). In arm 1, decreased FEV$_{1.0}$ as well as increased production and release of leukotrienes in BALF due to lysine-aspirin inhalation were significantly suppressed. In arm 1, FEV$_{1.0}$ improved more than 135% in 18 cases (56.3%), more than 125% in 4 cases (12.5%), and more than 110% in 1 case (3.1%), whereas in arm 2, no cases improved more than 135% and 125%, and 2 cases improved more than 110%.

8. Conclusions
Inhaled saibokuto therapy improved QOL and respiratory function.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Dysguesia (or altered sensation of taste) was observed in 5 cases (15.6%) in arm 1 and in 2 cases (6.3%) in arm 2. Cacosmia (or imagining of unpleasant odors) was observed in 7 cases (21.9%) in arm 1 and in 4 cases (12.5%) in arm 2. None of these adverse effects caused withdrawal from the study.

11. Abstractor's comments
Although the “global QOL assessment method” developed by the authors is used as the index of mental suffering, there is no documentation validating the use of this method in this paper, which claims improvement in mental suffering. Despite the resemblance to “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Bronchospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test. Jihi-inkoka Tenbo (Oto-Rhino-Laryngology Tokyo) 2001; 44: 5-13 (text in Japanese with English abstract)”, this report differs as follows: use of distilled water as solvent instead of saline, and use of a non-random cross-over design instead of a randomized design.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

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1. **Objectives**
   To investigate the clinical effect of saibokuto (柴朴湯) for the treatment of atopic asthma.

2. **Design**
   Randomized controlled trial (cross over) (RCT-cross over).

3. **Setting**
   One university hospital and one hospital.

4. **Participants**
   Adult patients with atopic asthma, n=33.

5. **Intervention**
   Cross-over design (administration of saibokuto (柴朴湯) or placebo [2.5 g, t.i.d.] for 4 weeks, and then, after a washout period of at least 4 weeks, patients crossed over to receive the alternative treatment), n=33.
   - Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96).
   - Arm 2: placebo.

6. **Main outcome measures**
   - Clinical symptoms, respiratory function test, methacholine provocation testing, eosinophil counts in blood and sputum, and eosinophilic cationic protein (ECP) in blood and sputum.

7. **Main results**
   - Symptom score (which employed similar severity classification according to Guidelines for Asthma Prevention and Management 2004 [JGL 2004]) before treatment was 1.65±0.38 in arm 1 and 1.66±0.43 in arm 2. After treatment, it was significantly decreased in arm 1 (0.73±0.25 in arm 1 and 1.63±0.39 in arm 2, \( P=0.001 \)). Forced expiratory volume in 1 second (FEV\(_{1.0}\)) improved slightly but not significantly in arm 1. Response to provocation challenge with methacholine was significantly better in arm 1. Significant decreases in eosinophil counts and ECP in blood and sputum but not neutrophil counts were observed in arm 1.

8. **Conclusions**
   Saibokuto improves clinical symptoms in patients with atopic asthma. Although FEV\(_{1.0}\) and FVC were unaffected, saibokuto was able to attenuate eosinophilic inflammation.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    Not documented.

11. **Abstractor’s comments**
    This is an RCT of Kampo treatment for asthma assessed using a respiratory function test.

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. **Objectives**
To assess the efficacy and safety of inhaled shimpito (神秘湯) for the control of aspirin-induced asthma.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Several clinics and others, Osaka prefecture.

4. **Participants**
Patients with histories of aspirin-induced asthma, whose threshold levels of inhaled lysine-aspirin are determined, n=114.

5. **Intervention**
Arm 1: inhalation of TSUMURA Shimpito (神秘湯) Extract Granules, 500 μg in four divided doses, n=53.
Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=61.
Duration of the study was 1 year.

6. **Main outcome measures**
The effect was evaluated by assessing 1) leukotrienes levels in bronchoalveolar lavage (BAL) fluid, 2) forced expiratory volume in 1 second (FEV$_{1.0}$) after lysine-aspirin inhalation, and 3) frequency of asthma attacks (or exacerbations).

7. **Main results**
The decrease in FEV$_{1.0}$ after lysine-aspirin inhalation was significantly greater in arm 1 than arm 2. Also, the frequency of asthma attacks and leukotriene levels in BAL fluid were decreased in arm 1 relative to arm 2.

8. **Conclusions**
Inhaled shimpito is more efficacious than inhaled cromoglycate for the management of aspirin-induced asthma.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
The frequency of both abnormal laboratory findings and adverse reactions were higher in arm 2 than in arm 1 (number of cases are unclear because the results were omitted in this paper).

11. **Abstractor’s comments**
Despite the term “multicenter, randomized” in the title, the method of randomization is not described, and the facilities where this clinical trial was actually performed (not the research institute) are unspecified. This paper does not state the number of withdrawals and analyzed cases during the 1-year follow-up of 114 subjects. Might it mean no withdrawals during the 1-year treatment period? Aspirin-induced asthma comprises 4-10% of all asthma cases. Inhaled corticosteroids are the most commonly used asthma medications. This study implies the greater efficacy of inhaled shimpito therapy in the management of asthma when compared with that of inhaled cromoglycate therapy. Further studies are awaited to assess whether oral administration of shimpito also provides similar efficacy when used by subjects with the appropriate “sho.”

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

Ichushi Web ID: 2005016956

1. Objectives
To assess the efficacy and safety of inhaled shimpito (神秘湯) therapy for improving asthma symptoms in patients with aspirin-induced asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
Several clinics and other health care facilities, Osaka prefecture.

4. Participants
Patients with aspirin-induced asthma, whose thresholds for induction of asthma (attacks) have been determined, n=161.

5. Intervention
Arm 1: inhalation of shimpito (神秘湯), 500 μg in four divided doses, n=81.
Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=80.
Duration of the study was 3 years.

6. Main outcome measures
1) Frequency of asthma attacks (or exacerbations), 2) improvement in health-related QOL, 3) improvement in chronic pain, 4) leukotriene level in bronchoalveolar lavage (BAL) fluid.

7. Main results
In arm 1, frequency of asthma attacks and leukotriene level in BAL fluid were significantly reduced, and QOL and chronic pain were significantly improved when compared with arm 2.

8. Conclusions
Inhaled shimpito therapy suppressed production of leukotrienes, prevented exacerbation of aspirin-induced asthma, alleviated chronic pain, and improved QOL.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Fewer cases and subjects had abnormal laboratory findings and adverse reactions in arm 1 than in arm 2.

11. Abstractor’s comments
The authors do not specify the medical facilities where this clinical trial (described as multicenter trial) actually took place. In this prospective, randomized study, the number of withdrawals and cases analyzed during the 3-year period of observation for 161 enrolled subjects is not stated. It is unclear whether there were any withdrawals during this period. Aspirin-induced asthma comprises 4-10% of all cases of asthma. Inhaled corticosteroids are the most common medications used for asthma therapy. This study implies that inhaled shimpito therapy is more efficacious in the management of asthma than inhaled cromoglycate therapy. In patients with aspirin-induced asthma, health-related QOL is generally not good because of limitation on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and inflammation. However, shimpito can improve these symptoms. Further studies are awaited to assess whether oral administration of shimpito also has similar efficacy when used in subjects with the appropriate “sho.”

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To investigate the effect of saibokuto (柴朴湯) inhalation therapy in improving quality of life (QOL) in patients with aspirin-intolerant asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
One hospital and two clinics.

4. Participants
Patients with aspirin-intolerant asthma, n=214.

5. Intervention
The study duration was 3 years. For saibokuto (柴朴湯) inhalation, 500 μg of saibokuto was packed into capsules comparable to those used for sodium cromoglycate (DSCG) inhalation.
Arm 1: saibokuto (柴朴湯) (the manufacturer not identified), 500 μg q.i.d. inhalation, n=105.
Arm 2: DSCG 20 mg q.i.d. inhalation, n=109.

6. Main outcome measures
Subjective symptoms, various tests, chronic pain, and QOL were assessed using a visual analog “total disease-related symptoms” scale developed by the authors, and face rating scores.

7. Main results
Saibokuto inhalation improved various endpoints.

8. Conclusions
Symptom-related QOL of patients with exacerbated aspirin-intolerant asthma was improved.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
The incidence of adverse effects was higher in arm 1, however, there was no significant difference in the number of cases. These results were omitted from the original article.

11. Abstractor’s comments
This RCT resembles two other RCTs of saibokuto inhalation therapy, “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Brochospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test. Jibi-inkoka Tenbo (Oto-Rhino-Laryngology Tokyo) 2001; 44: 5-13 (text in Japanese with English abstract)” and “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. Itami to Kampo (Pain and Kampo Medicine) 2001; 11: 14-21 (text in Japanese with English abstract)”. The only difference between these studies is the method of administering the inhalant: inhalation of saibokuto dissolved in distilled water or saline, or as a powder using a spinhaler as mentioned in this paper. Inhalation of powder should further improve QOL because powder increases accessibility. Common to these three papers is their complicated format, poorly-described rationale, and omission of results, which makes understanding the contents more difficult.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference
Ichushi Web ID: 2003036732

1. Objectives
To assess the efficacy and safety of inhaled saibokuto (柴朴湯) while reducing the amount of inhaled beclomethasone during the course of treatment for bronchial asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
Several clinics and others, Osaka prefecture.

4. Participants
Patients with stable bronchial asthma whose peak expiratory flow rate was maintained at more than 70% of normal for 6 months by the use of inhaled beclomethasone (800 μg/day), n=94.

5. Intervention
Amount of inhaled beclomethasone was reduced from 800 μg/day to 400 μg/day at 4 weeks before the intervention.
Arm 1: inhaled saibokuto (柴朴湯), 500 μg q.i.d., n=49.
Arm 2: inhaled cromoglycate, 20 mg q.i.d., n=45.
Duration of the study was 12 months.

6. Main outcome measures
1) Intensity of subjective symptoms (visual analogue scale), 2) peak expiratory flow (respiratory function test), 3) frequency of the use of β2-agonist, 4) cytokine levels in bronchial lavage fluid, 5) nitric oxide (NO) concentrations in expired air, and so on.

7. Main results
In arm 1, subjective symptoms and respiratory function were significantly improved, and compared to arm 2, patients in arm 1 had significantly reduced frequency of β2-agonist use, NO concentration in expired air, and cytokine levels in bronchial lavage fluid. Less than 10% decrease in the peak expiratory flow rate occurred in 67.3% of arm 1 and 13.3% of arm 2.

8. Conclusions
Inhaled saibokuto therapy was suggested to maintain the efficacy of inhaled beclomethasone as treatment for bronchial asthma despite dosage reduction.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse effects occurred in 11 cases (22.4%) in arm 1, and in 8 cases (17.8%) in arm 2.

11. Abstractor’s comments
Although they mention a multicenter study, the authors cite only one research institute, and do not specify the facilities where the clinical trials were actually conducted. The number of withdrawals during the 1-year follow-up and the percentage of the 94 enrolled patients who were actually included for analysis were not stated. Perhaps no one withdrew during the 1 year of treatment. Inhaled saibokuto therapy is assumed to be efficient compared to inhaled cromoglycate. All participants in this study should be considered adult patients with mild asthma. In terms of Kampo medicine, bronchial asthma presents a variety of “sho (証, pattern/syndrome).” Previous studies demonstrated that oral administration of saibokuto shows only limited clinical efficiency for those who do not have “sho” for saibokuto.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

1. Objectives
To compare the efficacy of the anxiolytic-like agent saibokuto (柴朴湯) with that of shoseiryuto (小青竜湯) in patients with bronchial asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
The setting of this study is unstated; the authors of this paper work in clinics and are specialists in allergy and respiratory medicine.

4. Participants
Patients with bronchial asthma who fulfilled one of the following criteria were included (n=139): comprehensive asthma inventory score ≥20, both state trait anxiety inventory (STAI) I and II scores ≥41 in men and ≥42 in women, or self-rating depression scale (SDS) ≥40.

5. Intervention
Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=71.
Arm 2: TSUMURA Shoseiryuto (小青竜湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=68.

6. Main outcome measures
Scores on various types of mental and psychological tests, subjective symptoms, bronchoalveolar lavage (BAL) fluid levels of hormones of the hypothalamo-pituitary-adrenal system, the assessment of suffering from chronic and intractable medical diseases, improvement in global symptoms (rated on a scale from 1 [markedly improved] to 5 [worsened], taking into account disease-related symptoms and the development of adverse reactions).

7. Main results
Various types of psychological tests, subjective symptoms, BAL fluid findings, levels of hormones of the hypothalamo-pituitary-adrenal system, chronic and intractable medical diseases, and global symptom scores showed significantly greater improvement in arm 1 than arm 2. The conditions of 66.2% of subjects in arm 1 and 7.3% in arm 2 were improved or better at the end of the study.

8. Conclusions
Saibokuto is more effective than shoseiryuto in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Although the authors do not offer a detailed description, adverse effects were observed in 2 cases (2.8%) and 5 cases (7.4%) in arm 1 and 2, respectively. Abnormal laboratory findings were noted in 2 cases (2.8%) in arm 1 and 6 cases (8.8%) in arm 2.

11. Abstractor's comments
Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto and shoseiryuto are effective for asthma in patients with anxiety symptoms. As the authors refer to development of adverse reactions, the number of withdrawals and the reasons for withdrawal should have been included to make this report even better. Accumulation of the detailed comparative information about these two Kampo drugs will clarify understanding of how both drugs work.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To assess the efficacy of the anxiolytic-like agent, saibokuto (柴朴湯), in treating bronchial asthma.

2. Design
Randomized controlled trial (RCT).

3. Setting
The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine.

4. Participants
Patients with bronchial asthma who fulfill one of the following criteria were included (n=107): comprehensive asthma inventory score ≥ 20, both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40.

5. Intervention
Arm 1: administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. before meals for 3 years, n=51.
Arm 2: administration of clotiazepam 15-30 mg/day (mean 23.9 mg/day) t.i.d. before meals for 3 years, n=56.

6. Main outcome measures
Clinical effects, scores various types of mental and psychological tests, airway hyperreactivity, bronchoalveolar lavage (BAL) fluid, improvement in global symptoms (as assessed by a combination of the preceding measures and the development of adverse reactions indicating worsening).

7. Main results
Scores on various types of psychological tests, airway hyperreactivity, BAL fluid findings, and global symptoms showed significantly greater improvement in subjects in arm 1 than those in arm 2. The conditions of 68.6% of subjects in arm 1 and 21.3% of subjects in arm 2 were improved or better.

8. Conclusions
Saibokuto is significantly more effective than clotiazepam in reducing the severity of asthma symptoms in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
In arm 1, there were no adverse reactions or abnormal laboratory findings. In arm 2, there were 13 cases (23.2%) including cases of drowsiness and poor concentration.

11. Abstractor’s comments
Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto is effective for asthma in patients with anxiety symptoms. Withdrawal from the study is not documented in this paper, nor has it been stated whether bronchoscopy was performed in all cases. In the Results section, the authors often use the phrase “results omitted” and do not show the data. Because the results here indicate the efficacy of saibokuto for asthma patients with anxiety symptoms, these data should have been disclosed to further validate its efficacy. However this remains a well-designed study investigating the psychological and organic pathology of asthma and evaluating the long-term efficacy of a Kampo medicine. Further studies including other Kampo formulae are desired.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To evaluate the efficacy and safety of saibokuto (柴朴湯) in patients with asthma exacerbations based on anticipatory anxiety.

2. Design
Randomized controlled trial (RCT).

3. Setting
The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine.

4. Participants
Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations
Patients with bronchial asthma who fulfill one of the following criteria were included (among 174 subjects participated, data from 172 subjects were analyzed): comprehensive asthma inventory score ≥ 20, state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40.

5. Intervention
Arm 1: Administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day three times a day before meals for 6 months, n=87.
Arm 2: Administration of lactose 5.0 g/day three times a day before meals for 6 months, n=85.
Each drug was given in indistinguishable capsule.

6. Main outcome measures
Assessment of improvement in objective and subjective symptoms concerning bronchial asthma, various types of mental and psychological tests, assessment of autonomic dysfunction, bronchoalveolar lavage (BAL) fluid, numbers of inflammatory cells in bronchial mucosa biopsy, frequency of asthma exacerbations, levels of hypothalamic, pituitary, and adrenal cortex hormones, assessment of chronic pain, and others.

7. Main results
Autonomic dysfunction, clinical symptoms, and BAL fluid analysis were significantly improved in arm 1 compared to arm 2. In arm 1, the number of subjects with asthma exacerbations decreased from 87 to 14 and the mean duration of asthma exacerbation decreased from 31.5 to 3.1 days, while both indices were increased in arm 2 (descriptions of the results in the text were imprecise).

8. Conclusions
Saibokuto is effective in improving asthma symptoms and psychiatric symptoms in patients with autonomic dysfunction due to asthma.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were no differences between the two arms in the incidences of adverse effects and abnormal laboratory data (no precise description in the paper).

11. Abstractor’s comments
As the authors’ notes in the Discussion section, this is the first clinical trial in the world to evaluate the effect of saibokuto in patients with bronchial asthma in a randomized, double-blind, controlled design. Following up a number of subjects in detail in multicenter analysis should have required substantial efforts. Declaration of the missing details such as 1) the number of withdrawals during 6 months of observation, 2) the number of subjects who underwent bronchoscopy, and 3) precise data omitted in the Result section, would be effective in making the efficacy of saibokuto widely accepted. Accumulation of such detailed studies may lead to elucidation of the action mechanisms and the efficacy of Kampo medicine, and more similar studies are awaited.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To investigate whether hangekobokuto (半夏厚朴湯; banxia houp tang) improves cough reflex in elderly patients likely to have aspiration pneumonia.

2. Design
Randomized controlled trial (RCT).

3. Setting
University of Tokyo and Tohoku University, and their related facilities.

4. Participants
Elderly patients (mean age, 78) with cerebral atrophy and lacunar infarcts, who had at least one episode of aspiration pneumonia, n=16.

5. Intervention
Arm 1: hangekobokuto (半夏厚朴湯) extract (granules) 1.5 g t.i.d. orally for 4 weeks (n=7).
Arm 2: placebo (lactose) 1.5 g t.i.d. orally for 4 weeks (n=9)

6. Main outcome measures
Subjects inhaled nebulized citric acid solution (0.3-360 mg/mL) delivered by an ultrasonic nebulizer, and the cough threshold was defined as the concentration of citric acid at which subjects coughed at least five times.

7. Main results
In arm 1, the cough threshold decreased from 59.5 to 15.7. In arm 2, the values were 47.5 and remained unchanged.

8. Conclusions
The result suggests that hangekobokuto improves the (impaired) cough reflex in the elderly with an increased risk for aspiration pneumonia.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not documented.

11. Abstractor’s comments
It has been reported that angiotensin-converting enzyme inhibitor (ACE-I) improves silent aspiration, and that capsaisin improves cough reflex. This study suggests that hangekobokuto also affects the attenuated cough reflex in older patients with cerebral atrophy and lacunar infarcts. Larger RCTs to confirm its efficacy are awaited.

12. Abstractor and date
Respiratory Diseases (including Influenza and Rhinitis)

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1. **Objectives**
   To evaluate whether hangekobokuto (半夏厚朴湯) prevents aspiration pneumonia and pneumonia-related mortality in elderly people with dementia.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   Two hospitals (the authors belong to Tohoku University, Dokkyo University, and two hospitals).

4. **Participants**
   Elderly subjects with dementia, n=95.

5. **Intervention**
   Arm 1: Tsumura Hangekobokuto (半夏厚朴湯) Extract Granules 2.5 g t.i.d. (body weight ≥50 kg) or 2.5 g b.i.d. (body weight <50 kg) for 12 months, n=47.
   Arm 2: placebo (lactose) 1.0 g t.i.d. (body weight ≥50 kg) or 1.0 g b.i.d. (body weight <50 kg) for 12 months, n=48.

6. **Main outcome measures**
   The occurrence of pneumonia, and mortality due to pneumonia.

7. **Main results**
   Data from 92 of the 95 subjects were analyzed. One of four patients who developed pneumonia in arm 1 died as a result, whereas 6 of 14 patients who developed pneumonia in arm 2 died as a result. There was a significant decrease in pneumonia onset in arm 1 compared to arm 2 ($P<0.008$). Mortality related to pneumonia tended to be less in arm 1 than in arm 2 ($P=0.05$).

8. **Conclusions**
   Treatment with hangekobokuto reduced the risk of pneumonia and pneumonia-related mortality in elderly patients with dementia.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    The findings of this well-designed randomized controlled study suggest the efficacy of hangekobokuto in preventing aspiration pneumonia in elderly people with dementia. In addition, hangekobokuto administration tended to improve activities of daily living such as self-feeding and to reduce the number of febrile days. Further studies to assess these points are expected.

12. **Abstractor and date**
Respiratory Diseases (including Influenza and Rhinitis)

Reference

1. Objectives
To determine the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampo combination therapy for bacterial respiratory infections.

2. Design
Randomized controlled trial (RCT).

3. Setting
Obstetrics and Gynecology, Gifu University Hospital.

4. Participants
One hundred and sixteen patients diagnosed with acute bacterial respiratory infection.

5. Intervention
Arm 1: antibiotics alone group: treatment with levofloxacin for 5–10 days, n=51.
Arm 2: antibiotics + Kampo group A: treatment with levofloxacin for 5–10 days + juzentaihoto (十全大補湯) or hochuekkito (補中益気湯) for 5–10 days, n=37.
Arm 3: antibiotics + Kampo group B: treatment with levofloxacin for 5–10 days + kakkonto (葛根湯) or keishito (桂枝湯) or kososan (香蘇散) or 1–2 days + juzentaihoto (十全大補湯) or hochuekkito (補中益気湯) for 3–6 days, n=28.
None of the manufacturers of Kampo medicines used were specified.

6. Main outcome measures
Response rate, rate of recurrence within 7 days, and total medical cost.

7. Main results
The response rates were 96.1% in arm 1, 97.3% in arm 2, and 96.4% in arm 3; no statistically significant differences were observed. The recurrence rates were 3.9% in arm 1, 2.7% in arm 2, and 0% in arm 3; there were no significant between-group differences, although the rates were lower in arms 2 and 3. High recurrence rates were observed in cases of atypical pneumonia, caused by atypical pneumonia-related organisms. Total medical costs were significantly higher in arms 2 and 3, whereas for patients with recurrence, total costs tended to be reduced in these two arms.

8. Conclusions
Antibiotics plus Kampo combination therapy reduces the recurrence of bacterial respiratory infections. In patients infected with atypical pneumonia and prone to frequent recurrence, Kampo-combined therapy might reduce the total medical cost.

9. From Kampo medicine perspective
The drugs used in the intervention groups were selected on the basis of common applications: ephedra formulations such as kakkonto, are used to help generate body heat and sweat during the acute phase; shosaikoto is used for immune enhancement during the subacute phase; and hozai (補剤, formulations with tonic effects) such as hochuekkito and juzentaihoto are used during the recovery phase.

10. Safety assessment in the article
None.

11. Abstractor's comments
This is a very interesting RCT evaluating total medical cost as an outcome. We guess from the setting that all the participants were women. Inclusion of background factors (such as gender, age, and underlying disease) as well as standard criteria with which to evaluate outcomes (such as response and recurrence rates) would have helped readers understand the results. Also, using more uniform regimens in the intervention groups would have increased the value of the results. Further studies are anticipated to provide more data.

12. Abstractor and date
Tsuruoka K, 6 February 2009, 8 August 2009.
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To compare the efficacy of bakumondoto (麦門冬湯) versus cevimeline hydrochloride hydrate (Evoxac) or nizatidine (Acinon) for treating dry mouth.

2. Design
Randomized controlled trial (RCT).

3. Setting
Gustatory Outpatient Clinic, Department of Otolaryngology, Hyogo College of Medicine.

4. Participants
One hundred patients with dry mouth (13 males and 87 females; mean age, 69.0 years). Patients with a basal salivary secretion rate of 3 mL/10 min or lower and a chewing-gum-stimulated salivary secretion rate of 10 mL/10 min or lower were included in the study. Exclusion criteria were Sjögren syndrome, diabetes mellitus, use of oral antihistamine or antipsychotic, asthma, ischemic heart disease, epilepsy, prostatic hyperplasia, and glaucoma.

5. Intervention
Arm 1: treatment with bakumondoto (麦門冬湯) (manufacturer, not specified) 3.0 g t.i.d. for 90 days in 24 patients (4 males and 20 females; mean age, 67.4 years), as the bakumondoto (麦門冬湯) group.
Arm 2: treatment with cevimeline hydrochloride hydrate 30 mg t.i.d. for 90 days in 42 patients (3 males and 39 females; mean age, 72.0 years), as the cevimeline group.
Arm 3: treatment with nizatidine 150 mg b.i.d. for 90 days in 34 patients (6 males and 29 females; mean age, 66.0 years), as the nizatidine group.

6. Main outcome measures
The basal rate and chewing-gum-stimulated salivary secretion rate after 90 days of treatment. Subjective symptoms were assessed using a questionnaire on a 4-point scale (“improvement”, “mild improvement”, “no change”, or “worsening”).

7. Main results
The rate of basal salivary secretion increased from 1.0±0.2 mL/10 min to 1.3±0.2 mL/10 min after treatment with bakumondoto, from 1.1±0.1 mL/10 min to 1.6±0.2 mL/10 min after treatment with cevimeline, and from 1.1±0.2 mL/10 min to 2.4±0.3 mL/10 min after treatment with nizatidine. The rate increases in the cevimeline and nizatidine groups were significant ($P<0.001$). The change in the rate of chewing-gum-stimulated salivary secretion after treatment with cevimeline and nizatidine were similarly significant ($P<0.001$). Both the basal rate and chewing-gum-stimulated salivary secretion rate were significantly different between the bakumondoto- and the nizatidine-treated groups (both $P<0.01$) but not between the bakumondoto- and the cevimeline-treated groups. Treatment with cevimeline or nizatidine led to “improvement” in subjective symptoms in 50–57% of patients and “improvement” or “mild improvement” in 85.7% of cevimeline-treated patients and 74.2% of nizatidine-treated patients. In contrast, only 4% of bakumondoto-treated patients noted “improvement”.

8. Conclusions
Cevimeline hydrochloride hydrate and nizatidine but not bakumondoto significantly increased both basal and stimulated salivary secretions and relieved subjective symptoms in patients with dry mouth.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No patients reported “worsening” of symptoms. No adverse drug reactions occurred.

11. Abstractor's comments
This is a well-designed and well-conducted RCT. The authors speculate that saponins in ginseng, a component of bakumondoto, activate salivary cells by increasing cell membrane permeability. According to their discussion, increase in cell membrane permeability alone does not directly increase the amount of saliva. This was suggested by the fact that dry mouth in most subjects in this trial was due to age-related atrophy and impairment of salivary gland cells. Further studies are expected.

12. Abstractor and date
**Objectives**
To determine the efficacy of saibokuto (柴朴湯) compared with tranquilizer plus vitamin B complex combination therapy for patients with glossodynia.

**Design**
Randomized controlled trial (RCT).

**Setting**
Department of Oral and Maxillofacial Surgery Kyoto University Hospital.

**Participants**
Two hundred patients with glossodynia.

**Intervention**
Arm 1: treatment with TSUMURA Saibokuto (柴朴湯) Extract Granules, 2.5g, t.i.d. for 3 months. (n=100)
Arm 2: treatment with diazepam, 2mg, t.i.d. plus vitamin B complex formulation, 1 tablets, t.i.d. for 3 months. (n=100)

**Main outcome measures**
Each of the subjective symptoms (pain, burning sensation, and unpleasant feeling) was evaluated on a 10-point scale. ‘Excellent response’ was defined as disappearance of all symptoms, ‘good response’ as improvement of pain, and ‘no response’ as no improvement of pain.

**Main results**
In arm 1, the percentage of excellent and good responses was 70% at 1 month, 85% at 2 months, and 92% at 3 months after the start of treatment. These values in arm 2 were 74%, 71%, and 69%, respectively ($P<0.05$). Pain relief was experienced in a significantly higher percentage in arm 1 than in arm 2 at 3 months ($P<0.01$).

**Conclusions**
It is suggested that saibokuto (in particular, the three-month treatment) is more effective against glossodynia than the diazepam plus vitamin B complex formulation.

**From Kampo medicine perspective**
The discussion contains some speculations.

**Safety assessment in the article**
Mild anorexia and diarrhea were reported, respectively, in 3 and 1 patient receiving saibokuto, and severe sleepiness was reported in 33 patients receiving diazepam.

**Abstractor’s comments**
This study suggests that saibokuto monotherapy (for 3 months) is more effective against glossodynia than the combination therapy (tranquilizer plus vitamin B complex). Also, saibokuto treatment is safe, as indicated by the low frequency of adverse effects and the possibility of long-term treatment. Results similar to those of this paper were published in the following two papers: “Yamada T, Bessho K, Murakami K, et al. Clinical evaluation of Sai-boku-to (Kampo medicine) for glossodynia. Shika Yakubutsu Ryoho (Oral Therapeutics and Pharmacology) 1998; 17: 18-22 (text in Japanese with English abstract) [MOL, MOL-Lib]” and “Yamada T, Bessho K. Clinical evaluation of Sai-boku-to (Kampo medicine) for glossodynia. Kampo to Saishin-chiryo (Kampo & the Newest Therapy) 1999; 8: 261-5. [Ichushi Web ID: 2000085045]” Although the sample size of the study described in the above two papers was about half that in the present study, the results were very similar.

**Abstractor and date**
Reference

1. Objectives
To determine the preventive effect of rikkunshito (六君子湯) on postoperative reflux esophagitis.

2. Design
Randomized controlled trial (RCT).

3. Setting
No description of the setting is available; the authors belong to the First Department of Surgery, Mie University School of Medicine.

4. Participants
Forty-six patients who underwent resection of stage I to II gastric cancer.

5. Intervention
Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules, 7.5 g/day, every day from the start of postoperative oral intake in 25 patients.
Arm 2: no treatment in 21 patients.

6. Main outcome measures
1) Gastrointestinal symptoms including heartburn, dysphagia, nausea/vomiting, dyspepsia, and anorexia;
2) endoscopic findings based on the Los Angeles classification; and 3) mean length of postoperative hospital stay.

7. Main results
At postoperative week 2, gastrointestinal symptoms were observed in 7 untreated patients (33%) and 4 rikkunshito-treated patients (16%). All the symptoms occurred less commonly in the treated patients than in the untreated patients. At postoperative week 4, reflux symptoms and heavy stomach were each seen in only 1 (4%) patient in arm1, whereas reflux symptoms, heartburn, dyspepsia, and anorexia developed in 3 (14%), 1 (5%), 1 (5%), and 2 (10%), respectively, in arm 2. As for endoscopic findings at postoperative week 3, there were grade A in 2 patients (10%) and grade B in 1 (5%) in arm 2, but grade A in only 1 (5%) in arm 1. At postoperative week 6, grade A esophagitis was observed in 1 patient (5%) in arm 2, and none in arm 1. Mean length of postoperative hospital stay was not significantly different between the two arms (47 ± 13 days [arm 2] vs 39 ± 13 days [arm 1]), but a reduction of hospital days was noted.

8. Conclusions
Rikkunshito is highly effective not only for the treatment of reflux esophagitis after gastric cancer surgery, but also for the prevention of this disease.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
Studies 1 and 2 are described in the article. Study 1 was conducted to examine the therapeutic effect of rikkunshito on postoperative reflux esophagitis. Rikkunshito at a daily dose of 7.5 g was administered between meals every day from the onset of symptoms in 7 patients with stage-I-II gastric cancer. The authors reported that symptoms disappeared in most patients at week 4. But since Study 1 had no control group and provided no details such as evaluation criteria, it was excluded from this structured abstract.

Only part of Study 2 was included. In Study 2, ‘randomization into two groups’ was reported, but the details were not clear. Also, other details, such as statistical procedures and methods of assessing subjective symptoms, were not provided. This study is clinically valuable, but most of the article, which is published in a conference record, lacks adequate descriptions. Thus, submission as an original article is desired.

12. Abstractor and date
Arai M, 1 April 2008, 8 August 2009.
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy of rikkunshito (六君子湯) combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).

2. Design
Randomized controlled trial (RCT).

3. Setting
One general hospital.

4. Participants
Fifty-six patients with gastroesophageal reflux disease.

5. Intervention
Arm 1: oral administration of omeprazole (20 mg), as the PPI alone group.
Arm 2: oral administration of omeprazole (20 mg) plus TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group.

6. Main outcome measures
Endoscopic healing rates of reflux esophagitis and Gastrointestinal Symptom Rating Scale (GSRS) scores. The follow-up was scheduled at 8 weeks.

7. Main results
The endoscopic healing rates of reflux esophagitis at 8 weeks were not significantly different between the two groups. The PPI + rikkunshito group achieved significantly better scores on the following three GSRS domains: overall gastrointestinal symptoms, reflux, and abdominal pain.

8. Conclusions
Rikkunshito combined with PPI improves the quality of life (QOL) in GERD patients.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
Rikkunshito-combined therapy resulted in further improvement of QOL in GERD patients, especially in those with endoscopy-negative GERD (non-erosive reflux disease: NERD). On this basis, the authors concluded that PPI + rikkunshito is effective for “the improvement of QOL, particularly in NERD patients who are unlikely to respond to PPI.”

12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy of hangekobokuto (半夏厚朴湯)-combined treatment in patients with respiratory symptoms associated with refractory gastroesophageal reflux disease (GERD).

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

3. Setting
No description of the setting is available; the authors belong to the Department of Cardiology and Pneumology, Dokkyo Medical University.

4. Participants
Nineteen GERD patients whose digestive symptoms but not respiratory symptoms (including cough, sputum, throat discomfort, and mild dyspnea) were relieved by conventional western medical treatments. All patients had no history of smoking or respiratory disease.

5. Intervention
Arm 1: treatment with TSUMURA Hangekobokuto (半夏厚朴湯) Extract Granules (7.5 g/day) in 10 patients.
Arm 2: no treatment in 9 patients.
In arm 1, hangekobokuto (半夏厚朴湯) was administered in addition to the usual western medical treatment for 6 months, and then hangekobokuto (半夏厚朴湯) was discontinued. The course of respiratory symptoms was examined for a total of 12 months in both the hangekobokuto (半夏厚朴湯)-combined and no-treatment arms.

6. Main outcome measures
Cough, sputum, throat discomfort, and mild dyspnea.

7. Main results
The degree of improvement was evaluated on a 5-point scale. Respiratory symptoms were significantly improved after a month of treatment in arm 1, compared with arm 2 (P<0.01). This effect persisted up to 6 months after start of combined treatment (P<0.01) and 6 months after discontinuation of hangekobokuto (P<0.01).

8. Conclusions
Hangekobokuto relieves respiratory symptoms, including cough, sputum, throat discomfort, and mild dyspnea, that are unresponsive to western medical treatments in GERD patients.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
Respiratory or ear-nose-throat symptoms are reported to occur in 30–50% of GERD patients, depending on the literature. Western medical treatments combine proton pump inhibitors, H2 blockers, or stomachics, with theophylline formulations, expectorants, antitussives, erythromycin antibiotics, or inhaled steroids. In some patients, however, these treatments fail to improve these symptoms. This study can be praised for examining these clinically difficult-to-treat patients. The study method has several problems including failure to measure inter-subject variability of GERD scores evaluated according to the Los Angeles classification, small sample size, and lack of a safety and adverse drug reactions assessment.

12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for treatment of non-erosive reflux disease (NERD) unresponsive to proton pump inhibitors (PPIs).

2. Design
Randomized controlled trial (RCT).

3. Setting
No description of the setting is available; the author belongs to a clinic.

4. Participants
One hundred and eighteen patients with PPI-unresponsive NERD.

5. Intervention
Arm 1: treatment with omeprazole (200 mg), as the PPI alone group, n=37.
Arm 2: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the rikkunshito alone group, n=39.
Arm 3: treatment with omeprazole (200 mg) and TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group, n=42.
The duration of treatment was 4 weeks in all arms.

6. Main outcome measures
Gastrointestinal Symptom Rating Scale (GSRS) score (which includes ratings of overall gastrointestinal symptoms, reflux, abdominal pain, and dyspepsia).

7. Main results
Scores of overall gastrointestinal symptoms and reflux were significantly more improved in arm 3 than in arms 1 and 2; the scores in arms 1 and 2 were similar. The abdominal pain score was similarly improved in all three arms. Dyspepsia score was significantly more improved in arms 2 and 3 than in arm 1, but the scores in arms 2 and 3 were similar.

8. Conclusions
TSUMURA Rikkunshito Extract Granules is effective for relieving clinical symptoms of NERD.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study deserves praise for conducting a RCT using TSUMURA Rikkunshito Extract Granules as a study drug in patients with treatment-unresponsive NERD. Unfortunately, the mechanism was not discussed, and endoscopic findings and other features were not mentioned. Publication of the latter is expected in the future.

12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy of rikkunshito (六君子湯) as an agent to improve symptoms before endoscopy in patients with upper abdominal symptoms and need for endoscopy of the upper gastrointestinal tract.

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

3. Setting
None; the authors are members of the Department of Medical Oncology, Graduate School of Medicine, Chiba University.

4. Participants
One hundred and twenty patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

5. Intervention
Arm 1: treatment with H2-receptor blocker (H2RB; ranitidine 150 mg; n=39).
Arm 2: treatment with proton pump inhibitor (PPI; omeprazole 20 mg; n=40).
Arm 3: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g (n=41).
The duration of treatment was not specified (the administration was continued until the upper gastrointestinal endoscopy was performed).

6. Main outcome measures
Acid reflux (heartburn, reflux), abdominal pains (epigastric pain, hunger, and nausea), dyspepsia (borborygmus, abdominal distention, eructation, and flatus), diarrhea (diarrhea, loose stool, and rectal urgency), and constipation (constipation, hard stool, feeling of incomplete evacuation).

7. Main results
Overall, gastrointestinal symptoms associated with impaired quality of life (QOL) were significantly improved after the treatment in all arms; the improvement was significantly greater in arm 3 than in arms 1 and 2. Also improved were acid reflux associated with impaired QOL in arm 1, acid reflux and abdominal pains associated with impaired QOL in arm 2, and acid reflux, abdominal pains, and dyspepsia associated with impaired QOL in arm 3. Significantly greater improvements were found for acid reflux in arm 3 than in arm 1; for abdominal pains in arms 2 and 3 than in arm 1; for dyspepsia in arm 3 than in arms 1 and 2. Considering only patients with reflux esophagitis, gastrointestinal symptoms were also significantly improved by treatment in all arms. Acid reflux improved in arm 1, and acid reflux, abdominal pains, and dyspepsia improved in arms 2 and 3. H2RB, PPI, and rikkunshito had similar effectiveness.

8. Conclusions
The efficacy of rikkunshito as a pre-endoscopic medication, even as monotherapy, is comparable to that of other gastric acid secretion inhibitors in patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study is considered to be a follow-up to the following studies: 1) Koide A. Adoption of rikkunshito before endoscopy in patients with upper abdominal symptoms. *Nikkei Medical* 2002; 31: 22-3 and 2) Koide A. The improvement of QOL by rikkunshito in patients with need for endoscopy. *Medical Tribune* 2004: 45 (in Japanese). This clinically valuable study showed that the efficacy of rikkunshito against upper abdominal symptoms including gastroesophageal reflux disease is comparable to that of other gastric acid secretion inhibitors. The present study also deserves praise for assessing each clinical symptom objectively using the GSRS (Gastrointestinal Symptom Rating Scale). The cost-effectiveness of rikkunshito is mentioned without detail in the conclusion of this paper, but it is addressed more completely in paper 2). The present paper provides very interesting insights, but its first half is too general. Therefore, publication as an original article is desired.

12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To evaluate the efficacy and safety of TJ-43 TSUMURA Rikkunshito (六君子湯) in patients with dyspepsia caused by dysfunction of the upper gastrointestinal tract.

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

3. Setting
A total of 54 institutions.

4. Participants
Patients (30–80 years old) with a chief complaint of persistent or intermittent (for more than 4 weeks) dysmotility-like dyspepsia, characterized by anorexia (or poor appetite), gastric distress, and heavy stomach feeling (presumably due to dysfunction of the upper gastrointestinal tract), and indicating “kyo-sho (deficiency pattern/syndrome)” by gastroptosis, physical weakness, etc.

5. Intervention
Arm 1: oral administration of TSUMURA Rikkunshito (六君子湯) Extract Granules (TJ-43) 2.5 g t.i.d. before or between meals for 2 weeks (n=147).
Arm 2: oral administration of low-dose (1:4 dilution) TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 2 weeks (n=133).

6. Main outcome measures
Five symptoms associated with dysmotility-like dyspepsia (anorexia, abdominal distension, stomach discomfort, heavy stomach feeling, and nausea).
Three symptoms associated with ulcer-like dyspepsia (upper abdominal/epigastric pain, heartburn or pyrosis, and eructation).

7. Main results
A total of 235 subjects (TJ-43 group, n=118; low-dose group, n=117) were included for analysis. Dysmobility-like dyspepsia symptoms were improved in 59.3% of the TJ-43 group and 40.2% of the low-dose group; overall symptoms including ulcer-like dyspepsia symptoms were also improved in 60.2% of the TJ-43 group and 41.0% of the low-dose group. These indicate that efficacy is significantly higher in the TJ-43 group. Furthermore, a significantly higher percentage of the TJ-43 group than the low-dose group (58.8% versus 39.3%) deemed the treatment useful.

8. Conclusions
The safety and effectiveness of TJ-43 was validated for the treatment of dysmotility-like dyspepsia in this double-blind study. We therefore conclude that TJ-43 Rikkunshi-to is clinically useful.

9. From Kampo medicine perspective
In this study, the inclusion criteria were “kyo-sho (虛証, deficiency pattern)” symptoms (i.e., decreased tone of abdominal wall, subjective/objective splashing sound, gastroptosis tendency, and mental/physical weakness) and the exclusion criteria were “jitsu-sho (実証, excess pattern)” symptoms (i.e., mental and physical strength, massive and muscular body, and reddish face).

10. Safety assessment in the article
Safety problems were detected in 2 cases in the TJ-43 group (diarrhea, elevated GOT) and 2 in the low-dose group (diarrhea, elevated GOT/GPT). Adverse effects (defined as symptoms undeniably caused by the drug) occurred in 7 of the TJ-43 group and 7 of the low dose group. None were serious.

11. Abstractor’s comments
There is a similar report by Harasawa: “The role of rikkunshito against NUD (non-ulcer dyspepsia) – especially its efficacy in dysmotility-like NUD”. Progress in Medicine 1999; 19: 843-8 (in Japanese).” Use of low-dose TH-43 in the control group and use of Kampo diagnostic considerations when selecting the inclusion and exclusion criteria are appreciated. Improvement in “kyo-sho” symptoms is demonstrated.

12. Abstractor and date
## Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference


### 1. Objectives

To determine the efficacy of TSUMURA Rikkunshito Extract (六君子湯) Granules for stimulating gastrointestinal emptying in patients after pylorus-preserving gastrectomy (PPG).

### 2. Design

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

### 3. Setting

Not indicated (the author belongs to a university hospital).

### 4. Participants

Eleven patients after PPG.

### 5. Intervention

Arm 1: no treatment for 4 weeks followed by treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules (2.5 g t.i.d.) for 4 weeks, n=5.

Arm 2: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules (2.5 g t.i.d.) for 4 weeks followed by no treatment for 4 weeks, n=6.

### 6. Main outcome measures

Gastrointestinal Quality of Life Index (GIQLI) and rate of gastric retention as shown by gastric emptying scintigraphy.

### 7. Main results

Although no significant difference was observed in GIQLI, 8 patients preferred to continue the rikkunshito treatment.

Scintigraphy showed reduced rate of gastric retention of solids (but not of liquids) in patients treated with TSUMURA Rikkunshito Extract Granules.

### 8. Conclusions

TSUMURA Rikkunshito Extract Granules delays gastric emptying of solids in patients after PPG.

### 9. From Kampo medicine perspective

None.

### 10. Safety assessment in the article

None.

### 11. Abstractor’s comments

This trial is of high clinical interest, since it made objective evaluations based on gastric-emptying scintigraphy of solids and liquids separately. However, some questions about the design (including the randomization step) remain. So-called “between-group comparisons” will be desirable in the future.

### 12. Abstractor and date

Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

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1. **Objectives**
   - To determine the safety and efficacy of hangeshashinto (半夏瀉心湯) (TJ-14) for CPT-11-induced diarrhea during combination chemotherapy with cisplatin (CDDP) plus irinotecan hydrochloride (CPT-11) for advanced non-small-cell lung cancer (NSCLC).

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

3. **Setting**
   - One hospital; the authors belong to the Department of Respiratory Disease, Tochigi Cancer Center.

4. **Participants**
   - From among inpatients with NSCLC who received dual therapy with CDDP plus CPT-11 from November 1993 through December 1996, forty one patients who met the following selection criteria were enrolled: 1) treatment-naïve with unresectable NSCLC (stage III, IV); 2) performance status 0 to 2; 3) preserved major organ function; 4) 75 years or younger; and 5) informed consent. Patients with serious complications, diarrhea, severe pleural effusion, or symptomatic cerebral metastasis were excluded from the study.

5. **Intervention**
   - **Arm 1:** treatment with TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (TJ-14) 2.5 g t.i.d. before meals in 18 patients.
   - **Arm 2:** no treatment in 23 patients.
   - In the arm 1, hangeshashinto was administered every day from at least 3 days before through 21 days or more after the start of chemotherapy.

6. **Main outcome measures**
   - Stool properties and frequency of defecation, presence and severity of abdominal pain associated with defecation, presence or absence of bowel movements at night and bloody diarrhea.

7. **Main results**
   - The onset and the highest daily frequency of diarrhea were respectively recorded at 6.3 and 9.2 days after the start of chemotherapy in arm 1, and at 5.9 and 9.0 days in arm 2. During the first cycle of chemotherapy, the severity of diarrhea was significantly improved and the incidence of grade 3 or higher diarrhea was lower in arm 1 than in arm 2. The number of diarrhea episodes and the duration (in days) of diarrhea were not significantly different between the two arms.

8. **Conclusions**
   - Hangeshashinto is effective for preventing and relieving CPT-11-induced diarrhea in advanced NSCLC.

9. **From Kampo medicine perspective**
   - None.

10. **Safety assessment in the article**
    - Mild constipation was reported in 2 hangeshashinto-treated patients. Other significant adverse effects were not observed.

11. **Abstractor’s comments**
    - This clinical study indicated that the concomitant use of hangeshashinto is effective for diarrhea, which can occur during chemotherapy containing CPT-11. This study lacked a placebo control group and was not double-blinded. In a study using Kampo medicines as a control, it is difficult to prepare the placebo because Kampo medicines have specific textures and smells. Nonetheless, double-blind design should be considered in order to improve the quality of study. Similar results as this were reported in “Mori K, Hirose T, Machida S, et al. Kampo medicines for the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Gan to Kagaku Ryoho* (Japanese Journal of Cancer and Chemotherapy) 1998; 25: 1159-63 (text in Japanese with English abstract) [CENTRAL ID; CN-00153138, Pubmed ID: 9679578] [MOL, MOL-Lib]” and “Mori K. Hangeshashin-to (Kampo medicined) in the prevention of irinotecan-induced diarrh ea in advanced non-small cell lung cancer. *Progress in Medicine* 1999; 19: 886-90 (text in Japanese with English abstract).”

12. **Abstractor and date**


Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy and safety of daikenchuto (大建中湯) for improving intestinal peristalsis in patients with intestinal paralysis after surgery for abdominal aortic aneurysm (AAA).

2. Design
Randomized controlled trial (RCT).

3. Setting
No description of the setting is available (the authors are cardiovascular surgeons at community or university hospitals).

4. Participants
Twenty-one patients who underwent elective surgery for non-ruptured infrarenal AAA during the same time period.

5. Intervention
Arm 1: treatment with infusion of daikenchuto (大建中湯) dissolved in lukewarm water (5 g/20 mL) through a gastric tube, followed by clipping of the tube for 30 minutes, three times daily from the first postoperative day, in 7 patients.
Arm 2: treatment with infusion of lukewarm water (20 mL) in the same manner as arm 1 in 7 patients, as a control group.
Arm 3: treatment with infusion of lukewarm water (20 mL) and intravenous panthenol (100 mg/day) in 7 patients.

6. Main outcome measures
Degree of abdominal distension, and presence or absence of bowel sounds, passage of flatus, and small bowel gas on the abdominal X-ray.

7. Main results
Bowel sounds were heard immediately after the infusion of the study drug in all patients of arm 1, but not in any patient of arms 2 and 3. Time to the first passage of flatus after surgery was 3.1±0.8 days in arm 1, 5.1±1.3 days in arm 2, and 3.7±0.8 days in arm 3; significantly earlier passage of flatus was observed in arms 1 and 3 (P<0.05), but there was no significant difference in time to first passage of flatus between these two arms. Small bowel gas disappeared at 3.3±1.4 days after surgery in arm 1, at 6.1±1.2 days in arm 2, and at 6.3±2.8 days in arm 3; the gas disappeared significantly earlier in arm 1 than in arms 2 and 3 (P<0.05). No patients developed symptoms of ileus due to decreased intestinal peristalsis after resumption of oral intake.

8. Conclusions
Oral daikenchuto is effective for improving decreased intestinal peristalsis after surgery for non-ruptured AAA.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse drug reactions associated with daikenchuto treatment were not reported.

11. Abstractor’s comments
AAA is caused by arteriosclerosis and common in the elderly, for whom elective surgery is indicated and achieves good outcome. In such cases, early ambulation and early resumption of oral intake are important for the prevention of early postoperative delirium. Administration of daikenchuto promotes significantly earlier recovery of intestinal peristalsis and is therefore clinically useful. Although three arms were compared in this study, other studies commonly compare just two arms - daikenchuto and panthenol as a standard treatment. This study was also limited by the small number of patients in each group. Thus, a review of the study design and number of subjects will be needed.

12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. **Objectives**
To evaluate the efficacy and safety of kumibinroto (九味檳榔湯) for chronic constipation in elderly dialysis patients.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Clinics and other services (Osaka, Japan).

4. **Participants**
Three-hundred and eighteen patients who were 75 years or older and on dialysis were enrolled during 15 years.

5. **Intervention**
Arm 1: treatment with Kotaro Kumibinroto (九味檳榔湯) Extract Fine Granules 2g, t.i.d., n=160.
Arm 2: treatment with magnesium laxative 2.0 g/day in three divided doses, n=158.
Duration of the study was 9 months.

6. **Main outcome measures**
Number of urges to have bowel movements and dosage of the laxatives (Western medicines) combined with the study drug.

7. **Main results**
Both the number of urges to have bowel movements and the dosage of the combined laxatives were significantly more improved in arm 1 than in arm 2. Symptoms associated with bowel movements were also significantly improved.

8. **Conclusions**
Kumibinroto was more effective than magnesium laxative for improving the number of bowel movements and the dosage of the combined laxatives in elderly dialysis patients with chronic constipation.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
Fewer adverse effects were reported in arm 1 than in arm 2 (data not shown). There were no abnormal examination findings.

11. **Abstractor’s comments**
Although the word “multicenter” was mentioned in this article, none of the actual clinics, in contradistinction to research laboratories where this clinical trial was conducted, was specified. The authors conducted a 9-month, prospective, randomized study in 318 patients over a long period (15 years). Unfortunately, neither the number of withdrawals from the study nor the number of subjects included in the analysis was reported. Kumibinroto does not have a potent laxative effect. This study suggested that kumibinroto, combined with western laxatives, is more effective and safer than magnesium laxative for chronic constipation in elderly dialysis patients. Magnesium laxative, however, needs to be carefully administered and may cause hypermagnesemia in patients with renal impairment. Therefore, this type of laxative is usually avoided in patients undergoing hemodialysis. Regarding this point, the types and dosage of the western laxatives combined with the study drug are to be reported.

12. **Abstractor and date**
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the efficacy of liver protectors for preventing carcinogenesis in patients with chronic hepatitis C.

2. Design
Randomized controlled trial (RCT).

3. Setting
None (the author belongs to a specialized hospital).

4. Participants
One hundred and fifty-six patients with hepatitis C virus-related cirrhosis (stage Child A).

5. Intervention
Arm 1: target alanine aminotransferase (ALT) level ≤80; monotherapy with Stronger Neo-Minophagen C (SNMC; 40–100 mL, two or three times per week), ursodeoxycholic acid (UDCA), shosaikoto (小柴胡湯), or juzentaihoto (十全大補湯) (manufacturers, not specified) was administered. When the target level was not achieved in 2–3 months, dual therapy with SNMC + UDCA, UDCA + juzentaihoto (十全大補湯), or UDCA + shosaikoto (小柴胡湯) was administered. If the target level was still not achieved, triple therapy with SNMC + UDCA + shosaikoto (小柴胡湯) or SNMC + UDCA + juzentaihoto (十全大補湯) was administered. The choice of the therapy in each patient was not described, n=78.
Arm 2: monotherapy with UDCA, SNMC, shosaikoto (小柴胡湯), or juzentaihoto (十全大補湯) was administered; the choice of the drug was based on the ALT-lowering effect. Details, including the drug used, dose, and the number of patients who received each drug, were not available, n=50.

6. Main outcome measures
Incidence of liver cancer.

7. Main results
The incidence of liver cancer was lower in arm 1 than in arm 2.

8. Conclusions
Therapy consisting of combined Kampo medicines for liver protection is effective for suppressing carcinogenesis in patients with chronic hepatitis C.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study reports an effective treatment for suppressing carcinogenesis in patients with chronic hepatitis C. But since the specific design was not described and details (such as the choice of the therapy or the number of patients who received each drug in arm 2) were unclear, we cannot decide which of the treatments resulted in response. Studies employing easy-to-understand designs are desired.

The interim reports of this study are:

12. Abstractor and date
## Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

### Reference


### 1. Objectives
To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

### 2. Design
Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

### 3. Setting
A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]).

### 4. Participants
Seventy-two patients with liver cirrhosis due to hepatitis B or C virus (B, n=14; C, n=58). However, one patient who had liver cancer within half a year after entry into the study was excluded.

### 5. Intervention
Arm 1: juzentaihoto (十全大補湯)-treated group (B, n=8; C, n=18).
Arm 2: juzentaihoto (十全大補湯)-untreated group (B, n=6; C, n=39).

### 6. Main outcome measures
- Cumulative survival curve by Kaplan-Meier method (log-rank test [Mantel-Cox]).
- Cumulative hazard curve for hepatocellular carcinoma development by Kaplan-Meier method (log-rank test [Mantel-Cox]).
The threshold of liver cancer development was set at the time when liver cancer was first detected on imaging-based clinical diagnosis.

### 7. Main results
For overall liver cirrhosis, there was no significant difference in the cumulative survival curve between arms (chi-square=3.167, \(P = 0.0751\)), but juzentaihoto-treated patients tended to have a more favorable prognosis. For overall liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed the risk was significantly lower in the juzentaihoto-treated group than in juzentaihoto-untreated group (chi-square=5.832, \(P = 0.0157\)). Analysis limited to liver cirrhosis type C also revealed significantly lower risk in the juzentaihoto-treated group (chi-square=4.197, \(P = 0.0405\)).

### 8. Conclusions
It is suggested that administration of juzentaihoto prevents hepatocellular carcinoma from developing in patients with liver cirrhosis.

### 9. From Kampo medicine perspective
None.

### 10. Safety assessment in the article
None.

### 11. Abstractor’s comments
This study is valuable, since hepatocellular carcinoma frequently develops as a result of underlying hepatitis virus infection. Using sealed envelopes for allocation, this study is regarded as a randomized controlled trial. Information on the method of juzentaihoto administration and blinding may have made this report clinically more meaningful.

### 12. Abstractor and date
Reference

1. **Objectives**
To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

2. **Design**
Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. **Setting**
A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]).

4. **Participants**
Fifty-two patients with liver cirrhosis due to hepatitis B or C virus. However, patients who had liver cancer within a year after entry into the study and those who received shosaikoto or interferon were excluded.

5. **Intervention**
Arm 1: juzentaihoto (十全大補湯)-treated (type B, n=8; type C, n=15; type B + type C, n=1).
Arm 2: juzentaihoto (十全大補湯)-untreated (type B, n=5; type C, n=22; type B + type C, n=1).

6. **Main outcome measures**
Cumulative survival curves were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). Cumulative hazard curves for hepatocellular carcinoma development were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). The threshold of liver cancer development was set when liver cancer was first detected on imaging-based clinical diagnosis.

7. **Main results**
For all liver cirrhosis, the cumulative survival curve showed that vital prognosis was significantly more favorable in arm 1 than arm 2, with chi-square values of 4.066, 6.467, and 5.217 (P=0.0438, 0.0190, and 0.0224) by the log-rank test (Mantel-Cox test), Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test, respectively. Analysis of the cumulative survival curve limited to patients with liver cirrhosis type C showed a tendency toward more favorable vital prognosis in arm 1, but no significant between-group difference. For all liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed significantly lower incidence of hepatocellular carcinoma in arm 1 than in arm 2, with chi-square values of 5.265, 5.578, and 5.921 (P=0.0218, 0.0182, and 0.0150) by these tests, respectively. Analysis limited to liver cirrhosis type C revealed significantly lower incidence of hepatocellular carcinoma in arm 1 by the Bleslow Gehan-Wilcoxon test and Peto-Peto-Wilcoxon test (chi-square=4.659, 4.483, respectively; P=0.0309, 0.0342, respectively).

8. **Conclusions**
It is suggested that in liver cirrhosis, administration of juzentaihoto prevents hepatocellular carcinoma development.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
None.

11. **Abstrator's comments**
This study is valuable since hepatocellular carcinoma frequently develops from underlying hepatitis virus infections. This study seems to be similar to the study published in Methods in Kampo Pharmacology (2000; 5: 29-33). There were fewer participants in the present study because stricter exclusion criteria were followed: liver cancer development within a year vs half a year in the previous study, and shosaikoto or interferon not permitted. Furthermore, use of diverse statistical tests made the results more meaningful, particularly clinically. Use of a placebo and blinding may have made the results more reliable.

12. **Abstractor and date**

### 1. Objectives
To determine the efficacy of daikenchuto (大建中湯) for the treatment of postoperative ileus and the improvement of postoperative conditions.

### 2. Design
Randomized controlled trial (RCT).

### 3. Setting
One hospital (Cancer Research Institute of Kanazawa University)

### 4. Participants
Out of 154 abdominal surgery patients, 24 developed postoperative ileus were enrolled.

### 5. Intervention
Arm 1: treatment with daikenchuto (大建中湯) 15.0 g in 13 patients.
Arm 2: treatment with placebo (the same quantity and frequency of doses as arm 1) in 11 patients.
The study drugs were administered orally for 14 days.

### 6. Main outcome measures
Frequency of surgery for ileus and recurrence of ileus.

### 7. Main results
Surgery for postoperative ileus could be avoided significantly more frequently in the daikenchuto arm than in the placebo arm. In addition, daikenchuto tended to decrease, though not significantly, the recurrence rate of ileus.

### 8. Conclusions
Daikenchuto is a cost-effective and noninvasive therapeutic agent for postoperative ileus after abdominal surgery and has no adverse effects.

### 9. From Kampo medicine perspective
None.

### 10. Safety assessment in the article
None.

### 11. Abstractor’s comments
This RCT examined the efficacy of daikenchuto for postoperative ileus. This seems to be clinically relevant after abdominal surgery since the treatment for postoperative ileus is not established. Although mentioned in the conclusion, the safety and cost effectiveness of daikenchuto treatment were not described in the main text. It might have been better to mention those outcomes, and examine the dependence of these differences on subjects’ underlying diseases or surgical procedures.

### 12. Abstractor and date
Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

1. Objectives
To determine the effects of daikenchuto (大建中湯) on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction.

2. Design
Randomized crossover controlled trial (RCT-cross over).

3. Setting
Osaka University Hospital.

4. Participants
Seventeen patients who underwent total gastrectomy with jejunal pouch interposition reconstruction for gastric cancer (mean age, 62 years).

5. Intervention
Arm 1: treatment with daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. before meals for 2 weeks followed by no treatment for 2 weeks (n=10).
Arm 2: no treatment for 2 weeks followed by treatment with daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. before meals for 2 weeks (n=7).

6. Main outcome measures
Gastrointestinal symptoms, emptying, motility, and quality of life (QOL) (using Visick grading scale with modification).

7. Main results
Daikenchuto significantly relieved postprandial stasis-related symptoms including upper abdominal fullness, discomfort, and abdominal pain. Scintigraphy with 111In- and 99mTc-labeled meals showed that daikenchuto significantly accelerated clearance of both the liquid (P<0.01) and solid (P=0.015) components of food from the jejunal pouch. Manometric assessment of pouch motility (contraction time in 6 patients found a significant increase from the pretreatment levels after daikenchuto treatment (P=0.028).

8. Conclusions
Daikenchuto accelerates gastrointestinal emptying and motility and improves QOL after total gastrectomy followed by jejunal pouch interposition reconstruction.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor's comments
This paper reports the effects of daikenchuto on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction. The authors evaluated a small number of patients in a RCT crossover and obtained highly accurate results. They deserve high praise, especially for exploring not only subjective symptoms but also gastrointestinal emptying and motility measured by relatively invasive procedures.

12. Abstractor and date
Objectives
To determine the clinical effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.

Design
Randomized controlled trial (RCT).

Setting
University of Occupational and Environmental Health Hospital.

Participants
Fifty patients with depressive disorder (mean age, 40.2 years).

Intervention
Arm 1: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) and TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 8 weeks, n=25.
Arm 2: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) alone for 8 weeks, n=25.

Main outcome measures
Gastrointestinal symptoms (assessed by Gastrointestinal Symptom Rating Scale [GSRS] score) and depressive symptoms (by Self-rating Depression Scale [SDS] score).

Main results
Overall gastrointestinal symptoms due to fluvoxamine treatment were significantly relieved to a greater extent in arm 1 (GSRS total score, 1.97±0.81) than in arm 2 (2.52±0.99). No significant between-arm difference was observed in post-treatment SDS score.

Conclusions
Rikkunshito reduces fluvoxamine-induced gastrointestinal adverse reactions, especially nausea, without affecting the antidepressant effect of fluvoxamine.

From Kampo medicine perspective
None.

Safety assessment in the article
During the treatment, adverse reactions occurred significantly less frequently in arm 1 (6 patients) than in arm 2 (13 patients). In particular, the frequency of nausea was significantly lower in arm 1 (3 patients) than in arm 2 (9 patients).

Abstrator’s comments
This paper reports that rikkunshito reduced nausea and other gastrointestinal adverse reactions induced by selective serotonin reuptake inhibitors (SSRI), such as fluvoxamine. Although sample size was relatively small, this trial was well-designed and valuable since it showed the usefulness of Kampo medicines from the perspective of reducing the adverse reactions to western medicines.

Abstractor and date
References

1. Objectives
To assess the efficacy of hochuekkito (補中益気湯) for the treatment of atopic dermatitis.

2. Design
Randomized controlled trial (RCT).

3. Setting
Three university hospitals.

4. Participants
Patients with atopic dermatitis and “qikyo” (気虚, qi deficiency), n=77.

5. Intervention
Arm 1: hochuekkito (補中益気湯) group. Oral administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (KB-41) 7.5 g/day in two divided doses. (n=37)
Arm 2: placebo group. Oral administration of placebo 7.5 g/day in two divided doses. (n=40)
Duration of administration and observation was 24 weeks for both arms.

6. Main outcome measures
Skin lesion score (according to Japanese Dermatology Association criteria), and change in the dosage of topical steroid and topical tacrolimus hydrate used.

7. Main results
The dosage of topical steroid and topical tacrolimus hydrate was significantly less in arm 1 than arm 2. The reduction in skin lesion score in arm 1 indicated nonsignificant improvement in these lesions when compared with arm 2.

8. Conclusions
Hochuekkito was effective in decreasing the amount of topical corticosteroid and topical tacrolimus hydrate used by patients with atopic dermatitis.

9. From Kampo medicine perspective
“Qikyo” was one of the inclusion criteria for enrollment in this trial. Changes in “qikyo” scores were not significantly different between the two arms.

10. Safety assessment in the article
Although the authors mention that “safety (including biochemical tests) was assessed,” the results of this assessment are not described.

11. Abstractor’s comments
This paper provides objective data on the efficacy of hochuekkito as an adjunctive therapy for atopic dermatitis.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy of boiogitokashuchibushimatsu (防己黃耆湯加修治附子末) for gonarthrosis.

2. Design
Randomized controlled trial (RCT).

3. Setting
University hospital (Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine; Pain Clinic, Department of Anesthesiology, Shiga University of Medical Science; and Graduate School of Pharmaceutical Sciences, Osaka University) and 4 other hospitals.

4. Participants
Two hundred eleven patients with gonarthrosis.

5. Intervention
Arm 1: administration of boiogitokashuchibushimatsu (防己黃耆湯加修治附子末) (manufacturer unknown) (n=110); age at completion, 81.5±3.4 years; male/female ratio, 8:102.
Arm 2: administration of loxoprofen (n=101); age at completion, 82.0±3.1 years; male/female ratio, 9:92.
Ten-year trial. Capsules were taken with 350 mL of water 30 min before meals. No more details (e.g. dose, dose frequencies) were indicated in the original paper.

6. Main outcome measures
Exercise capacity (EC), range of motion of knee, various chronic pains (CP), health-related quality of life (Hr-QOL), adiponectin, leptin, and orexin levels, knee circumference, synovial fluid retention as assessed by ultrasound, degree of joint space narrowing as assessed by CT scan, (direct, indirect, total) medical expenses monitored over a 10-year period.

7. Main results
All EC parameters (continuous walking distance, continuous upslope walking distance, number of steps in continuous downslope walking) were larger in arm 1 than in arm 2 (P<0.001). All parameters used to evaluate activities of daily living (ADL) (pain in passive exercise, spontaneous pain, pain on pressure, patella ballottement/soft tissue swelling, local heat, etc.), various CP, and Hr-QOL were significantly improved in arm 1 compared with arm 2 (P<0.001).

8. Conclusions
The treatment significantly improves EC, ADL, CP, and Hr-QOL and lowers total medical expenses.

9. From Kampo medicine perspective
The sho (pattern/syndrome) concept was a criterion for inclusion. Although “gonarthrosis complying with the sho for boiogitokabushi” was used as a criterion, the sho concept was not defined. The authors appear to consider that all patients with gonarthrosis in the study satisfy the sho for boiogitokabushi. There was no sho concept as an exclusion criterion and no subgroup analyses according to sho.

10. Safety assessment in the article
A significantly larger number of adverse events occurred in arm 2 (P<0.001 for all items): gastric ulcer (0 event in arm 1 vs. 24 events in arm 2), eruption/sleepiness/stomach discomfort/oedema (11 events vs. 348 events), and laboratory abnormality (3 events vs. 417 events).

11. Abstractor’s comments
The filling of capsules to make the investigational products indistinguishable from each other is necessary for double-blind study of Kampo medicine. However, the dose of loxoprofen is missing from this paper (misprint?). This study assumed that “patients with gonarthrosis satisfy the sho for boiogitokashuchibushi.” This assumption should have been verified in a pilot study. However, it is extremely rare that a particular disease corresponds one-on-one to an effective Kampo treatment; the treatment of most diseases needs several Kampo medicines selected according to patient conditions. Furthermore, prolonged administration of drugs (including loxoprofen used as the control drug in this study) causing potentially fatal adverse reactions in the elderly such as gastric mucosal disorder is problematic. Also problematic is the therapeutic use of fixed doses for painful disease. Moreover, duration of the study was too long, given the nature of this disease and the old age of most subjects. Conclusion should be drawn in a shorter term.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

Reference

1. **Objectives**
To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for dryness associated with primary Sjögren’s syndrome.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Not mentioned

4. **Participants**
One-hundred and six patients with primary Sjögren’s syndrome.

5. **Intervention**
Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. for 1 year. (n=51)
Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year. (n=54)

6. **Main outcome measures**
Dryness, amount of salivation/lacrimation, and inflammatory reaction.

7. **Main results**
Salivation was increased in both groups but was significantly increased in the bakumondoto group. Lacrimation was significantly increased only in the bakumondoto group. Dryness was also improved only in the bakumondoto group. The inflammatory reaction remained unchanged in both groups.

8. **Conclusions**
Bakumondoto is more effective than bromhexine hydrochloride and safe in the treatment of dryness associated with primary Sjögren’s syndrome.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not specified).

11. **Abstractor’s comments**
This study provides objective evidence for the efficacy of bakumondoto for relieving dryness associated with primary Sjögren’s syndrome.

12. **Abstractor and date**
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for salivary hyposecretion associated with primary Sjögren’s syndrome.

2. Design
Randomized controlled trial (RCT).

3. Setting
Two clinics, three university hospitals, and one general hospital.

4. Participants
Two-hundred and twenty-nine patients with primary Sjögren’s syndrome.

5. Intervention
Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 6 months (n=115).
Arm 2: placebo 3 g t.i.d. before meals for 6 months (n=114).

6. Main outcome measures
Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud’s symptom, limb skin temperature, and inflammatory reaction.

7. Main results
Salivation was increased in the bakumondoto group but decreased in the placebo group. Subjective symptoms were improved in the bakumondoto group but remained unchanged or were aggravated in the placebo group. Inflammatory reaction improved significantly only in the bakumondoto group.

8. Conclusions
Bakumondoto is effective and safe for the relief of subjective symptoms and salivary hyposecretion associated with primary Sjögren’s syndrome.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were fewer adverse drug reactions (ADRs) or laboratory abnormalities or fewer patients with ADRs or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group. There were no serious ADRs or laboratory abnormalities leading to treatment discontinuation in either group (the number of events not specified).

11. Abstractor’s comments
This study provides objective evidence for the efficacy of bakumondoto in the treatment of dryness associated with primary Sjögren’s syndrome.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of secondary Sjögren’s syndrome.

2. Design
Randomized controlled trial (RCT).

3. Setting
Three clinics and 3 university hospitals.

4. Participants
Eight-hundred and forty-seven patients with secondary Sjögren’s syndrome.

5. Intervention
Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 1 year (n=424).
Arm 2: bromhexine hydrochloride 4 g t.i.d. before meals for 1 year (n=423).

6. Main outcome measures
Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud’s symptom, limb skin temperature.

7. Main results
The amount of salivation was increased in both arms but was significantly higher in the bakumondoto group. Among bakumondoto-treated patients, those with mild disease showed significantly larger increases, whereas those with severe disease showed larger percent increases. The amount of lacrimation was significantly increased only in the bakumondoto group. Only in the bakumondoto group, the following variables were also improved: dryness, Raynaud’s symptom, joint pain, cough/amount of sputum, and lowered temperature of the limb skin.

8. Conclusions
Bakumondoto is more effective and safer than bromhexine hydrochloride and therefore beneficial for treatment of mouth dryness associated with secondary Sjögren’s syndrome.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor’s comments
This study provides objective evidence for the efficacy of bakumondoto for the treatment of dryness associated with secondary Sjögren’s syndrome. In the text, the dose of bromhexine hydrochloride was indicated as 120 mg, instead of the correct dose of 12 mg.
This paper seems to include data from the preliminary clinical trial published in *Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society)* 2003; 44: 65-70.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

1. Objectives
To evaluate the efficacy and safety of bakumondo-tō (麦門冬湯) for treatment of dryness associated with secondary Sjögren’s syndrome.

2. Design
Randomized controlled trial (RCT).

3. Setting
None.

4. Participants
Seven-hundred and fifty-six patients with secondary Sjögren’s syndrome.

5. Intervention
Arm 1: bakumondo-tō extract granules 3 g t.i.d. for 1 year (n=380).
Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year (n=374).

6. Main outcome measures
Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud’s symptom.

7. Main results
The amount of salivation was increased in both arms, but it was significantly higher in the bakumondo-tō group. The amount of lacrimation was significantly increased only in the bakumondo-tō group. The following outcome measures were also improved only in the bakumondo-tō group: dryness, Raynaud’s symptom, joint pain, and cough/amount of sputum. The inflammatory reaction remained unchanged in both groups.

8. Conclusions
Bakumondo-tō is more effective and safer than bromhexine hydrochloride and therefore useful for treating dryness associated with secondary Sjögren’s syndrome.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondo-tō group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor’s comments
This study provides objective evidence for the efficacy of bakumondo-tō for treating dryness associated with secondary Sjögren’s syndrome. The duration and dosage of bakumondo-tō treatment was correlated with the amount of salivation, suggesting a dose-dependent effect.

12. Abstractor and date

Reference
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy for Sjögren’s syndrome.

2. Design
Quasi-randomized controlled trial (quasi-RCT).

3. Setting
Outpatient Department of Rheumatology, Samitama Medical University Hospital.

4. Participants
Sixty-four patients with Sjögren’s syndrome.

5. Intervention
Arm 1: 4-week administration of 2.5 g t.i.d. of TSUMURA Hochuekkito (補中益気湯) Extract Granules (n=32; after 4 dropped out, 28 included for analysis).
Arm 2: 4-week administration of Kampo medicine extracts that affect salivary secretion (3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules alone [n=23]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Rokumigan (六味丸) Extract Granules [n=3]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules [n=4]) according to sho (証, pattern/syndrome) (n=32; after 2 dropped out, 30 included for analysis).

6. Main outcome measures
Change in salivary secretion from pre- to post-administration, measured using a chewing gum test.

7. Main results
27 out of 30 patients in Arm 1 demonstrated increase in salivary secretion, with a significant increase in mean pre-treatment secretion of 8.2±1.2ml to post-treatment average of 12.0±1.4ml (p<0.005). There was no statistical significance between pre- and post-treatment secretions in Arm 2. The amount of increase in salivary secretions before and after the treatment in Arm 1 was significantly greater than Arm 2 (p<0.005).

8. Conclusions
A Kampo medicine with moisturizing effect (but not a medicine without this effect) increased the amount of salivary secretion.

9. From Kampo medicine perspective
Arm 1 used “bensho (弁証)” (Kampo diagnosis) to allocate patients, specifically “jinkyo” (腎虚, kidney deficiency) which included 3 or more of the following 6 symptoms: 1) heaviness of the back; 2) heaviness in the lower legs with pain in heels and lateral surface of the lower legs; 3) tinnitus/hearing loss; 4) loss of hair and hair luster; 5) looseness or loss of teeth; and 6) sexual dysfunction (impotence, nocturnal emission). Kampo formulations for Arm 1 were selected based on the status of jinkyo: 1) bakumondoto alone for negative jinkyo; 2) bakumondoto plus rokumigan for jinkyo without chills; and 3) bakumondoto plus hachimijiogan for jinkyo with chills.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This is an interesting quasi-randomized controlled trial that is plausible for its attempt in incorporating “sho” (証) diagnosis for selection of treatment. Results from the trial demonstrated that bakumondoto, moisturizing formula, with other Kampo formulations combination effectively enhanced salivary secretion in patients with Sjögren’s syndrome than hochuekkito which was used as a control. A total of three pattern of combinations of Kampo formulation(s) were established for Arm 1 based on various manifestations of jinkyo. 23 out of 30 patients (77%) in Arm 1 received bakumondoto only. Future studies with improved RCT design and comparison with placebo or Western drug as a control appear warranted.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy of hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸), and shuchibushi (修治附子) powder for relief of residual symptoms after surgical treatment of cervical spinal stenosis.

2. Design
Randomized controlled trial (RCT).

3. Setting
One university hospital.

4. Participants
Twenty-four patients with residual symptoms following surgical treatment of cervical spinal stenosis.

5. Intervention
Arm 1: 2-month administration of hachimijiogan (八味地黄丸).
Arm 2: 2-month administration of goshajinkigan (牛車腎気丸).
Arm 3: 2-month administration of goshajinkigan (牛車腎気丸) + 1.0 g of shuchibushi powder (修治附子末).
No between-arm difference was noted in operative effect. Administration started at postoperative 2 months in all arms.
No details in original paper.

6. Main outcome measures
Subjective symptoms (pain and paresthesia) evaluated on a visual analogue scale (VAS).

7. Main results
Pain was improved in 24.8%, 37.1%, and 45.5% of patients receiving hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder, respectively. The efficacy of goshajinkigan + shuchibushi powder was significantly higher than that of hachimijiogan. Paresthesia was improved in 21.4%, 24.2%, and 28.5%, respectively, showing no difference between arms.

8. Conclusions
Hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder were all effective for residual symptoms of surgically treated cervical spinal disease, with the highest efficacy achieved by goshajinkigan + shuchibushi powder.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No adverse drug reactions (ADRs) or withdrawals occurred (the number of ADRs not indicated).

11. Abstractor’s comments
This study provides evidence that Kampo formulations can be a therapeutic option for residual symptoms of surgically treated cervical spinal diseases. Given the higher efficacy at higher doses of shuchibushi, the authors infer that shuchibushi acts on opioid receptors.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

Reference

1. Objectives
To evaluate the efficacy of goshajinkigan (牛車腎気丸) and shuchibushi powder (修治附子末) for relief of chronic low back pain associated with lumbar spinal stenosis.

2. Design
Randomized controlled trial (RCT).

3. Setting
One university hospital.

4. Participants
Eighty-nine patients with chronic low back pain associated with lumbar spinal stenosis for which surgery is not indicated.

5. Intervention
Arm 1: 3-month administration of western medicines including non-steroidal anti-inflammatory drugs (NSAIDs), prostaglandin E2, vitamin B12, and/or H2 blockers (n=29).
Arm 2: 3-month administration of goshajinkigan (牛車腎気丸) alone (n=30).
Arm 3: 3-month administration of goshajinkigan (牛車腎気丸) + 2.0 g of shuchibushi powder (修治附子末) (n=30).
No details indicated in the original paper.

6. Main outcome measures
Low back pain and lower limb paresthesia evaluated on a visual analogue scale (VAS).

7. Main results
Lower back pain score was decreased from 6.7, 6.5, and 6.8 to 3.5, 4.5, and 3.2 in arms 1, 2, and 3, respectively. Lower limb paresthesia score was decreased from 5.6, 5.7, and 5.9 to 4.2, 3.9, and 3.2, respectively. Thus, there were no significant between-arm differences in therapeutic effects.

8. Conclusions
Both goshajinkigan and shuchibushi powder were as effective as western medicines for the relief of chronic low back pain and lower limb paresthesia associated with lumbar spinal stenosis.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No adverse drug reactions (ADRs) or withdrawals occurred in either arm (the number of ADRs not indicated).

11. Abstractor’s comments
This study is of clinical significance since it provides evidence that Kampo medicines can be a therapeutic option for lumbar spinal stenosis, expanding the range of therapeutic options.

12. Abstractor and date
Diseases of the musculoskeletal system and connective tissue

1. **Objectives**
   To evaluate the efficacy of juzentaihoto (十全大補湯) combined with hachimijiogan (八味地黄丸) in patients with disuse syndrome.

2. **Design**
   Randomized controlled trial (envelope method) (RCT-envelope).

3. **Setting**
   One community hospital.

4. **Participants**
   Patients after a prolonged period of bed rest and tube feeding.

5. **Intervention**
   Arm 1: Tsumura Juzentaihoto (十全大補湯) Extract Granules and Tsumura Hachimijiogan (八味地黄丸) Extract Granules 2.5 g b.i.d. each for 24 weeks, n=13.
   Arm 2: No administration of Kampo drugs, n=15.

6. **Main outcome measures**
   Laboratory tests: hemograms and urine tests performed at 0, 4, 8, 12, 16, 20, and 24 weeks. CD4 count, CD8 count, CD4/CD8 ratio, neutrophil phagocytotic activity, levels of immunoglobulins (IgM, IgG, and IgA) examined at 0, 12, and 24 weeks.

7. **Main results**
   CD4/CD8 ratio and CD4 count were significantly increased in arm 1 compared to arm 2 at 12 weeks; however, no significant difference was observed at 24 weeks. There were no significant between-arm differences in the results of other tests.

8. **Conclusions**
   In many cases, CD4/CD8 ratio and CD4 count were elevated at 12 weeks of administration.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    Not documented.

11. **Abstractor’s comments**
    Immunoregulatory effect of the combination two Kampo drugs was assessed using lymphocyte surface markers CD4 and CD8. The finding of significant increases in CD4/CD8 ratio and CD4 count at 12 weeks, but not at 24 weeks, demands the conduct of further studies designed to reveal whether immune status was restored or regulated.

12. **Abstractor and date**
1. **Objectives**
   To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) and propiverine hydrochloride for overactive bladder.

2. **Design**
   A randomized controlled trial (RCT).

3. **Setting**
   Not mentioned (authors belong to Nishizawa Clinic, Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine and Department of Anesthesiology, Shiga University of Medical Science).

4. **Participants**
   Seven hundred and four patients with overactive bladder, aged 45 years or older, prospectively enrolled over a 10-year period (1997–2006).

5. **Intervention**
   Arm 1: administration of goshajinkigan (牛車腎気丸) (manufacturer not specified), 4.5 g/day, for 1 year (n=352).
   Arm 2: administration of propiverine hydrochloride, 60 mg/day, for 1 year (n=352).

6. **Main outcome measures**
   Symptoms of overactive bladder (urge to urinate, daytime urinary frequency, nocturia, and urine leak).
   Quality of life (pain, erection dysfunction, cold sensation, etc.).

7. **Main results**
   Symptoms of overactive bladder were significantly more improved in arm 2 than in arm 1 during the first month after treatment initiation, but significantly more improved in arm 1 than arm 2 during the second and subsequent months. At the completion of the study, the other concomitant symptoms and quality of life (QOL) were also significantly more improved in arm 1 than in arm 2.

8. **Conclusions**
   It was suggested that goshajinkigan is effective for overactive bladder.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    Four and 375 events of adverse drug reactions occurred in arm 1 and arm 2, respectively.

11. **Abstractor’s comments**
    This 1-year prospective randomized controlled trial in 704 patients suggests the efficacy of goshajinkigan for overactive bladder. Its efficacy for concomitant symptoms and QOL was also suggested. However, there is no mention of the number patients who withdrew, the facility or facilities where this trial was actually conducted, and the method of randomization. Future studies considering these points are awaited.

12. **Abstractor and date**
### Genitourinary Tract Disorders (including Climacteric Disorders)

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1. **Objectives**  
   To evaluate the effect of single-dose administration of maobushisaishinto (麻黄附子細辛湯) on urine flow.

2. **Design**  
   Randomized cross-over controlled trial (RCT-cross over).

3. **Setting**  
   Department of Urology, Nagoya City University Medical School and associated facilities.

4. **Participants**  
   Thirteen young male volunteers (mean age: 38.0 years) and six elderly male volunteers (mean age: 64.5 years).

5. **Intervention**  
   Arm 1: administration of 2 capsules of Kotaro Maobushisaishinto (麻黄附子細辛湯) in the 1st course followed by 2 capsules of placebo in the 2nd course, with 4-week withdrawal between courses.  
   Arm 2: administration conducted in the reverse order of arm 1.

6. **Main outcome measures**  
   Maximum urine flow rate at 3 hr after administration, mean urine flow rate, and voiding efficiency.

7. **Main results**  
   Regardless of the order of administration, no significant differences were observed in the maximum urine flow rate at 3 hr after administration, mean urine flow rate, or voiding efficiency between maobushisaishinto - and placebo-groups. There was no significant difference in the maximum urine flow rate, mean urine flow rate, or voiding efficiency between pre- and post-dose levels when treated with maobushisaishinto in the elderly.

8. **Conclusions**  
   It is suggested that single-dose administration of maobushisaishinto has no effect on urine flow in both young and old men.

9. **From Kampo medicine perspective**  
   None.

10. **Safety assessment in the article**  
    None.

11. **Abstractor’s comments**  
    In elderly males with impaired urination due frequently to prostatic hyperplasia, ephedrine-containing formulations such as mao have been shown to aggravate the problem. This study concludes that single-dose administration of maobushisaishinto does not adversely affect urine flow in the elderly. However, since treatment with a Kampo formulation usually requires repeated administration for a certain period, the results of a clinical study with repeated administration will also need to be considered.

12. **Abstractor and date**  
Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

1. Objectives
To evaluate the hachimijiogan (八味地黄丸)-induced improvement in postoperative discomfort associated with surgery for uterine prolapse and quality of life (QOL).

2. Design
A randomized controlled trial (RCT).

3. Setting
Department of Obstetrics and Gynecology, National Hospital Organization Oita Medical Center.

4. Participants
Nineteen patients with uterine prolapse who did not respond to hochuekkito and underwent vaginal radical operation for uterine prolapse at the above facility between December 2005 and March 2006.

5. Intervention
Arm 1: oral administration of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before meals, n=12.
Arm 2: no treatment, n=7.

6. Main outcome measures
Frequency of urination per day and mean residual urine volume at the start and 1 and 2 weeks after the start of hachimijiogan.

7. Main results
There was no significant difference in urination frequency. Residual urine volume was significantly decreased after hachimijiogan treatment for 1 week (21±2.3 mL vs. 13±4.2 mL, \(P<0.05\)) and 2 weeks (12±1.7 mL vs. 8.3±1.5 mL, \(P<0.05\)). In addition, 2 weeks of treatment with hachimijiogan decreased residual urine volume more significantly in patients with shofukufujin (小腹不仁, soft, weak lower abdomen) than in those without fukusho (腹証, abdominal pattern) (8.3±1.5 mL vs. 5.3±2.5 mL, \(P<0.05\)).

8. Conclusions
Hachimijiogan administered after surgery for uterine prolapse may accelerate tissue repair postoperatively, thereby improving patient QOL, particularly in patients with shofukufujin.

9. From Kampo medicine perspective
Traditionally, hochuekkito has been considered to be the effective treatment for uterine prolapse. However, because of a change in nutritional status, many women do not present conventional \(\text{“sho”}\), leaving room for reconsideration of the appropriate agent. Hachimijiogan is highly effective for decreasing residual urine volume after surgery for uterine prolapse and aiding recovery of the bladder and surrounding tissues.

10. Safety assessment in the article
No adverse drug reactions occurred after hachimijiogan treatment.

11. Abstractor’s comments
This research raises questions about what Kampo medicine should be or how it should be utilized in an aging society. None of the existing treatments for genitourinary prolapse (including surgery, pessary insertion, and pharmacotherapy) are totally effective, raising concerns among clinicians. This research demonstrated that hachimijiogan is highly effective in decreasing postoperative residual urine volume particularly in patients with shofukufujin. Future research is desired to determine whether this clinical approach fusing western and oriental medicines can prevent recurrent uterine prolapse and how Kampo medicine can be used to treat uterine prolapse for \(\text{sho of unclear jinkyo (腎虛, kidney deficiency)}\).

12. Abstractor and date
### Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

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

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1. **Objectives**
   To evaluate the efficacy and safety of kyukikyogaito (キュウ帰膠艾湯) for menometrorrhagia.

2. **Design**
   Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
   Obstetric and gynecologic practitioner, Yamagata.

4. **Participants**
   The analysis population included 183 out of 200 randomized patients with menometrorrhagia.

5. **Intervention**
   - Arm 1: administration of 9.0 g of TSUMURA Kyukikyogaito (キュウ帰膠艾湯) Extract Granules for 7 days (n=100). Ninety-three patients were included for analysis.
   - Arm 2: administration of tranexamic acid (3 tablets of Transamin) and carbazochrome/VK mixture (3 tablets of Ophtharum K) for 7 days (n=100). Ninety patients were included for analysis.

6. **Main outcome measures**
   Number of days from exploratory endometrial curettage to hemostasis.

7. **Main results**
   The time to hemostasis was significantly shorter in arm 1 (4.29±1.54 days) than in arm 2 (5.45 ± 2.13 days). When response was determined by the criterion of ‘hemostasis by day 7’, the response rate was significantly higher (94.6%) in arm 1, compared with 72.2% in arm 2. By *sho* (証, pattern/syndrome), cases of hypofunction or intermediate function required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of hyperfunction showed no difference in the days to hemostasis between arms. By the appearance of the endometrium on imaging, cases of the proliferative phase or simple hyperplasia required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of stationary phase, atrophic phase and mixed proliferative/secretory phase or secretory phase showed no difference in the days to hemostasis between arms.

8. **Conclusions**
   Kyukikyogaito is more effective for hemostasis in menometrorrhagia, compared with hemostatic drugs tranexamic acid and carbazochrome/VK mixture.

9. **From Kampo medicine perspective**
   After, but not before, dosing, differential diagnosis of *sho* was made visually and by abdominal palpation, and it was concluded that kyukikyogaito is effective regardless of *sho*.

10. **Safety assessment in the article**
    A 32-year-old patient complained of feeling bad after receiving 1 sachet of kyukikyogaito, and of stomach discomfort and nausea after receiving 2 sachets, and then discontinued the medicine after receiving 4 sachets and was switched to another drug.

11. **Abstracter’s comments**
    Various pathogenic mechanisms can cause menometrorrhagia in Kampo medicine, as in western medicine. Kyukikyogaito is a combination of a single medicine that acts on one of these mechanisms, called *shoninkyoson* (衝任虚損), and a hemostatic drug *[Kinkiyoryaku* [金匱要略]: synopsis of prescriptions of the golden chamber]. Presence of both responders and non-responders to this combination suggests that the disease has a more than one pathogenesis. Although this study is a quasi-randomized controlled trial, in which patients were alternately randomized and placed in the order of visitation, a certain efficacy of kyukikyogaito for menometrorrhagia is suggested.

12. **Abstracter and date**
Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

1. Objectives
To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.

2. Design
Randomized controlled trial (RCT).

3. Setting
None. The author belonged to the Department of Obstetrics and Gynecology, Tokyo Women’s Medical University.

4. Participants
Ninety-six postmenopausal or ovariectomized patients with climacteric disorders.

5. Intervention
Arm 1: HRT (0.625 mg of conjugated estrogen and 2.5 or 5 mg of medroxyprogesterone acetate) (n=50).
Arm 2: Kampo therapy (keishibukuryogan (桂枝茯苓丸), n=19; kamishoyosan (加味逍遙散), n=11; goshajinkigan (牛車腎気丸), n=8; tokishakuyakusan (当帰芍薬散), n=2; tokujikokito (桃核承気湯), n=2; kihito (帰脾湯), n=2; nyoshinsan (女神散), n=2) (n=46).
No details indicated in the original paper.

6. Main outcome measures
Score on Keio modified menopause index, measured at baseline, 1, 6, and 12 months after the start of administration. Severity was defined as mild for 0–10 points, moderate for 10–20 points, and severe for 20–30 points, and response was defined as a change from severe to moderate, moderate to mild, or a score reduction by two-thirds in mild cases.

7. Main results
HRT improved the following 6 symptoms in 1 month: vasomotor manifestations; nervousness; low back and back pain; depression; insomnia; and headache. In contrast, Kampo therapy did not improve any symptoms in 1 month but improved the following 4 symptoms in 6 months: vasomotor manifestations; malaise; low back and back pain; and nervousness. Among Kampo medicines, only goshajinkigan was effective for low back and back pain.

8. Conclusions
The therapeutic effect of HRT is superior for hot flashes, perspiration, depression, and insomnia, whereas that of Kampo therapy is superior for malaise and chill.

9. From Kampo medicine perspective
The number of patients receiving keishibukuryogan (n=19), kamishoyosan (n=11), or tokishakuyakusan (n=2) was explained by the small number of cases with kyo-sho (虚証, deficiency pattern).

10. Safety assessment in the article
None.

11. Abstractor’s comments
This paper outlines the characteristics of Kampo medicines and HRT. It recommends that Kampo medicine be administered in more responsive cases with specific symptoms. Subsequent publication of a study of individual Kampo medicines with more sensitive design is awaited.

12. Abstractor and date
Nakata H, 1 April 2008, 8 August 2009.
### Reference


### 1. Objectives

To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-sho-based (非随証) Kampo medicines for gynecological disease.

### 2. Design

Quasi-randomized controlled trial (quasi-RCT).

### 3. Setting

Departments of Obstetrics and Gynecology, Tokyo Women’s Medical University (1) and Keio University Hospital (2).

### 4. Participants

(1) Seventy women receiving ambulatory treatment for climacteric disorders between November 2000 and January 2002.

(2) One hundred women receiving ambulatory treatment for climacteric disorders between January 1993 and December 2000.

### 5. Intervention

Comparison of clinical efficacy of HRT and Kampo medicine

**Arm 1:** administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules, TSUMURA Kamishoyosan (加味逍遙散) Extract Granules or TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=70).

**Arm 2:** continuous coadministration of 0.625 mg t.i.d. of Premarin (conjugated equine estrogen) and 2.5 mg of Provera (medroxyprogesterone acetate) before meals for 4–8 weeks (n=110).

Evaluation of the efficacy of non-sho-based therapy with three major Kampo medicines for gynecological disease.

**Arm 1:** administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules before meals for 4–8 weeks (n=23).

**Arm 2:** administration of 2.5 g t.i.d. of TSUMURA Kamishoyosan (加味逍遙散) Extract Granules before meals for 4–8 weeks (n=23).

**Arm 3:** administration of 2.5 g t.i.d. of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=24).

### 6. Main outcome measures

Presence/absence and improvement of symptoms self-evaluated on a 4-point symptom severity scale using the Keio modified menopause index questionnaire.

### 7. Main results

Overall response rates for HRT and Kampo therapy were comparable (78.0% responders to HRT and 68.6% responders to Kampo therapy), although improvement was greater in patients receiving Kampo therapy (severity reduced by 2 or more points in 83.0% of patients receiving HRT and 21.4% of those receiving Kampo therapy). There was no difference in the percent who responded to the three non-sho-based therapies (65.2% were responders to tokishakuyakusan, 74.0% were responders to kamishoyosan, and 70.8% responders to keishibukuryogan). Kampo therapy was particularly effective for psychiatric manifestations including excitability, depression, irritability, anxiety, and brooding.

### 8. Conclusions

Using the same questionnaire, this study demonstrated that Kampo therapy has some effect on climacteric disorders, in particular, relieving subjective symptoms at almost the same rate as HRT and showing high efficacy against psychotic manifestations.

### 9. From Kampo medicine perspective

None.

### 10. Safety assessment in the article

None.

### 11. Abstractor’s comments


### 12. Abstractor and date


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**Genitourinary Tract Disorders (including Climacteric Disorders)**
Genitourinary Tract Disorders (including Climacteric Disorders)

References

1. **Objectives**
To investigate the equivalence between non-extracted keishibukuryogan (桂枝茯苓丸) and keishibukuryogan (桂枝茯苓丸) extract.

2. **Design**
Randomized controlled trial (RCT).

3. **Setting**
Twenty facilities (the Department of Obstetrics and Gynecology, Osaka City University School of Medicine, the Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, the Department of Obstetrics and Gynecology, Osaka Medical College School of Medicine, et al.).

4. **Participants**
One-hundred and ninety-three patients who were diagnosed with climacteric disorders during a 1 year and 5 month period from November 1999 to March 2001, untreated with hormone replacement therapy within 4 weeks before the start of the study, and having body mass index (BMI) ≥20 and body fat <35%. (The per-protocol population included 158 out of these 193 patients).

5. **Intervention**
Arm 1: oral administration of 6 keishibukuryogan (桂枝茯苓丸) pills containing 5 ingredients (TK-061) t.i.d. (18 tablets/day), n=75.
Arm 2: oral administration of 2.5 g of TEIKOKU Keishibukuryogan (桂枝茯苓丸) Extract Granules (TKK-25) t.i.d. (7.5 g/day), n=83.

6. **Main outcome measures**
Simple Menopause Index (SMI) improvement rated on a 5-point scale; improvement in blood stasis score; changes in blood hormone concentrations; adverse events.

7. **Main results**
Response rate to TK-061 and TKK-25 were similar (55.8% vs 51.0%, respectively). Blood stasis score was decreased with time after the start of treatment to similarly reduced levels for both arms at week 8. Blood concentrations of estradiole (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) remained unchanged from baseline. The incidences of adverse drug reactions were similar: 22.4% with TK-061 and 23.2% with TKK-25. These adverse drug reactions disappeared naturally or were relieved by symptomatic therapy, suggesting that a causal relationship with treatment cannot be ruled out.

8. **Conclusions**
TK-061 was equivalent or superior to TKK-255 in increasing the SMI improvement rating, the primary endpoint. Both increased blood stasis score to a similar extent. In addition, neither affected the endocrine system.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
Adverse events occurred in 22 patients receiving keishibukuryogan pills (22.4%) and 23 patients receiving keishibukuryogan extract granules (23.2%). No serious adverse events occurred. Adverse drug reactions occurred in 12 patients (12.2%) and 9 patients (9.1%), respectively. The global safety was “satisfactory” in 79 patients (80.6%) and 88 patients (88.9%), respectively.

11. **Abstractor’s comments**
This paper describes a clinical trial comparing keishibukuryogan pills to its extracted formulation, and demonstrates the efficacy of both for climacteric symptoms. Regrettably, however, ganzai (丸剤, pills), which proved more effective than the extract in the per-protocol population, is not on the NHI Drug Price list. For the moment, keishibukuryogan pill is only available as an OTC drug.

12. **Abstractor and date**
Nakata H, 1 April 2008, 8 August 2009.
**Genitourinary Tract Disorders (including Climacteric Disorders)**

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1. **Objectives**
   To evaluate the efficacy of unkeito unkeito (温経湯) for climacteric disorders with depressive symptoms.

2. **Design**
   Randomized cross-over controlled trial (RCT-cross over).

3. **Setting**
   One university hospital and one clinic.

4. **Participants**
   Twenty-four women with climacteric disorders with depressive symptoms and unresponsive to hormone replacement therapy (HRT).

5. **Intervention**
   Arm 1: administration of 7.5 g/day of unkeito (温経湯) extract granules for 6 months followed by administration of 7.5 g/day of tokishakuyakusan (当帰芍薬散) extract granules for 6 months, with 1-month washout between interventions.
   Arm 2: administration of 7.5 g/day of tokishakuyakusan (当帰芍薬散) extract granules for 6 months followed by administration of 7.5 g/day of unkeitounkeito (温経湯) extract granules for 6 months, with 1-month washout between interventions.
   HRT was continued in both arms.

6. **Main outcome measures**
   Zung’s Self-Rating Depression Scale (ZSDS), State-Trait Anxiety Inventory (STAI-1, 2).

7. **Main results**
   Administration of unkeito produced significant improvement in ZSDS and STAI-1, 2 at 3 months, which persisted to 6 months. The improvement in ZSDS and STAI-1, 2 was significantly greater after unkeito than tokishakuyakusan at both 3 months and 6 months.

8. **Conclusions**
   Unkeito is effective as an adjuvant therapy for climacteric disorders with depressive symptoms in patients unresponsive to HRT, and has superior efficacy to that of tokishakuyakusan.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    No adverse drug reactions occurred.

11. **Abstractor’s comments**
    This study is a randomized cross-over trial of unkeito and tokishakuyakusan. It suggests that the mechanism of efficacy is the promotion of secretion of cytokine-induced neutrophil chemoattractant (CINC).

12. **Abstractor and date**
Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

1. **Objectives**
   To compare the efficacy of keishibukuryogan (桂枝茯苓丸) and hormone replacement therapy (HRT) for relief of hot flashes and chills.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College.)

4. **Participants**
   Three-hundred and fifty-two postmenopausal patients with hot flashes untreated with HRT in the past 3 months and without past history of chronic diseases, aged 46–58 years. Patients with coronary artery anomaly, thrombotic diseases, cerebral infarction, hypertension, renopathy, and allergic conditions were excluded.

5. **Intervention**
   Arm 1: oral administration of 2.5 g of TSUMURA Keishibukuryogan (桂枝茯苓丸) (TJ-25) t.i.d. (daily dose 7.5 g).
   Arm 2: oral administration of 0.625 mg of Premarin and 2.5 mg of Provera s.i.d. (i.e., HRT).

6. **Main outcome measures**
   Peripheral blood flow, measured pre- and post-administration by a laser Doppler velocimeter at 3 sites (jaw, finger tips, and toes).

7. **Main results**
   Both HRT and keishibukuryogan reduced blood flow in the jaw and finger tips. Blood flow in the toes was increased by keishibukuryogan but unchanged by HRT.

8. **Conclusions**
   Keishibukuryogan is effective for chills, especially in the legs, in patients with hot flashes. HRT is ineffective for chills. Although both HRT and keishibukuryogan are effective for hot flashes, the latter is more effective.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This study is a controlled trial of HRT and keishibukuryogan. It ensures objectivity by measuring hot flashes and chills in terms of blood flow. It would also be interesting to investigate how well these medicines change blood flow in patients without hot flashes.

12. **Abstractor and date**
    Nakata H, 1 April 2008, 8 August 2009.
# References


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## 1. Objectives

To evaluate the usefulness of Kampo medicine for treatment of depressive patients refractory to hormone replacement therapy (HRT).

## 2. Design

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

## 3. Setting

None (the authors belonged to the Department of Obstetrics and Gynecology, Kanazawa University School of Medicine).

## 4. Participants

Twenty-four depressive outpatients who visited the menopause clinic and were unresponsive to 6 months of HRT.

## 5. Intervention

Arm 1: combination of 6-month administration of HRT (1 sheet/2 days administration of estradiol formulation [dose not indicated] and 10-day administration of 5 mg/day of medroxyprogesterone) and 2.5 g of TSUMURA Unkeito (温経湯), (TJ-106) t.i.d, n=12.  
Arm 2: combination of 6-month administration of HRT (1 sheet/2 days administration of estradiol formulation [dose not indicated] and 10-day administration of 5 mg/day of medroxyprogesterone) and 2.5 g of tokishakuyakusan (当帰芍薬散) (TJ-23) t.i.d, n=12.  
Patients were crossed over to the other treatment after 6 months with 1-month washout between arms.

## 6. Main outcome measures

Changes in Self-Rating Depression Scale (SDS) and State Trait Anxiety Inventory (STAI) scores after 6-month treatment with the unkeito or tokishakuyakusan combination.

## 7. Main results

In arm 1, SDS depression score was significantly decreased ($P<0.01$, testing method not indicated). STAI state and trait anxiety scores were significantly improved ($P<0.01$, testing method not indicated).

## 8. Conclusions

HRT + unkeito combination therapy is effective for relief of HRT-refractory depression.

## 9. From Kampo medicine perspective

None.

## 10. Safety assessment in the article

None.

## 11. Abstractor’s comments

This paper is based on the previously published “Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine Unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. Clinical Neuropharmacology 2004; 27: 157-62.” This study demonstrated the efficacy of unkeito for depressive and anxiety symptoms refractory to HRT administered as treatment for climacteric disorders. However, something seems wrong with the definition of “depressive and anxiety symptoms refractory to hormone replacement therapy.” Kampo medicine as treatment of depressive and anxiety symptoms would be better assessed in comparison with antidepressants and anxiolytics. In addition, the statement in the text that 3-month oral administration produced an effect lasting 6 months raises the concern that a 1-month washout in the cross-over comparison is sufficient. Future research is expected.

## 12. Abstractor and date

Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

1. Objectives
To compare the effects of unkei-to (温経湯) and vitamin E on peripheral blood flow.

2. Design
Randomized controlled trial (RCT).

3. Setting
Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine.

4. Participants
One hundred and eighty post-menopausal women (42–61 years old) with chilly sensation in the lower extremities and no treatment by hormone replacement within 3 months.

5. Intervention
Arm 1: administration of unkei-to (温経湯) (TSUMURA Unkeito Extract Granules 7.5 g/day) for 8 weeks (60 patients; of these, 58 were included for analysis).
Arm 2: administration of vitamin E (tocopherol nicotinate 600 mg/day) for 8 weeks (60 patients; of these, 55 were included for analysis).
Arm 3: no treatment for 8 weeks (60 patients; of these 48 were included for analysis).

6. Main outcome measures
Items evaluated by questionnaire on a 4-point scale and submandibular, middle finger, and middle toe blood flow measured by Doppler.

7. Main results
Chilly sensation evaluated by questionnaire was significantly improved in arm 1. Doppler blood flow evaluation revealed improved peripheral blood flow in the lower extremities in arm 1 and arm 2. While vitamin E significantly increased middle finger blood flow, unkei-to suppressed blood flow (that was originally too high) and increased poor blood flow.

8. Conclusions
Unkei-to is superior to vitamin E in improving blood flow and reducing chill.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No special problems noted.

11. Abstractor’s comments
This paper compared the ability of unkei-to and vitamin E to improve peripheral blood flow. It concluded that unlike vitamin E, unkei-to improves chill by increasing poor circulation and improves hot flushes by decreasing excessive blood flow, well characterizing the Kampo medicine.

12. Abstractor and date
Nakata H, 10 January 2009, 8 August 2009.
Ante/Post-partum Diseases

1. **Objectives**
   To evaluate the efficacy of kyukikyogaito as a therapeutic drug for imminent abortion in patients with uterine hemorrhage.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College and the Department of Obstetrics and Gynecology, Takatsuki Red Cross Hospital.)

4. **Participants**
   Seventy-two patients who visited the hospital with a complaint of uterine hemorrhage and were given a diagnosis of imminent abortion.

5. **Intervention**
   Arm 1: bed rest and administration of 2.5 g of TSUMURA Kyukikyogaito Extract Granules (TJ-77) t.i.d. (n=36).
   Arm 2: bed rest and administration of human chronic gonadotropin (hCG) (alternate-day administration of 5,000 U) (n=36).

6. **Main outcome measures**
   EFS (echo free space), number of days to hemostasis.

7. **Main results**
   Statistical analysis was carried out using the chi-square test and Wilcoxon’s signed-rank test. Significantly fewer days were required for hemostasis and for EFS disappearance in arm 1 (both \( P < 0.0001 \)). EFS on day 7 of treatment was significantly smaller in arm 1 \( (P<0.0001) \).

8. **Conclusions**
   Kyukikyogaito (TJ-77) shortens the time to hemostasis in patients with imminent abortion and uterine hemorrhage.

9. **From Kampo medicine perspective**
   The explanation of the efficacy of kyukikyogaito for imminent abortion is based on the blood replenishing effect of toki, shakuyaku, and senkyu as well as the hemostatic effect of akyo and gaiyo.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This paper shows that EFS disappears significantly earlier in patients with imminent abortion after treatment with a Kampo medicine. Considering that in principle, bed rest is the only treatment for imminent abortion with no effective therapeutic method having been established, the effects of kyukikyogaito are worthy of attention. However, without significant differences in the final outcome of fetal mortality, kyukikyogaito is reasonably considered to have limited efficacy and to contribute to better patient QOL through a reduction in length of hospital stay, etc.

12. **Abstractor and date**
    Nakata H, 1 April 2008, 8 August 2009.
**Ante/Post-partum Diseases**

**Reference**
Ichushi Web ID: 2002032923 MOL, MOL-Lib

1. **Objectives**
To evaluate the usefulness of kyukichoketsuin (キュウ帰調血飲) for control of puerperium.

2. **Design**
Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
None (authors belong to the Department of Obstetrics and Gynecology, Yamato Municipal General Hospital).

4. **Participants**
Forty-seven puerperants, who had a vaginal delivery after the 36th week of pregnancy and no abnormal bleeding of more than 1,000 mL, were randomized to receive either kyukichoketsuin or methylergometrine maleate.

5. **Intervention**
   - Arm 1: oral administration of 1 sachet (2.0 g) of TAIKODO Kyukichoketsuin (キュウ帰調血飲) Extract Granules (EK-230) t.i.d. (n=23)
   - Arm 2: oral administration of 1 tablet (0.125 mg) of Metenarin t.i.d. (n=24)

6. **Main outcome measures**
Uterine volume, length of uterine fundus, lower abdominal pain score, and amount of lactation during 1 to 5 days postpartum. Improvement in outcome measures compared between groups. Adverse drug reactions: described symptoms.

7. **Main results**
   - Statistical analysis used t-test, chi-square test, and Wilcoxon’s signed-rank test. There was no significant between-group difference in uterine volume or length of uterine fundus. Lower abdominal pain was significantly less frequent in patients receiving kyukichoketsuin on postpartum days 1 ($P<0.0028$), 2 ($P<0.0005$), and 4 ($P<0.0232$). Patients receiving kyukichoketsuin secreted significantly more milk on postpartum days 3 ($P<0.0345$), 4 ($P<0.0368$), and 5 ($P<0.0177$). Regarding safety, pain associated with uterine contraction was so severe in patients receiving Metenarin as to preclude continued treatment in 2 patients, whereas no adverse drug reactions occurred in the kyukichoketsuin group.

8. **Conclusions**
Kyukichoketsuin could be an alternative medication to methylergometrine maleate.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
   - Treatment was discontinued in two patients receiving methylergometrine maleate because of severe lower abdominal pain (associated with uterine contraction), whereas no adverse drug reactions occurred in the kyukichoketsuin group.

11. **Abstractor’s comments**
The routine use of postpartum methylergometrine maleate has been criticized and is now limited only to cases such as uterine subinvolution. Therefore, this paper highlighting the effect of kyukichoketsuin, which is associated with few adverse drug reactions, is meaningful. However, since this paper does not address the effect of suckling stimulation and breast massage on uterine contraction and lactation promotion, further investigation of the effectiveness of oral kyukichoketsuin is expected.

12. **Abstractor and date**
Nakata H, 1 April 2008, 8 August 2009.
Ante/Post-partum Diseases

References


1. **Objectives**
   To evaluate the efficacy and safety of kyukichoketsuin (キュウ帰調血飲) for puerperal psychosomatic disorder.

2. **Design**
   Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. **Setting**
   Osaka Medical College Hospital and associated facilities.

4. **Participants**
   One-hundred and seventy-one women who had a normal delivery.

5. **Intervention**
   Arm 1: daily administration of 6.0 g/day of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granules for up to 1 month from the day of delivery (n=85).
   Arm 2: administration of 0.375 mg/day of ergometrine (n=86).

6. **Main outcome measures**
   Length of uterine fundus, blood hemoglobin concentration, body temperature, and amount of lactation measured 1 to 6 days postpartum.
   Lochia, lactation, and mental state evaluated by questionnaire.

7. **Main results**
   In arm 1, uterine contraction on postpartum day 5 was significantly greater, blood hemoglobin concentration was significantly higher, and mean amount of lactation was significantly increased from postpartum day 4 onward. The number of patients with subjectively rated depression in arm 1 was approx. half that in arm 2.

8. **Conclusions**
   Kyukichoketsuin is more effective than ergometrine for some patients with puerperal psychosomatic symptomatology.

9. **From Kampo medicine perspective**
   The crude-drug components of kyukichoketsuin associated with oxytocic, lactogenic, or psychotropic activity are mentioned in the discussion.

10. **Safety assessment in the article**
    No adverse drug reactions occurred in either arm.

11. **Abstractor’s comments**
    In Japan, randomization by the RCT-envelope method tends not to be maintained. This study suggests the partial efficacy of kyukichoketsuin for some patients with puerperal psychosomatic symptoms. Kyukichoketsuin is also known by a name of kyukihoketsuto and considered to be effective for various postpartum symptoms including giketsukyoson (気血虚損, qi and blood deficiencies), hiikyoyaku (脾胃虚弱, hypofunctioning of the spleen and stomach), orofugyo (惡露不行, lochiometra), kyoketsukata (去血過多, hypermenorrhea), inshokusissetsu (飲食失節, crapula), and dokisosho (怒氣相衝, anger) (*Manbyokaishun [万病回春]: Recovery from All Ailments]*).

12. **Abstractor and date**
Ante/Post-partum Diseases

Reference

1. Objectives
To evaluate the clinical usefulness of kyukichoketsuin (キュウ帰調血飲) for “postpartum restoration”

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

3. Setting
Single facility (Wada Obstetric and Gynecologic clinic).

4. Participants
Sixty multiparas who visited the above facility between January and the end of December 2001 and had a normal delivery.

5. Intervention
Arm 1: administration of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Granules (EK-230) 2.0 g t.i.d. (before meals) from immediately to 2 weeks postpartum in 30 patients.
Arm 2: administration of methylergometrine maleate (MME) 0.125 mg t.i.d. (after meals) from immediately to 5 days postpartum in 30 patients.

6. Main outcome measures
Uterine subinvolution: evaluated based on the length of the uterine fundus at 1 and 4 days postpartum and the amount of lochia at 1 month postpartum.
Amount of lactation: evaluated based on the amount of lactation at 4 days postpartum and the amount of lactation expressed as a percentage of the lactation amount after the previous delivery.
Clinical symptoms: complaint of afterpains evaluated by interview.
Drug compliance: evaluated on a 4-point scale by interview.

7. Main results
There was no between-group difference in the length of uterine fundus (11.4±0.7 cm [kyukichoketsuin] vs 11.8±2.8 cm [MME]) at 4 days postpartum and lactation at 4 days postpartum. The lactation index (i.e., amount of lactation in relation to the amount for the previous delivery of 100) was 81.7±15.0 with MME and 136.7±71.0 with kyukichoketsuin, showing a lactation-promoting effect of kyukichoketsuin, although the difference was not significant. There were more complaints of afterpains in the MME group (46.7%) than in the kyukichoketsuin group (23.3%). Drug compliance was significantly higher in patients receiving kyukichoketsuin (P<0.001).

8. Conclusions
Compared with MME, kyukichoketsuin (“a medicine for postpartum restoration”) is a better restorer of postpartum health and some physiological functions in puerperants.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstrator’s comments
This study follows up a randomized study published in 2002 that verified the efficacy of kyukichoketsuin for “postpartum restoration” as described in Manbyokaishun (万病回春, Recovery from All Ailments) using objective parameters. The present results showing that kyukichoketsuin has clinical efficacy support the results of the previous study. The psychosomatic condition of postpartum health is referred to as “giketsukyoson (気血虚損, qi and blood deficiencies)” in Kampo medicine, for which kyukichoketsuin is indicated. It is hoped that “giketsukyoson,” a Kampo medical pathology, will be scientifically elucidated based on objective clinical parameters as in the present study.

12. Abstrator and date
Ushiroyama T, 1 April 2008, 8 August 2009.
Ante/Post-partum Diseases

Reference

1. Objectives
To evaluate the clinical usefulness of kyukichoketsuin during puerperium.

2. Design
A randomized controlled trial (RCT).

3. Setting
Department of Obstetrics and Gynecology, Ogori-Daiichi General Hospital.

4. Participants
Eighty women who had normal vaginal delivery at the above facility between July 2000 and March 2001.

5. Intervention
Arm 1: postpartum administration of an oral antibiotic for 5 days + kyukichoketsuin (キュウ帰調血飲) (manufacturer not specified) 2.0 g t.i.d. before meals for 4 weeks, n=40.
Arm 2: postpartum administration of an oral antibiotic and methylergometerine maleate for 5 days, n=40.

6. Main outcome measures
Incidence of poor uterine contraction at 4 weeks postpartum, amount of milk sucked at 2 days postpartum, percentage of participants with ≥15 g/day of lactation, total amount of milk sucked, and incidences of “maternity blues” and depression at 5 days postpartum.

7. Main results
No poor uterine contraction or intrauterine infection occurred in either arm. Those receiving Kampo medicine suffered significantly less afterbirth pains (P<0.05). Kampo medicine suppressed the decrease in newborn weight in all participants, especially in primiparas (P<0.05). Postpartumly, kyukichoketsuin significantly reduced the frequency of hot flushes and twilight state. There was no between-arm difference in the incidence of maternity blues and no incidence of depression in either arm.

8. Conclusions
Kyukichoketsuin safely promotes the physical and mental restoration of puerperants, ultimately contributing to growth of newborns.

9. From Kampo medicine perspective
The increase in lactation is due to the ingredients of kyukichoketsuin (jio [地黄], toki [当帰], kobushi [香附子], chinpi [陳皮], and uyaku [烏薬]), which are also involved in nutritional fortification and physical reconditioning. In addition, kobushi and uyaku have a qi-conditioning effect and prevent postpartum depression.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study verified the efficacy of kyukichoketsuin for “restoration of the postpartum psychosomatic condition” as described in Manbyokaishun (万病回春, Recovery from All Ailments). Although difference in uterine contraction should have been evaluated by measuring the length of the uterine fundus, the study should be praised for evaluating lactation by accurately measuring the amount of sucked milk. Biological evidence of the contribution of mental and physical factors to the restoration of puerperants should be sought. Scientific verification of the efficacy of kyukichoketsuin in various combinations (frequent in Manbyokaishun) is desired.

12. Abstractor and date
Ante/Post-partum Diseases

Reference

1. Objectives
To evaluate the postpartum lactation-promoting effect and safety of kyukichoketsuin (キュウ帰調血飲).

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

3. Setting
Osaka Medical College Hospital.

4. Participants
Eighty-two women who had normal spontaneous delivery.

5. Intervention
Arm 1: TAIKODO Kyukichoketsuin (キュウ帰調血飲) Extract Granules (Kanebo) 2.0 g t.i.d. for 6 days, n=41.
Arm 2: methylergometerine maleate 0.375 mg/day in 3 divided doses for 6 days, n=41.

6. Main outcome measures
Amount of lactation, blood prolactin concentration.

7. Main results
The amount of lactation was significantly increased in arm 1 on day 4 to 276.5±21.4 g (compared with 155.3±61.2 g in arm 2; \( P < 0.042 \)), on day 5 to 342.6±43.6 g (compared with 245.5±59.4 g in arm 2; \( P < 0.038 \)), and on day 6 to 413.7±68.1 g (compared with 293.3±98.5 g in arm 2; \( P < 0.046 \)). In addition, blood prolactin concentration was significantly elevated in arm 1 (compared with arm 2) on day 1 (\( P < 0.037 \)) and 6 (\( P < 0.0024 \)) after delivery.

8. Conclusions
Kyukichoketsuin may increase postpartum lactation.

9. From Kampo medicine perspective
Mentioned in discussion.

10. Safety assessment in the article
No adverse drug reactions occurred.

11. Abstractor's comments
While in Japan the RCT-envelope method of allocation often fails to maintain randomization, this study can suggest that kyukichoketsuin increases postpartum lactation. Kyukichoketsuin, also known as kyukihoketsuto, is considered to be effective for various postpartum symptoms including giketsukyoson (気血虚損, qi and blood deficiencies), hiikyokaku (脾胃虚弱, hypofunctioning of spleen and stomach), orofugyo (惡露不行, lochiometra), kyoketsukata (去血過多, hypermenorrhea), inshokusissetsu (飲食失節, crapula), and dokisosho (怒気相衝, anger) (Manbyokaishun [万病回春], Recovery from All Ailments).

12. Abstractor and date
Ante/Post-partum Diseases

Reference

1. Objectives
To determine a Kampo medicine effective for relieving the feeling of lactation deficiency.

2. Design
Randomized controlled trial (RCT).

3. Setting
None (authors belong to the Department of Obstetrics and Gynecology, Fukuda Hospital).

4. Participants
Seventy-two puerperants who complained of feeling of lactation deficiency at 4 to 6 days postpartum between September 2002 and February 2002.

5. Intervention
Arm 1: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules t.i.d.
Arm 2: oral administration of 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d.
Arm 3: oral administration of 2.5 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granules t.i.d.
Arm 4: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules combined t.i.d.
Arm 5: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) Extract Fine Granule combined t.i.d.
Arm 6: oral administration of 2.5 g of TSUMURA Kikyoto (桔梗湯) Extract Granules t.i.d.
Arm 7: breast massage.

6. Main outcome measures
Total score from a questionnaire evaluating the amount of breast milk, degree of breast engorgement, milk supplementation, and satisfaction on a 10-point scale.

7. Main results
At 3 weeks after treatment, the score in the juzentaihoto monotherapy group was significantly higher than those in the kyukichoketsuin monotherapy, kakkonto + juzentaihoto combination therapy, and kikyoto monotherapy groups, but not significantly different from that in the breast massage group.

8. Conclusions
Juzentaihoto is effective treatment for feeling of lactation deficiency.

9. From Kampo medicine perspective
Administration according to “sho (証, pattern/syndrome)” is recommended.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This study is valuable because it demonstrates the differing effects among Kampo prescriptions on lactation after birth and the importance of therapy according to sho. However, given that there was no significant effect on lactation deficiency and no difference between juzentaihoto and breast massage, the present data fail to provide evidence for an effect of juzentaihoto as a stimulant of lactation. Further investigations including combined use with breast massage are expected.

12. Abstractor and date
Nakata H, 1 April 2008, 8 August 2009.
**Evidence Reports of Kampo Treatment 2009**
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

### Ante/Post-partum Diseases

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1. **Objectives**
   To determine whether rikkunshito (六君子湯) combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   One hospital (one obstetrics and gynecology clinic).

4. **Participants**
   One hundred and twenty pregnant women (duration of pregnancy ≥ 5 months) with a hemoglobin (Hb) level of less than 11.0 g/dL, a hematocrit (Ht) of less than 33%, and a mean corpuscular volume (MCV) of less than 85 μm³.

5. **Intervention**
   Arm 1: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d., and rikkunshito (六君子湯) 2.5 g t.i.d. for 14 days in patients with a mean age of 28.2 (20 - 42) years and a mean gestational age of 28.7 (18 - 38) weeks.
   Arm 2: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d. for 14 days in patients with a mean age of 28.8 (20 - 38) years and a mean gestational age of 28.4 (18 - 37) weeks.

6. **Main outcome measures**
   Post-treatment Hb level.

7. **Main results**
   Increase in Hb from the pre-treatment level was significantly greater after the sodium ferrous citrate plus rikkunshito therapy (arm 1; 0.8 [2.4 to -0.9] g/dL) than after sodium ferrous citrate monotherapy (arm 2; 0.3 [2.1 to -1.2] g/dL) (P=0.002). Also, oral administration of sodium ferrous citrate was better tolerated in arm 1.

8. **Conclusions**
   It was suggested that rikkunshito combined with oral iron for anemia in pregnancy is effective for reducing adverse reactions associated with the administration of iron.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    There were no adverse reactions to rikkunshito treatment.

11. **Abstractor’s comments**
    Oral iron preparations are commonly associated with gastrointestinal adverse reactions. Thus, many patients stop the treatment. Great clinical relevance is suggested by the present results, which showed that treatment with iron could be continued in combination with rikkunshito. Although this study was classified as an RCT because of the random assignment, data necessary for the assessment of bias, including the presence or absence of blinding, were inadequate, and further assessment cannot be made. Further studies are expected.

12. **Abstractor and date**
1. **Objectives**
   To confirm the efficacy of kyukichoketsuin (キュウ帰調血飲) for the “maternity blues.”

2. **Design**
   Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. **Setting**
   Osaka Medical College Hospital and associated facilities.

4. **Participants**
   Two-hundred and sixty-eight puerperants who had a normal single delivery and no pregnancy toxemia, diabetes mellitus, premature rupture of the membrane, etc. They were randomized to either kyukichoketsuin group or control group.

5. **Intervention**
   Arm 1: administration of 2.0 g of Kanebo Kyukichoketsuin (キュウ帰調血飲) t.i.d., n=134.
   Arm 2: control group without treatment, n=134.

6. **Main outcome measures**
   Four items (including mood swings, crying over 5 min, and irritation) as judged by questionnaire.
   Depressive symptoms as judged on the Edinburgh Postpartum Depression Scale.
   Maternity blues as judged on a self-rating maternity blues scale.

7. **Main results**
   Within 3 weeks postpartum, the kyukichoketsuin group had significantly decreased incidences of moderate or severe depressive symptom, crying lasting over 5 minutes, irritation, and maternity blues. During 3 to 6 weeks postpartum, there was no significant difference between arms. The incidence of maternity blues, especially within 3 days postpartum, was decreased in the kyukichoketsuin group.

8. **Conclusions**
   Kyukichoketsuin can be used to stabilize postpartum mood.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    No adverse drug reactions occurred.

11. **Abstractor’s comments**
    This study provides objective evidence for efficacy of kyukichoketsuin in the treatment of classic postpartum maternity blues. Maternity blues disappear within 3 weeks postpartum and are followed up without treatment in clinical practice. Thus, in emphasizing importance of postpartum care, this study seems significant. Further study results are expected.

12. **Abstractor and date**
    Nakata H, 1 April 2008, 8 August 2009.
Symptoms and Signs

Reference

1. Objectives
To evaluate the efficacy of bakumondo-to (麦門冬湯) for persistent cough after infection in the elderly.

2. Design
Randomized controlled trial (RCT).

3. Setting
Two hospitals and three clinics.

4. Participants
Two-thousand and sixty-nine patients with intense dry cough persisting for 3 weeks or more after common cold syndrome, aged ≥ 65 years.

5. Intervention
Arm 1: administration of TSUMURA Bakumondo-to (麦門冬湯) Extract granules 3.0 g t.i.d. between meals (n=1,039).
Arm 2: administration of fominoben hydrochloride 160 mg in three divided doses between meals (n=1,030).

6. Main outcome measures
Antitussive effect
Salivation degree, skin temperature, joint pain
Pain improvement rating
Global improvement rating

7. Main results
The antitussive effect and reduction in sputum expectoration (as measured on a visual analogue scale [VAS]) was superior in arm 1 than arm 2. Improvement in the following items after treatment, compared with baseline, was significant only in arm 1: the amounts of salivation and lacrimation determined by Saxon’s test and Schirmer’s test; joint pain judged on a VAS; and skin temperature measured with an upper and lower extremity-patch-type skin temperature indicator.
On the global scale, improvement, principally in cough, was better in arm 1 than arm 2. The condition of 89.5% of patients in arm 1 and 46.9% in arm 2 was rated “improved or better,” showing the significantly higher efficacy of bakumondo-to.

8. Conclusions
Bakumondo-to was effective for not only cough but other symptoms in the elderly.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor's comments
The “total-disease-related symptoms,” a scale for acute pain severity developed by the present authors, is not described but referenced to their previous paper. This, however, should be detailed since the title refers to pain severity. In addition, except for the global improvement rating, the specific numbers of patients are not indicated, except in the graphs, making evaluation of the efficacy for pain impossible.

12. Abstractor and date
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Symptoms and Signs

References

1. Objectives
To evaluate the efficacy and safety of goreisan (五苓散) for vomiting in young children.

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

3. Setting
A single facility (the department of pediatrics of a hospital).

4. Participants
Thirty-five patients who vomited three or more times within 24 hr before visiting the pediatric department and experienced vomiting/nausea during the visit. One of these patients ejected the medicine immediately after insertion and was excluded, resulting in the inclusion of 34 patients (21 males and 13 females, aged 1 – 9 years with a mean of 3.9 years) for analysis.

5. Intervention
Arm 1: administration of a home-prepared suppository containing 1 g of TSUMURA Goreisan (五苓散) Extract Granules (n=16, 10 males and 6 females).
Arm 2: administration of a home-prepared suppository containing 1 g of TSUMURA Hochuekkito (補中益気湯) Extract Granules (n=18, 11 males and 7 females).

6. Main outcome measures
Complete response (disappearance of both vomiting and nausea); partial response (presence of nausea without vomiting); and no response (vomiting of supplied water).

7. Main results
The distribution of baseline characteristics (age, sex, underlying disease, frequency of vomiting, and complication with diarrhea) were similar between arms. Complete response, partial response, and no response were achieved in 12 (75%), 2, and 2 patients receiving goreisan, and in 5 (28%), 2, and 11 patients receiving hochuekkito, respectively. The difference between arm 1 and arm 2 was statistically significant (P<0.05).

8. Conclusions
Goreisan suppository reduced vomiting and nausea in young children more effectively than hochuekkito suppository.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No adverse drug reactions occurred.

11. Abstractor's comments
Goreisan is generally indicated for thirst, decreased urine output, and gastrointestinal diseases such as watery diarrhea and acute gastroenteritis with nausea, vomiting abdominal pain, headache, or edema. This study demonstrated the efficacy of goreisan suppository (in-home formulation) for reducing acute vomiting in young children. The usefulness has also been demonstrated in a multicenter, double-blind study, as mentioned below. Since the study period was in winter, the target diseases included common-cold-associated dyspepsia, winter diarrhea, vomiting, and common cold. Since it is generally difficult to administer a medicine orally or by drip infusion to young children with vomiting, the suppository is considered to be a clinically useful alternative dosage form. Therefore, it is very meaningful that this study demonstrated usefulness. However, this paper does not describe the methods of randomization and statistical analysis, which should be specified. In addition, another Kampo medicine and not a true placebo was used as the control, therefore it would be useful in the future to conduct a placebo-controlled study. Future development is expected. Notably, the formulation of goreisan extract is only approved for oral use, not for use in suppositories.
A multicenter, case-series study with the same design and evaluation methods. The study population consisted of 87 patients (43 males and 44 females, aged 0 – 9 years with a mean of 2.4 years). Complete response was achieved in 72 patients (83%), and partial response in 2 patients. No difference in efficacy for underlying diseases was shown; complete response was achieved in 43 (88%) of 49 patients with winter infantile diarrhea, 22 (76%) of 29 patients with common-cold-associated diarrhea, and 5 (83%) of 5 patients with acute gastroenteritis. No difference in baseline characteristics was shown; there was no statistically significant difference in age, frequency of vomiting, complication with diarrhea, and use of enema between patients with complete or partial response, and patients with no response.

12. Abstractor and date
Symptoms and Signs

Reference

1. Objectives
To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for relief of muscle cramp.

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

3. Setting
A total of 23 nationwide facilities including university hospitals (departments of internal medicine and gastroenterology).

4. Participants
One-hundred and twenty-six patients with 2 or more episodes of muscle cramp weekly during the observation period (4 or more bi-weekly), aged ≥20 years and ≤70 years. These patients were also taking other drugs for a variety of problems including serious hepatic, renal, and cardiac diseases, pregnancy, hepatic failure, complications of hepatocellular carcinoma, electrolyte abnormality, and hypertension. After excluding 12 ineligible patients and 13 with incomplete data, 101 patients were included for statistical evaluation.

5. Intervention
Arm 1: administration of 7.5 g/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules in 3 divided doses (before meals) for 2 weeks following a 2-week observation period (n=65).
Arm 2: administration of the same dose of placebo granules at the same frequency for 2 weeks following a 2-week observation period (n=61).

6. Main outcome measures
Frequency of episodes of muscle cramp, duration of each episode, severity of pain (at completion of the study compared with baseline values determined during the observation period).

7. Main results
The percentage of patients with frequency of muscle cramp episodes rated “improved” or higher was significantly larger in the shakuyakukanzoto group than in the placebo group (67.3% vs 37.5%, respectively). The percentage of patients with improved final global rating, which takes duration of each episode and severity of pain into account, was significantly larger in the shakuyakukanzoto group (69.2% vs 28.6%, respectively). The percentage of patients with a utility rating of “useful” or higher was also significantly larger in the shakuyakukanzoto group (63.3% vs 34.1%, respectively).

8. Conclusions
Shakuyakukanzoto is a clinically useful Kampo formulation with excellent efficacy and safety for muscle cramp.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse drug reactions occurred in 7 patients (14.3%) receiving shakuyakukanzoto and 2 patients (4.9%) receiving placebo. The main adverse drug reaction was pseudoaldosteronism in the shakuyakukanzoto group and gastrointestinal symptoms in the placebo group. No serious adverse drug reactions occurred.

11. Abstractor's comments
This original article re-evaluates shakuyakukanzoto. The larger total amount of kanzo, contained in shakuyakukanzoto, is associated with higher incidence of pseudoaldosteronism. Since in the present study incidence of adverse drug reactions tended to be higher in the shakuyakukanzoto group, although there was no significant between-group difference in incidence, reduction in the dose is recommended in the future. This paper is similar to “Kumada T, Kiriyama I, Sone Y, et al. EBM-based Kampo therapy for gastrointestinal diseases 3. Efficacy of shakuyakukanzoto for “muscle cramps in the calves” associated with hepatic cirrhosis”. *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2003; 54: 536-8 (in Japanese)."

12. Abstractor and date
Symptoms and Signs

Reference

1. Objectives
To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for muscle cramps in the calves.

2. Design
Randomized controlled trial (RCT).

3. Setting
None.

4. Participants
Seventy-five patients with painful muscle cramps in the calves (PMC) associated with hepatic cirrhosis.

5. Intervention
Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (GJG) 30 mg/kg t.i.d. for 12 consecutive weeks, n=38.
Arm 2: oral administration of 50 mg/kg/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (SKT) in 3 divided doses for 12 consecutive weeks, n=37.

6. Main outcome measures
PMC rating (overall QOL, visual analog scale pain [VAS-P], face rating scale), QOL (modified health assessment questionnaire [MHAQ]), overall well-being (quality of well-being score), and psychological well-being (face scale).

7. Main results
GJG was significantly superior to SKT in improving the PMC rating and various QOL measures. The number of days until resolution of PMC was significantly shorter in the GJG group than in the SKT group.

8. Conclusions
Goshajinkigan is effective and safe for PMC associated with hepatic cirrhosis and is superior to shakuyakukanzoto in efficacy.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Adverse drug reaction symptoms and laboratory test abnormalities (increased AST, LDH, and CPK) were noted in 0 patients receiving goshajinkigan and 4 patients receiving shakuyakukanzoto, but these resolved after discontinuation of treatment.

11. Abstractor’s comments
This paper suggests that goshajinkigan may be the first-choice drug for PMC associated with hepatic cirrhosis.

12. Abstractor and date
Symptoms and Signs

Reference


1. Objectives
To evaluate the efficacy of goshuyuto (呉茱萸湯) for relief of chronic headache and to evaluate the associated adverse drug reactions.

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

3. Setting
Three university-associated outpatient headache clinics.

4. Participants
Fifty-three patients with chronic headache that responded to goshuyuto orally administered for 4 weeks.

5. Intervention
Arm 1: oral administration of 7.5 g/day of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules for 12 weeks (n=28).
Arm 2: oral administration of the same dose of placebo granules indistinguishable in appearance, taste, and odor from goshuyuto for 12 weeks (n=25).

6. Main outcome measures
Headache severity, headache frequency, and severity of cold, menstrual cramps, and shoulder stiffness evaluated in all participants.
Surface temperature of fingers and toes, skin blood flow, deep body temperature, brain and femoral oxygen saturation, rigidity of the trapezius muscle, and blood serotonin concentration evaluated in some participants.

7. Main results
After a 12-week treatment, the number of days with headache was significantly decreased from baseline by 2.6 in arm 1 but remained unchanged in arm 2 (decreased by 0.3), showing significantly greater improvement in arm 1 than in arm 2. In addition, the number of doses of an analgesic taken was significantly decreased from baseline by 2.2 in arm 1 but remained unchanged (decreased by 1.4) in arm 2, indicating no between-arm difference. Comparison limited to migraine disclosed the same trend. There were no significant changes in the other parameters in both arms.

8. Conclusions
Goshuyuto decreased the frequency of headache episodes in patients with chronic headache, thereby reducing the number of analgesic doses.

9. From Kampo medicine perspective
This study considers sho, since its first stage involved selection of only goshuyuto-responders as “sho for goshuyuto,” and these were enrolled in a double-blind, randomized controlled trial at the second stage.

10. Safety assessment in the article
No adverse drug reactions occurred except for increases in ALT, AST and γ–GTP in 1 patient receiving goshuyuto. These reactions persisted 3 months after drug discontinuation, suggesting possible development of fatty liver.

11. Abstractor’s comments
In this study, goshuyuto was administered to 91 patients with chronic headache at its first stage to select responders (n=53) for a double-blind, randomized controlled trial at its second stage. Thus, it may be a groundbreaking study in that it focused on “sho.” Besides headache, menstrual cramps and shoulder stiffness also tended to be improved by treatment with goshuyuto, warranting investigation with a larger sample size to clarify “goshuyuto-sho.” More clinical studies in oriental medicine such as the present study are expected in the future. There is a similar report “Odaguchi H, Hanawa Y. Complementary alternative medicine in headache treatment. Igaku no Ayumi (Journal of Clinical and Experimental Medicine) 2005; 215: 1137-40 (in Japanese). [MOL, MOL-Lib]”

12. Abstractor and date
Goto H, 1 April 2008, 8 August 2009.
### Symptoms and Signs

#### Reference


1. **Objectives**
   To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) and L-glutamine for paclitaxel-induced myalgia and arthralgia.

2. **Design**
   Crossover randomized controlled trial (RCT-crossover).

3. **Setting**
   Department of Obstetrics and Gynecology, Okayama University Medical School.

4. **Participants**
   Fifteen patients with ovarian (n=13), cervical (n=1), or vulva (n=1) cancer who: 1) had received chemotherapy including paclitaxel (TXL) in December 1999 through July 2000; 2) had developed myalgia and arthralgia; and 3) were scheduled for 2 or more cycles of chemotherapy. The data from twelve of these patients were analyzed.

5. **Intervention**
   Arm 1: TXL treatment combined with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day, t.i.d. in the second cycle and with L-glutamine 2.0 g/day, t.i.d. in the third cycle, in 7 patients.
   Arm 2: TXL treatment combined with L-glutamine 2.0 g/day, t.i.d. in the second cycle and with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day, t.i.d. in the third cycle, in 8 patients.
   The first cycle (TXL monotherapy), in which pain occurred, was considered to be a control. Shakuyakukanzoto (芍薬甘草湯) and L-glutamine were orally administered from 1 week before the TXL treatment until the pain resolved.

6. **Main outcome measures**
   The efficacy was evaluated based on: 1) sum of pain scores; 2) duration of myalgia and arthralgia; 3) duration of grade 2 or greater myalgia and arthralgia; 4) number of analgesics used; and 5) final subjective impressions.

7. **Main results**
   Twelve patients were evaluated in the final analysis. Reductions of the duration of myalgia and arthralgia were significantly different between the control and the L-glutamine-treated patients. Reductions of the duration of grade 2 or greater myalgia and arthralgia in the shakuyakukanzoto- and the L-glutamine-treated patients differed significantly from that of the control patients. No significant differences occurred in any variable between the shakuyakukanzoto- and the L-glutamine-treated patients.

8. **Conclusions**
   Shakuyakukanzoto and L-glutamine had no dramatic effects on paclitaxel-induced myalgia and arthralgia, except for the reduction of the duration of grade 2 or greater pain.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    One L-glutamine-treated patient reported nausea and one shakuyakukanzoto-treated patient could not take the drug for an unspecified reason.

11. **Abstractor's comments**
    Shakuyakukanzoto is effective for pains associated with smooth and skeletal muscle spasm. In contrast, arthralgia (a paclitaxel-induced adverse reaction) is not included as an indication for treatment with shakuyakukanzoto. However, excellent responses were reported in the present study. The efficacy of this drug for this indication might be confirmed in the future by increasing the number of patients, as well as by identifying candidate patients for this treatment from an analysis of responders and non-responders.

12. **Abstractor and date**
## Symptoms and Signs

### Reference


1. **Objectives**

   To evaluate the efficacy of hochuekkito (補中益気湯) for the elderly with weakness.

2. **Design**

   Randomized controlled trial (RCT). N-of-1 randomized controlled trial restricted to hochuekkito-responders.

3. **Setting**

   Five hospitals associated with Toyama Medical and Pharmaceutical University (now Toyama University).

4. **Participants**

   Fifteen elderly patients (3 males and 12 females; age [mean ± SD], 78.4±7.8 years) with weakness satisfying the following 4 inclusion criteria: (1) complaint of discomfort and anorexia due to chronic debilitating disease; (2) no history of infection or vascular disorder within 1 month before the start of the trial; (3) no malignant diseases; and (4) aged ≥60 years and <90 years.

5. **Intervention**

   Responders during the 2-week run-in period were randomly assigned to the following 3 arms:
   - **Arm 1**: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of placebo at the same frequency for 6 weeks, with a 2-week washout between both administration periods.
   - **Arm 2**: administration of placebo (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods.
   - **Arm 3**: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods.

   Responders had to meet criterion (1) and one of the three other criteria (2) to (4): (1) good drug compliance; (2) subjective overall evaluation improved; (3) clinical symptoms improved; or (4) symptoms other than chief complaint improved.

6. **Main outcome measures**

   36-item short-form health survey (SF36), profile of mood states (POMS), natural killer (NK) activity, interleukin (IL)-2-producing activity of peripheral lymphocytes, lymphocyte-proliferating activity, and lymphocyte cell-surface antigens.

7. **Main results**

   PCS (physical component summary) of SF36 was significantly improved in the hochuekkito group ($P<0.05$). There were significant among-arm differences in 4 (anger-hostility, fatigue, tension-anxiety, confusion) of 6 subscales of the POMS ($P<0.01$, $P<0.05$, $P<0.01$, $P<0.05$, respectively). Lymphocyte cell-surface antigens, CD3-positive cells, and CD3/CD4 double-positive cells were significantly increased in the hochuekkito group ($P<0.05$).

8. **Conclusions**

   Hochuekkito improved the QOL of elderly patients with weakness and activated their immune systems.

9. **From Kampo medicine perspective**

   None.

10. **Safety assessment in the article**

    No adverse drug reactions occurred.

11. **Abstractor’s comments**

    This is a valuable N-of-1 RCT. Unlike the well-known parallel controlled design, this RCT has a self-controlled design, in which each patient receives both the candidate drug and placebo for before-after comparison. As RCT is considered difficult to perform in the Kampo field, this study opened new possibilities for clinical studies of Kampo medicines.

12. **Abstractor and date**

Symptoms and Signs

Reference

1. Objectives
To investigate the efficacy and safety of saireito (柴苓湯) on postoperative edema and inflammation after total hip arthroplasty (THA).

2. Design
Randomized controlled trial (RCT).

3. Setting
Two departments (Department of Kampo Medicine and Department of Orthopaedic Surgery) of Osaka University, and one hospital.

4. Participants
Female patients who underwent THA because of unilateral osteoarthritis, n=17.

5. Intervention
Arm 1: Tsumura Saireito (柴苓湯) Extract Granules 9.0 g/day for 2 days before surgery and for 2 weeks after surgery, n=8.
Arm 2: no administration, n=9.

6. Main outcome measures
The circumference of the lower limb at three locations (the lower leg, ankle, and forefoot), Merle d’Aubigne hip score for clinical evaluation including pain, and serum C-reactive protein (CRP) level.

7. Main results
At three weeks after surgery, the circumference of the lower leg was less in arm 1 than in arm 2. The serum CRP level became negative by 2 weeks after surgery in 6 of 8 patients in arm 1 and in 0 of 9 patients in arm 2 (P<0.001).

8. Conclusions
Administration of saireito was suggested to reduce postoperative lower leg edema and inflammation after THA.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
No side effects were reported in arm 1 and documented in arm 2.

11. Abstractor’s comments
This study suggests the efficacy of saireito for postoperative lower leg edema after THA. In this trial, all patients had a pneumatic foot compression device and wore compression stockings concurrently to prevent postoperative lower leg swelling. This study also indicated that saireito is effective in decreasing postoperative inflammation. All patients received an intravenous infusion of prophylactic antibiotics for 4 days, subsequently oral antibiotics for 4 days, and nonsteroidal anti-inflammatory drugs (NSAIDs) for 1 week after surgery. However, CRP level remained positive in all subjects in arm 2, two weeks after surgery. In general, a few days’ treatment with antibiotics should lead to a negative CRP level by two weeks after surgery. Further clinical studies with more patients and fewer concomitant therapies for knee replacement arthroplasty and bipolar hip arthroplasty are awaited and anticipated.

12. Abstractor and date
Symptoms and Signs

References


1. Objectives
To evaluate the efficacy and safety of bofutushosan (防風通聖散) in obese Japanese women with impaired glucose tolerance.

2. Design
A double-blind randomized controlled trial (DB-RCT).

3. Setting
An university hospital (Kyoto Prefectural University of Medicine).

4. Participants
Eighty-one obese women (mean body mass index, 36.5 kg/m²) with impaired glucose tolerance were included. Patients with kidney, heart and/or liver disease, any metabolic or endocrine disease, psychiatric disorders, or cancer were excluded.

5. Intervention
Arm 1: treatment with TSUMURA Bofutsushosan (防風通聖散) Extract Granules for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (44 patients; of these, 41 were included for analysis).
Arm 2: treatment with placebo for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (41 patients; of these, 40 were included for analysis).

6. Main outcome measures
Body weight, the proportion of body fat (% weight), visceral and subcutaneous fat accumulation, systolic and diastolic blood pressure, heart rate, biochemical data (triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, uric acid, glycosylated hemoglobin (HbA1c), and fasting glucose), and waist and hip circumference were measured before treatment, and after 12 and 24 weeks of treatment. Values for 2-h oral glucose tolerance test (OGTT) glucose, glucose area under the curve (AUC) 120, fasting insulin, insulin AUC120, and homeostasis model assessment of insulin resistance (HOMA-IR) were measured or calculated after 24 weeks.

7. Main results
Waist circumference decreased in both arms after 12- and 24-week treatment compared with before treatment. The decrease was significantly greater after 24 weeks in Arm 1 compared with Arm 2. There were significant differences in more measures after 24 weeks than after 12 weeks in both arms. In Arm 2, body weight, body fat (%), and subcutaneous fat decreased only after 24 weeks; systolic and diastolic blood pressure, triglyceride, and total cholesterol reduced after 12 and 24 weeks. In Arm 1, body weight, body fat (%), visceral and subcutaneous fat, systolic and diastolic blood pressure, biochemical data (LDL cholesterol, HDL cholesterol, uric acid, and insulin (fasting and AUC120)), 2-h OGTT glucose, and HOMA-IR improved after 24 weeks. The decrease in body weight in Arm 1 was associated with decreased visceral and subcutaneous fat but not with a decrease in adjusted resting metabolic rate, whereas the weight loss in Arm 2 was not associated with decreased visceral fat.

8. Conclusions
Bofutsushosan is useful in the treatment of obese patients with impaired glucose tolerance.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There was no effect on cardiovascular or central nervous system in the two arms. Although no subject had steatorrhea, 3 subjects in the bofutsushosan arm discontinued treatment and withdrew from the study because of diarrhea. One subject in the placebo arm dropped out of the study owing to noncompliance.

11. Abstractor’s comments
This DB-RCT (examining the efficacy and safety of bofutsushosan in obese Japanese women with impaired glucose tolerance) provides a high quality of evidence. Although body weight tended to decrease between 12 and 24 weeks of treatment in the placebo arm, it can still be concluded that the anti-obesity effect of bofutsushosan combined with diet and exercise therapies is more likely to persist potently. Further studies should be conducted to evaluate the effect of bofutsushosan monotherapy without diet and exercise therapies. Investigations with Kampo diagnostic considerations are also needed.


12. Abstractor and date
Reference

1. **Objectives**
   To evaluate the effect of bakumondoto (麦門冬湯) on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.

2. **Design**
   Randomized cross-over controlled trial (RCT-cross over).

3. **Setting**
   Single facility (university).

4. **Participants**
   Twenty-six healthy university students.

5. **Intervention**
   Arm 1: administration of bakumondoto (麦門冬湯) 3.0 g t.i.d. for 1 week followed by administration of the same dose of placebo at the same frequency for 1 week, with 2-week washout between both administration periods.
   Arm 2: administration of placebo 3.0 g t.i.d. for 1 week followed by administration of the same dose of bakumondoto (麦門冬湯) at the same frequency for 1 week, with 2-week washout between both administration periods.

6. **Main outcome measures**
   Urinary cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities (determined by a caffeine test).

7. **Main results**
   There were no significant differences in urinary cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities on days 1 and 7 from baseline in either arm.

8. **Conclusions**
   Caffeine test is a safe and noninvasive screening test for herb-drug interaction measuring the ratio of urinary caffeine metabolites (cytochrome p450 1A2, xanthine oxidase, N-acetyltransferase 2). Bakumondoto did not affect cytochrome p450 1A2 (a hepatic enzyme metabolizing theophylline), xanthine oxidase, or N-acetyltransferase 2 activity, suggesting the unlikeliness of interaction.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    No adverse drug reactions occurred in the subjects receiving bakumondoto.

11. **Abstractor’s comments**
    This study offers no data on direct clinical efficacy.

12. **Abstractor and date**
Reference

1. **Objectives**
   To evaluate the effect of shoseiryuto (小青竜湯) on blood carbamazepine concentration.

2. **Design**
   Randomized cross-over controlled trial (RCT-cross over).

3. **Setting**
   None (authors belong to the Department of Hospital Pharmacy, Kyoto Pharmaceutical University).

4. **Participants**
   Four healthy adult males.

5. **Intervention**
   Arm 1: administration of 9.0 g/day of TSUMURA Shoseiryuto (小青竜湯) Extract Granules in 3 divided doses before meals for 7 days and 200 mg of carbamazepine in the morning of day 4 (n=4).
   Arm 2: administration of 200 mg of carbamazepine (n=4).

6. **Main outcome measures**
   Concentrations of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood sampled before, and 1.5, 4, 8, 24, 48, and 72 hr after administration of carbamazepine.

7. **Main results**
   Combination with shoseiryuto did not affect the following parameters of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood: the maximum blood concentration; time to reach the maximum blood concentration; slope of the elimination phase; elimination half-life; area under the plasma concentration-time curve; and mean residence time.

8. **Conclusions**
   Oral administration of shoseiryuto does not affect blood carbamazepine concentration.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    This study objectively demonstrated that combination of shoseiryuto does not affect blood carbamazepine concentration, which is susceptible to the effects of various drugs. This study does not evaluate the efficacy of the Kampo medicine, but is considered meaningful, given that Western and Kampo medicines are commonly combined in clinical practice. There is a similar report “Yonekawa Y, Ohnishi N, Kitano N, et al. Drug interaction with Kampo medicines (2): kinetic characteristics of carbamazepine combined with shoseiryuto in healthy volunteers. *TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)* 1999; 16: 191-2.”

12. **Abstractor and date**
Reference

1. Objectives
To evaluate the effect of hachimiji-gan (八味地黄丸) on human central retinal artery.

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

3. Setting
Single Facility (the University of Tokyo).

4. Participants
Twelve healthy volunteers (6 males and 6 females; mean age, 26.0 years).

5. Intervention
Arm 1: single-dose administration of 27 g of hachimiji-gan (八味地黄丸) (n=12).
Arm 2: single-dose administration of 27 g of placebo (lactose) (n=12).

6. Main outcome measures
Systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity, and vascular resistance of the central retinal artery, measured by ultrasonic diagnosis device before administration and every 15 min after administration for 60 min.

7. Main results
In arm 2, there were no changes from baseline in systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity or vascular resistance of the central retinal artery. In arm 1, although vascular resistance did not change, there were increases in systolic velocity at 15 and 45 min, diastolic velocity at 45 min, and mean velocity at 30, 45, and 60 min. Group comparison revealed significantly higher systolic blood flow velocity at all postdose time points until 60 min, higher diastolic blood flow velocity at 45 min, and significantly higher mean blood flow velocity in the time period from 30 to 60 min in arm 1.

8. Conclusions
This study provided evidence that hachimiji-gan increases the blood flow velocity of the central retinal artery.

9. From Kampo medicine perspective
When compared with hachimiji-gan-non-responders (with unsuitable sho, n=9), hachimiji-gan-responders (with suitable sho, n=3) had higher systolic, diastolic, and mean flow rates in the time period from 15 to 60 min (statistical analysis not performed due to the small sample size).

10. Safety assessment in the article
None.

11. Abstractor’s comments
It was reported some time ago that hachimiji-gan acts on the central nervous system to improve hypobulia in the elderly, and to improve eye symptoms. The present report showed an increase in blood flow rate of the central retinal artery, providing evidence for efficacy in improving visual acuity. Moreover, it was shown that intracerebral blood flow may also increase, suggesting effects on the central nervous system. Also, this report provides a valuable discussion from a Kampo medicine perspective of increased blood flow velocity in responders. However, a larger sample size will be necessary in the future. Another problem is that the systemic blood pressure was not indicated, making it impossible to determine whether the increase in blood flow velocity is attributable to a systemic or local reaction. Furthermore, since this RCT did not evaluate clinical efficacy and used single-dose administration, it is hoped that clinical research examining the persistent effects of long-term oral administration will be conducted.

12. Abstractor and date
Objectives
To assess the efficacy and safety of hochuekkito (補中益気湯) on antibody production after influenza vaccination.

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

Setting
No description of the setting is available; the authors belong to the Division of Clinical Application, Institute of Natural Medicine, University of Toyama.

Participants
Of the 49 healthy males aged between 20 and 60 years who volunteered to enter this trial of hochuekkito, 36 were enrolled. None of the 36 had been taking any herbal medicine, hormone therapy, or anti-inflammatory drugs.

Intervention
Arm 1: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.
Arm 2: administration of placebo (consisted mainly of cane sugar) 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.

Main outcome measures
Blood samples were taken at weeks 0, 1, 2, 4, and 12. Hemagglutination inhibition (HI) was used to measure influenza antibody titer, and a chromium (Cr) -release assay was used to measure natural killer (NK) activity.

Main results
Three subjects in arm 2 (because of common cold and diarrhea) and one subject in arm 1 (for a personal reason) dropped out of the study. There were no significant between-arm differences in postvaccination titer and NK activity.

Conclusions
Oral administration of hochuekkito for 14 days before influenza vaccination did not affect postvaccination antibody production.

From Kampo medicine perspective
Subjects not intending to use hochuekkito, as well as subjects with easy fatigability, a high susceptibility to colds, slow recovery from colds, a high susceptibility to other infections like herpes and wound infection, poor appetite, loose bowels, and somnolence especially after meals, were excluded from the study.

Safety assessment in the article
No adverse effects were observed.

Abstractor's comments
This is a high-quality, well-designed, and double-blind clinical trial to assess the effect of hochuekkito on antibody production after influenza vaccination. A similar report (Yamaguchi H et al., Assessment of the effect of hochuekkito extract on antibody response to influenza vaccination. Kampo to Saishin-chiryo [Kampo & the Newest Therapy] 2006; 15: 235-7 [in Japanese]) concluded similarly that oral administration of hochuekkito for 1 week after the vaccination has no effect on antibody production. On the other hand, as mentioned in the discussion of this paper, Takagi et al. reported that hochuekkito increased antibody production in old mice (Takagi et al. Antibody response of Kampo-hozai after influenza B immunization in old mice. The Japanese Society for Vaccinology 2002; 6: 72 [abstract in Japanese]). Considering that all the clinical trials were conducted with healthy subjects, further investigation in the elderly with decreased ability to produce antibodies is awaited. The design of this clinical trial, based on the result from basic studies, should be emulated by researchers who conduct clinical trials of Kampo medicines.

Abstractor and date
Reference

1. Objectives
To evaluate the effect of maobushisaishinto (麻黄附子細辛湯) on antibody titer after influenza vaccination.

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

3. Setting
Two university hospitals.

4. Participants
One hundred and six healthy subjects aged 20–71 years.

5. The following drugs were orally administered from day –14 to –1 of influenza vaccination (A/H1N1, A/H3N2, B). All subjects were vaccinated in late November, before the influenza season.
Arm 1: Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Capsules (6 capsules/day), n=23.
Arm 2: placebo capsules, n=24.

6. Main outcome measures
Serum hemagglutination inhibition titers were measured at weeks 0, 1, 2, 4, and 12.

7. Main results
After excluding 57 subjects with antibody titers of more than 1:80 and 2 subjects diagnosed with influenza during the study period (one in each arm), 23 and 24 subjects were enrolled for analysis. There was no significant between-arm difference in antibody titer against A/New Caledonia/20/99(H1N1), A/New York/55/2004(H3N2), and B/Shanghai/361/2002. However, anti-H3N2 virus antibody titer was significantly higher in arm 2 than in arm 1 at week 4. Subgroup comparisons (smokers vs non-smokers and older subjects [≥40 years old] vs younger subjects [<40 years old]) found no significant between-arm differences in antibody titers.

8. Conclusions
No adjuvant effect of maobushisaishinto on antibody titer after influenza vaccination was observed.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
Not documented.

11. Abstractor’s comments
Previous studies have shown the adjuvant effect of maobushisaishinto on influenza vaccination in animals and in elderly subjects. This paper aims to verify this effect.

12. Abstractor and date
Objectives
To elucidate the mechanism of bushirichuto (附子理中湯) activity in raising gut-regulated peptide levels.

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

Setting
Department of Clinical Pharmacy, Oita University Hospital.

Participants
Five healthy male volunteers recruited at the facility mentioned above, n=5.

Intervention
Arm 1: Kanebo Bushirichuto (附子理中湯) Extract Fine Granules (EK-410) 4.5 g was orally administered with 100 mL of water for 4 weeks.
Arm 2: placebo was orally administered with 100 mL of water for 4 weeks.
Each subject was administered these drugs with an interval of four weeks.

Main outcome measures
Blood samples were obtained before administration, and at 20, 40, 60, 90, 120, 180, and 240 min after administration of the test substances, and plasma levels of calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and motilin-like immunoreactive substance (IS) were measured by enzyme immunoassay (EIA).

Main results
One dose of bushirichuto significantly increased CGRP, somatostatin, and VIP levels (which peaked at 40–60 min) and significantly increased substance P level (which peaked at 180 min). CGRP level increased 5.7-fold at 40 min (85.2±58.7 pg/mL in arm 1 vs. 14.9±1.9 pg/mL in arm 2) (P<0.01), somatostatin level increased 2.1-fold at 60 min (20.2±6.1 pg/mL in arm 1 vs. 9.8±2.1 pg/mL in arm 2) (P<0.01), VIP level increased 2-fold at 60 min (16.9±7.0 pg/mL in arm 1 vs. 8.3±1.4 pg/mL in arm 2) (P<0.01), and substance P increased 2-fold at 180 min (68.5±18.7 pg/mL in arm 1 vs. 34.3±17.9 pg/mL in arm 2) (P<0.01). On the other hand, plasma motilin-like IS level was unaffected during observation for 240 min after administration.

Conclusions
Administration of bushirichuto may reduce sensitivity to cold, gastrointestinal discomfort, and gastrointestinal dysfunction via increasing plasma levels of CGRP, somatostatin, VIP, and substance P.

From Kampo medicine perspective
The authors suggest that the taste and smell of bushirichuto may affect the kinetics of gut-regulated peptides.

Safety assessment in the article
Not documented.

Abstractor’s comments
Although this investigation had only a small number of subjects, the results helped us to reveal the mechanism of bushirichuto activity. As bushirichuto is an “onchu-sankan” (溫中散寒) medicine which contains herbs (Aconiti tuber [附子] and Zingiberis siccatum rhizome [乾姜]) with strong anti-coldness (“sankan”) activity, it is used for patients with “hie” (or a feeling of coldness in the body). However, the authors did not reveal whether the male volunteers had kan-sho (寒証, cold pattern). Most subjects treated with bushirichuto in clinical practice are frail women. From that point of view, to minimize the discrepancy between bushirichuto use in actual clinical practice and experimental study, clinical studies of “sho” in women with and without symptoms, and having the same study design as this trial, are awaited.

Abstractor and date
**Objectives**
To examine effects of rokumigan (六味丸) on serum amino acid concentrations.

**Design**
Randomized crossover controlled trial (RCT-cross over).

**Setting**
Department of Internal Medicine, the Komatsushima Hospital.

**Participants**
Six healthy men (mean age 35.5 years), n=6.

**Intervention**
Arm 1: lactose 5 g administered once at 9:00, n=6.
Arm 2: Asahi amino GET 5 tablets (contains a similar amount of amino acids as 10 g of Tsumura Rokumigan (六味丸) Extract Granules) administered once at 9:00, n=6.
Arm 3: Tsumura Rokumigan (六味丸) Extract Granules (TJ-87) 10 g administered once at 9:00, n=6.
There was a washout period of 3 months between treatments.

**Main outcome measures**
Serum amino acid concentrations before and at 1, 2, 4, and 6 h after the intervention.

**Main results**
In arm 1, concentrations of Ala, Gly, and Ile were significantly decreased from pretreatment levels at 6 h, and Arg, Glu, His, Leu, Lys, Phe, Ser, and Val levels were unchanged. In arm 2, concentrations of Ala, Glu, Gly, Ile, Leu, and Ser were significantly decreased at 6 h, but Arg, His, Lys, Phe, and Val levels remained unchanged. In arm 3, the levels of Ala at 2 h and Gly and Ser at 1 h were significantly increased, but Arg, Glu, His, Ile, Leu, Lys, Phe, and Val levels remained unchanged. In all three arms, serum levels of Asn, Cys, Gln, Met, Pro, Thr, Trp, and Tyr were not determined, and Asp were undetectable.

**Conclusions**
Serum amino acid concentrations are higher after administration of rokumigan than after administration of a supplement containing a similar amount of amino acids.

**From Kampo medicine perspective**
None.

**Safety assessment in the article**
Not documented.

**Abstractor’s comments**
This interesting well-designed cross-over clinical trial investigates the entry of amino acids from rokumigan into the blood. Changes in the concentration of amino acids after rokumigan administration were compared with those after administration of lactose or an amino acid mixture containing almost the same amount of amino acids. Amino acid levels (e.g., the pretreatment Ala level) were widely dispersed in all three arms, suggesting possible measurement errors in serum level for some amino acids. To adjust for dispersion in the data, relative changes in amino acid concentrations were calculated and are shown in Fig. 1. However, symbols a, b, and c are not defined. Also, the amino acid mixture administered in arm 2 contains several ingredients besides amino acids such as beer yeast, and their influence on absorption should be considered. Importantly, this study found that administration of rokumigan increased amino acid levels in blood and suppressed the gradual decrease observed in other arms. This observation may have important pharmacologic implications. Further studies on several Kampo medicines are anticipated.

**Abstractor and date**
Reference

1. Objectives
To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) combined with polyethylene glycol solution (PEG) in pretreatment for large bowel endoscopy.

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

3. Setting
None (authors belong to the Department of Colon and Rectal Surgery, Tohokamagaya Hospital).

4. Participants
Seventy patients who were scheduled to undergo large bowel endoscopy between November 2000 and March 2001 and gave informed consent to participate in this trial.

5. Intervention
Arm 1: oral administration of shakuyakukanzoto (芍薬甘草湯) (2.5 g t.i.d.) starting from lunchtime on the day before endoscopy (n=37).
Arm 2: non-treatment (n=33).
Endoscopy was performed by an experienced specialist.

6. Main outcome measures
Frequency of defecation on the day of endoscopy, time until defecation, presence or absence and severity of abdominal pain associated with pretreatment, presence or absence and severity of nausea, pretreatment condition (residue), and time required to reach cecum.

7. Main results
Frequency of defecation and time until defecation were 6.9±2.5 times and 234±36 min, respectively, in arm 1 and 7.6±3.4 times and 171±30 min, respectively, in arm 2, showing reduced frequency and extended time until defecation in arm 1, although there were no significant differences between arms. The incidence and score of abdominal pain were 11% and 0.6±0.4, respectively, in arm 1 and 12% and 0.5±0.4, respectively, in arm 2, showing no difference between arms. Nausea was more prevalent in arm 1 with the incidence of 33%, compared with 12% in arm 2, although there was no difference in nausea score between arms. Pretreatment score and time required to reach cecum were 0.9±0.8 and 7.9±5.4 min, respectively, in arm 1 and 0.7±0.8 and 7.9±5.5 min, respectively, in arm 2, showing no difference between arms.

8. Conclusions
Shakuyakukanzoto combined with PEG tends to slightly suppress the cleansing of the bowel needed prior to large bowel endoscopy and may induce nausea, suggesting its ineffectiveness in such pretreatments.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
To achieve adequate intestinal lavage in preparation for large intestine endoscopy, a large amount of PEG has to be swallowed. In terms of efficacy and patient satisfaction, however, currently available pretreatments are not always useful. Focusing on this issue, the present study is meaningful. To further enhance the quality of this clinical research, however, the control should be a placebo that has no effect on bowel motility rather than no treatment. With no other useful concomitant drugs available, it is hoped that new drugs and useful approaches will be investigated.

12. Abstractor and date
1. **Objectives**
   To evaluate the efficacy of directly sprayed shakuyaku-kanzoto (芍薬甘草湯) on large bowel spasm.

2. **Design**
   Randomized controlled trial (RCT).

3. **Setting**
   Single facility (university).

4. **Participants**
   One-hundred and thirty-one patients scheduled to undergo large bowel endoscopy for polyp surveillance, etc.

5. **Intervention**
   Arm 1: shakuyaku-kanzoto (芍薬甘草湯) group (0.5 g of TSUMURA Shakuyaku-kanzoto (芍薬甘草湯) Extra Granules dissolved in physiological saline to make 50 mL [concentration: 10 g/L]).
   Arm 2: peppermint oil group (0.4 mL of peppermint oil and 0.05 g of sorbitan fatty acid ester dissolved in water to make 50 mL [concentration: 8 mL/L]).
   Arm 3: Physiological saline group.
   In all arms, conventional fluoroscopy (CF) was performed in the left lateral position, and the contraction ring in the gastric antrum was sprayed, kept 1 cm from the tip of the endoscope inserted 20–25 cm from the anus.

6. **Main outcome measures**
   Contraction ring lumen area (presented as the number of pixels on videotaped digital images of contraction-relaxation motions of the contraction ring during the 3-min period beginning before and ending after each drug was sprayed), and area under the expanded area-time curve.

7. **Main results**
   Lumen area was significantly larger in the shakuyaku-kanzoto group and peppermint oil group than in the physiological saline group. The area under the expanded area-time curve was also significantly larger in both treatment groups than in the physiological saline group. There was no difference in outcome measures between the shakuyaku-kanzoto group and peppermint oil group.

8. **Conclusions**
   Shakuyaku-kanzoto and peppermint oil have comparable large intestinal wall-relaxing activity.

9. **From Kampo medicine perspective**
   None.

10. **Safety assessment in the article**
    None.

11. **Abstractor’s comments**
    Direct spray of large intestinal wall with shakuyaku-kanzoto may be applicable as an antispastic in the CF test.

12. **Abstractor and date**
1. **Objectives**
To evaluate the efficacy of pretreatment with shakuyakuzan-koto (芍薬甘草湯) for upper gastrointestinal tract endoscopy.

2. **Design**
Quasi-randomized controlled trial (quasi-RCT).

3. **Setting**
Single facility (clinic).

4. **Participants**
Fifty-eight subjects who underwent endoscopy.

5. **Intervention**
Arm 1: shakuyakuzan-koto (芍薬甘草湯) group (oral administration of 80 mg of dimethicone syrup followed by 5.0 g of shakuyakuzan-koto (芍薬甘草湯) extract granules) (n=11).
Arm 2: anticholinergic drug group (oral administration of 80 mg of dimethicone syrup followed by subcutaneous injection of 40 mg of scopolamine butylbromide) (n=28).

6. **Main outcome measures**
Symptoms during endoscopy (pain evaluated subjectively on a visual analogue scale), peristalsis (Niwa’s classification).

7. **Main results**
Among those under 70 years, the anticholinergic drug was significantly superior to shakuyakuzan-koto in suppression of peristalsis, but was more frequently associated with experience of pain/discomfort.

8. **Conclusions**
Shakuyakuzan-koto provides as much pain relief as the anticholinergic drug.

9. **From Kampo medicine perspective**
None.

10. **Safety assessment in the article**
None.

11. **Abstractor’s comments**
Of 58 subjects, only 39 were actually assigned to either group (arm 1, n=11; arm 2, n=28). This sample size seems to be slightly too small to evaluate efficacy.

12. **Abstractor and date**
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Others

Reference

1. Objectives
To evaluate the efficacy of daikenchuto (大建中湯) combined with polyethylene glycol solution (PG solution) in pretreatment for large bowel endoscopy.

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

3. Setting
None (authors belong to the 3rd Department of Surgery, Toho University School of Medicine).

4. Participants
Two-hundred and eighty-five patients who underwent total large bowel endoscopy between January and December 2001, gave informed consent to participate in this trial, and remained after excluding those under 18 years old, pregnant women, and other ineligible patients.

5. Intervention
Arm 1: combination of PG solution and TSUMURA Daikenchuto (大建中湯) Extract Granules (oral administration of 2.5 g each at 12:00 and 21:00 on the day before and 7:00 on the day of large bowel endoscopy) (n=144).
Arm 2: PG solution alone (n=141).
Endoscopy was performed by an experienced specialist.

6. Main outcome measures
Frequency of defecation on the day of endoscopy, time until defecation, presence or absence of abdominal pain, abdominal score, presence or absence of nausea, nausea score, pretreatment score, and time required to reach the ileocecal area.

7. Main results
The PG solution/daikenchuto combination group and PG solution group defecated 7.9±3.1 times and 7.7±3.6 times, respectively, and required 3.3±1.6 hr and 3.0±1.5 hr until defecation, respectively. The incidence of abdominal pain (score) was 17% (0.17±0.38) and 15% (0.15±0.35), respectively, and the incidence of nausea (score) was 24% (0.28±0.55) and 21% (0.21±0.43), respectively. Thus, there were no significant between-group differences in these parameters. Pretreatment score was significantly improved in the PG solution/daikenchuto combination group (0.28±0.52 vs 0.81±0.77 in the PG solution group; P<0.01). The time required to reach the ileocecal area was also significantly reduced in the PG solution/daikenchuto combination group (6.4±3.6 min vs 7.3±4.0 min in the PG solution group; P=0.04).

8. Conclusions
PG solution/daikenchuto pretreatment for large bowel endoscopy is a more patient-friendly effective method for facilitating insertion (compared with pretreatment with PG solution alone) and does not increase the level of uncomfortable symptoms such as abdominal pain, nausea, and frequent defecation.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This randomized controlled trial demonstrated that daikenchuto combined with PG solution is superior to PG alone in the preparation of the large intestine for endoscopy. This study has a large sample size and is well designed, but fails to explain pretreatment score and abdominal pain score. It has been presented in a previous report “Saida Y. The 15th Surgery and Kampo Medicine Study Meeting 1. Efficacy of combined use of daikenchuto in pretreatment for large bowel endoscopy - 6 prospective studies - . Progress in Medicine 2005; 25: 3058-9 (in Japanese).”

12. Abstractor and date
Evidence Reports of Kampo Treatment 2009
Task Force for Evidence Reports Special Committee for EBM, the Japan Society for Oriental Medicine

Others

Reference

1. Objectives
To evaluate the efficacy and safety of direct spraying of shakuyakukanzo (芍薬甘草湯) on the colonic mucosa for suppression of bowel movement during colonoscopy.

2. Design
A randomized controlled trial (RCT).

3. Setting
Not specifically mentioned (the authors belong to one university hospital).

4. Participants
One-hundred and ten patients with suspected intestinal hemorrhage, acute abdomen due to acute enteritis, inflammatory bowel disease, or a history of abdominal surgery, and treated with an oral drug affecting bowel movement, who visited our hospital between July 2002 and March 2004.

5. Intervention
Arm 1: spray of 0.5 g/50 mL of a solution of TSUMURA Shakuyakukanzo (芍薬甘草湯) Extract Granules in physiological saline maintained at 36°C over the area of spasms in the intestine, 10 mm apart (n=51).
Arm 2: spray of physiological saline maintained at 36°C in the same manner as arm 1.

Colon preparation involved oral administration of Magcorol (59 g/250 mL) on the day before colonoscopy and 2 L of Niflec on the day of colonoscopy. No sedatives were used during colonoscopy (n=50). Five patients in arm 1 and 4 patients in arm 2 were excluded from the study population because of poor or incomplete bowel preparation.

6. Main outcome measures
Lumen area (pixels) × time (min), determined before and after spraying over the area of spasms.

7. Main results
Before spraying, there was no significant difference between arms. After spraying, the area × time value was significantly larger in arm 1.

8. Conclusions
Direct spray of shakuyakukanzo is effective for suppression of bowel movement during colonoscopy.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
There were no complications throughout the study period.

11. Abstractor’s comments
This is an excellent study because it quantifies bowel movement by monitoring digital images over time, enabling objective evaluation.

12. Abstractor and date
Reference

1. Objectives
To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) solution in preparation for colonoscopy used with the water method of distension.

2. Design
A quasi-randomized controlled trial (quasi-RCT).

3. Setting
Not mentioned (the authors belong to one specialty hospital).

4. Participants
Forty-two males undergoing colonoscopy who gave consent to participate in the study.

5. Intervention
Arm 1: intrarectal injection of a solution of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (1.25 g/100 mL) instead of water used in preparation for colonoscopy used with the water method, simultaneously performed with colonoscope insertion (n=21).
Arm 2: intramuscular injection of butylscopolammonium bromide (Buscopan) (20 mg/mL/A), simultaneously performed with colonoscope insertion (n=21).
One patient in each arm was considered unresponsive because of failure to achieve spasmolysis during the test and was excluded.

6. Main outcome measures
Duration of spasmolysis determined by measuring the time between the first and second appearance of colonic ring contractions. Pulse rate measured before and 10 min after endoscope insertion. Pain evaluated on a 5-point scale.

7. Main results
There was no significant difference in duration of spasms or pain scale score between arms. Percent increase in pulse rate from before to 10 min after insertion was significantly larger in arm 2. Spasmolytic effect persisted until completion of the test in 68.8% of subjects in arm 1 and 25.0% of subjects in arm 2, showing a significant between-arm difference.

8. Conclusions
Shakuyakukanzoto solution in preparation for colonoscopy, used with the water method, prolongs spasmolysis.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor's comments
This excellent paper suggests the potential of a Kampo medicine as a bowel pretreatment for colonoscopy. Evaluation of spasmolysis by colonoscopy is limited to the visual field. Combined use of fluoroscopy may enable observation to be extended to the whole intestine. Studies on the effects of distension methods other than the water method during colonoscopy are expected.

12. Abstractor and date
Reference

1. Objectives
To determine the bowel cleansing effect of precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage solution (PG solution) combined with daikenchuto (大建中湯) and mosapride.

2. Design
Randomized controlled trial (RCT).

3. Setting
None (the authors belong to the Third Department of Surgery, Toho University School of Medicine and/or Tohokamagaya Hospital).

4. Participants
Two hundred and twenty-two patients (155 males and 67 females) who underwent colonoscopy between April 2004 and October 2004 and gave informed consent, including consent to disclose relevant information.

5. Intervention
Arm 1: treatment with 2 L of polyethylene glycol (PG) solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) (n=116).
Arm 2: treatment with 2 L of PG solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) and mosapride (15 mg; 3 tablets) (n=106).
PG solution was administered orally for about 2 hours, at least 6 hours prior to the colonoscopy. Daikenchuto (大建中湯) and mosapride were administered in three divided doses, starting at noon one day before colonoscopy.

6. Main outcome measures
Number of bowel movements, duration time of defecation, presence and severity of abdominal pain and nausea, ease/difficulty of taking the combined medication, adequacy of bowel preparation, and cecal intubation time.

7. Main results
The mean number of bowel movements was significantly higher in arm 2 (7.8) than in arm 1 (7.0). Defecation time tended to be slightly longer in arm 2 (3 h 18 min) than in arm 1 (2 h 59 min). No between-arm differences in abdominal pain (13% of patients in arm 1 and 17% in arm 2) and nausea (24% and 25%, respectively) were observed. The percentage of patients who reported that taking the combined medication was “difficult” or “slightly difficult” was significantly higher in arm 2 (38%) than in arm 1 (28%). No between-arm differences in mean bowel preparation scores (0.9 in both arms) and median cecal intubation times at colonoscopy (6 minutes in both arms) were observed.

8. Conclusions
The addition of mosapride offers no benefit to precolonoscopy bowel preparation with PG solution plus daikenchuto alone.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This paper follows up a previous paper that discussed the efficacy of precolonoscopy bowel preparation with PG solution plus daikenchuto: Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, an herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. Digestive Endoscopy 2005; 17: 50-3. The present trial had a large sample size and was well-designed. There are yet some drawbacks, including the following: 1) possible dependence of some results on skills of the colonoscopist is not mentioned; and 2) the method used for scoring bowel preparation quality was not described. Further studies, like this one, are anticipated.

12. Abstractor and date
1. Objectives
To determine the effectiveness of daikenchuto (大建中湯) in bowel preparation for barium enema X-ray study.

2. Design
Randomized crossover controlled trial (RCT).

3. Setting
Ohashi Hospital, Toho University School of Medicine.

4. Participants
Forty-five patients who underwent barium enema X-ray study on an outpatient basis between March and August 2001.

5. Intervention
Arm 1: conventional bowel preparation plus oral administration of daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. on the day before the X-ray examination (n=24).
Arm 2: conventional bowel preparation plus oral administration of mosapride citrate 10 mg t.i.d. on the day before the X-ray examination (n=21).

6. Main outcome measures
The number and amount of fecal residues and the adherence of barium.

7. Main results
No significant between-arm differences were observed in the number and amount of fecal residues or in the adherence of barium.

8. Conclusions
Daikenchuto is suggested to be as effective as mosapride citrate in bowel preparation for barium enema X-ray study.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This paper compares the effectiveness of daikenchuto with that of mosapride citrate in bowel preparation for barium enema X-ray study. Prokinetic agents combined with conventional bowel preparation for barium enema X-ray decreases the number and amount of fecal residues and improves the adherence of barium. The authors of the present paper concluded that daikenchuto is as effective as a prokinetic agent. The effectiveness of daikenchuto in preparation for lower gastrointestinal endoscopy has been suggested in a previous report and the usefulness of shakuyukan zoto has already been demonstrated. The use of Kampo medicines in this field is expected to increase in the future.

12. Abstractor and date
Others

Reference

1. Objectives
To evaluate the effects of hochuekkito (補中益気湯) on prevention of MRSA carriage, prevention of Pseudomonas aeruginosa carriage, prevention of infection development, neutrophil count, and C-reactive protein (CRP) value.

2. Design
Randomized controlled trial (RCT).

3. Setting
Single facility (Osaka University Hospital ER).

4. Participants
Twenty patients with trauma (aged 16 years or older) who were hospitalized in the above facility for at least 1 week.

5. Intervention
Arm 1: hochuekkito group (補中益気湯) (n=8 [2/10 enrolled were excluded]; male: female = 3:1; mean age, 46.8 years; injury severity score [ISS], 26.1).
Arm 2: non-treatment group (n=12; male: female = 3:1; mean age, 31.2 years; ISS, 24.0).

6. Main outcome measures
Incidences of MRSA and Pseudomonas aeruginosa colonization and infection, CRP level, and neutrophil count.
Bacteriological examination of nasopharyngeal swabs, sputum, midstream urine, feces, and wound scraping was performed on the 1st, 3rd and, 7th day of hospitalization.

7. Main results
There was no significant between-arm difference in neutrophil count and CRP level. Meningitis occurred in 0 of 2 treated patients and 4 of 5 untreated patients. There was no difference in the incidence of pneumonia. MRSA was detected in 1 of 8 treated patients and 4 of 12 untreated patients, although the difference was not significant. Pseudomonas aeruginosa was detected in 1 of 8 treated patients.

8. Conclusions
Hochuekkito tended to prevent MRSA carriage and infections in trauma patients.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor’s comments
This is a valuable RCT performed in an emergency setting. As admitted by the authors in the text, the timing of hochuekkito administration varied. Specification of the method, duration of hochuekkito administration, and presence or absence of blinding, would increase the reliability of this assessment. More results from their study, now underway with a new protocol, are expected.

12. Abstractor and date
Structured Abstract
(1 abstract describing a meta-analysis)
Ante/Post-partum Diseases

Reference

1. Objectives
To evaluate the efficacy of kyukichoketsuin (キュウ帰調血飲) (KCL) in puerperal care in comparison with methylergometrine maleate (MME) by conducting a meta-analysis.

2. Data source
Articles in Igaku Chuo Zasshi (Japana Centra Revuno Medicina) (1983 – 2004) and Medline (1966 – 2004) were searched and collected using key words such as kyukichoketsuin, etc.

3. Selection of study
Inclusion criteria: 1) RCT; 2) original article; 3) study population consisting of puerperal primipara and pluripara who had normal delivery; 4) use of KCL as an intervention drug and MME as control; and 5) indices of therapeutic effect including length of uterine fundus, amount of lactation, and severity of afterbirth pains.

4. Data extraction
Data extraction was performed independently of data integration by a different researcher. Extracted data were baseline characteristics of subjects, sample size, method of randomization, method of blinding, method of administering the investigational and control drugs, dosage, number of daily doses, number of days of administration, concomitant drugs, and study endpoints. If study end points data were shown just graphically without numerical values, points on the graph with calipers were measured and converted graphical values to numerical values. The quality of selected RCTs was evaluated using the Chalmers’ scoring system.

5. Main results
Of 44 RCTs gathered, 5 satisfied the selection criteria. One of these 5 overlapped and was excluded, leaving 4 RCTs for analysis. These RCTs were equivalent in quality. Analysis of three RCTs evaluating breast pain revealed that KCL significantly attenuated afterbirth pains compared with MME (combined odds ratio: 0.32 [95%CI, 0.17 – 0.60]). On day 5 after delivery, there was statistically significant difference in the length of the uterine fundus between groups treated with KCL and MME in 1 trial, but no difference based on the combined data from all 4 trials. On day 4 after delivery, neither data from individual trials nor the combined data showed significant differences in the length of the uterine fundus, suggesting comparable effect of KCL and MME on involution of the uterus. Combined data form 2 contradictory articles compared the amount of lactation on day 4 after delivery, one showed no difference and another showed that both KCL and MME increased the amount of lactation, demonstrated significantly less lactation with KCL (combined odds ratio: -8.20 [95%CI, -16.17 to -0.23]). Combined data on day 5 after delivery revealed that KCL increased the amount of lactation, although not significantly, showing the efficacies of KCL and MME for inducing lactation were similar.

6. Conclusions
Compared to MME, KCL is more effective in attenuating afterbirth pains. Analysis of safety is necessary.

7. From Kampo medicine perspective
None.

8. Safety assessment in the article
None.

9. Abstractor’s comments
The authors deserve praise for conducting a meta-analysis of RCTs restricted to Kampo medicine. As the point of meta-analysis is to gather data from all related studies, it would be better to provide the details of the gathering process; for example, whether the search was exhaustive and included a hand-search of textbooks, reference books, and specialists' opinions. Considering current movement towards evidence based medicine (EBM) in Kampo field, the authors' meta-analysis is epoch-making. It is expected that this study will stimulate further meta-analyses and systematic reviews of Kampo medicine studies.

10. Abstractor and date