Efficacy and Safety of the Japanese Herbal Medicine Daikenchuto (DKT) in Elderly Fecal Incontinence Patients: A Prospective Study

Kazufumi Shimazutsu¹, Yusuke Watadani² and Hiroki Ohge³

¹) Department of Surgery, Gion Ushita Hospital, Hiroshima, Japan
²) Department of Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
³) Department of Infectious Diseases, Hiroshima University Hospital, Hiroshima, Japan

Abstract

Objectives: This study has investigated the efficacy and safety of daikenchuto (DKT) in elderly patients with fecal incontinence (FI).

Methods: This was an open-label, single-arm study (UMIN Clinical Trials Registry as UMIN000030252). DKT at 15 g/day was orally administered to patients for 28 days. Patients over 70 years old with FI, who scored over 11 in the Mini-Mental State Examination, are capable of oral intake, and provided written informed consent, were enrolled in this study. Changes in abdominal pain and bloating, Cleveland Clinic Incontinence Score (CCIS), FI Quality of Life Scale (FIQLS), maximum resting pressure (MRP), FI frequency, and stool form were evaluated.

Results: In total, 21 patients (1 requested to withdraw) were enrolled in this study. The compliance rate was 95.2%, and no serious adverse drug reactions were observed. Improvements in terms of abdominal pain and bloating were observed at 2 weeks (p < 0.01). In the CCIS, the total score, leakage of solid stool, and leakage of liquid stool improved after 2 weeks (p < 0.01), while pad use and lifestyle alteration improved after 4 weeks (p < 0.05). Improvement in FIQLS was also observed at 2 weeks (p < 0.01). MRP demonstrated significant improvement at 2 weeks (p < 0.01). Eleven (52.4%) patients had no FI during the study period.

Conclusions: DKT improves MRP and quality of life in patients with abdominal symptoms; moreover, it is considered to be a safe and effective drug for elderly patients with FI.

Keywords

daikenchuto, Kampo, fecal incontinence, elderly, maximum resting pressure

J Anus Rectum Colon 2022; 6(1): 32-39

Introduction

Fecal incontinence (FI) is a pathology defined by the International Consultation on Incontinence as an involuntary loss of liquid or solid stool that is considered a social or hygienic problem[1]. The Japanese practice guidelines for FI show that FI is defined as involuntary or uncontrollable loss of feces and demonstrate the epidemiology, etiology, pathophysiology and causes, risk factors, clinical evaluations, and symptomatic scores and quality of life (QOL) questionnaire for clinical evaluations[2].

Causes of FI and its pathophysiology remain inconsistent as it involves many factors: anal sphincter dysfunction; reservoir dysfunction due to reduced rectal sensation, volume, and compliance; stool form; abnormal anorectal innervation; and cognitive impairment in the central nervous system for
sensing defecation[3]. Several reports have demonstrated the prevalence of FI in the United States and Japan focusing on physical and social factors[2-7]. Risk factors for developing FI include physical conditions, i.e., age and sex, obstetrical conditions such as parturition, and comorbidities including diabetes and spinal disorders. Intestinal motility disorders including constipation and irritable bowel syndrome (IBS) and diseases that cause abnormal feces are also risk factors for FI, which is often accompanied by abdominal pain and bloating. Among these, age is identified as a clear risk factor[4,5]. The estimated prevalence of FI in non-institutionalized US adults was 8.3%; it was noted to increase with age, from 2.6% in 20-29-year-olds up to 15.3% in elderly aged 70 and over[5]. It is considered that aging is accompanied by reduced physical abilities, such as muscular strength and cognitive function, and increased comorbidities. FI not only causes patients to lose dignity and self-confidence, it also imposes a heavy physical burden on caregivers and an economic burden on the healthcare system, which could become a major social issue in an aging society[6,8]. There are various treatment strategies for FI by surgery[9,10] and/or drug[11,12]; however, no effective and safe treatment for FI in the elderly has been established.

The Japanese herbal (Kampo) medicine, daikenchuto (DKT), which originated from ancient China, was developed in Japan and approved by the Japanese Ministry of Health, Labour and Welfare for the treatment of abdominal cold sensation and pain accompanied by abdominal bloating. The basic and clinical studies have been reported well[13-20], making DKT to be prescribed widely in Japan. Recent findings suggest that DKT increases rectal sensation and maximum resting pressure (MRP)[21,22]. Abe et al.[23] conducted a retrospective study evaluating the effect of DKT in patients with FI which showed improvement of MRP, voluntary squeeze pressure, and FI score.

This single-center, open-label, single-arm study investigated the efficacy and safety of DKT in elderly patients with FI.

### Methods

#### Study design

This open-label, single-arm study was conducted at Gion Ushita Hospital and affiliated nursing home (Hiroshima, Japan).

The efficacy of DKT for FI was evaluated at the start of DKT administration (baseline), 2 weeks, and 4 weeks after the baseline using the following measurements: (1) an 11-point Numeric Rating Score (NRS) ranging from 0 to 10 (best to worst) was evaluated for abdominal pain and bloating, respectively[24]. (2) A 5-point Cleveland Clinic Incontinence Score (CCIS) ranging from 0 (never) to 4 (always or to once a day) was evaluated for five types of incontinence (solid, liquid, gas, wears pad, lifestyle alteration)[25]. The sum of the frequencies was added up to a total score that may range from 0 to 20. (3) A 4-point FI QOL Scale (FIQLS) ranging from 1 (QOL alteration present most of the time) to 4 (none of the time) was evaluated for patient QOL[26]. This instrument is composed of 29 questions within 4 domains, that is, lifestyle issues, coping/behavior, depression/self-perception, and embarrassment. (4) Anorectal pressure (maximum resting pressure, MRP, and maximum squeeze pressure, MSP) for anal sphincter function; patient’s bowel diary for the number of bowel movements and incidents of FI. (5) A 7-point Bristol Stool Form Scale (BSFS) ranging from 1 (separate hard lumps like nuts) to 7 (watery, no solid pieces) was evaluated for stool form[24]. Safety was evaluated by performing blood tests (AST, ALT, γ-GTP, ALP, T-BIL) at the baseline and at 2 weeks and 4 weeks after the baseline (Figure 1).

#### Study participants

Participants were enrolled between December 2017 and March 2019. Elderly candidates over the age of 70 with abdominal pain or bloating, having two episodes of involuntary soiling for over 4 weeks within the past 6 months, scoring over 11 points in Mini-Mental State Examination (MMSE)[27], who are capable of oral intake, and who are able to provide written informed consent were enrolled in this study. Participants with anal sphincter injury, anal symptoms including rectal prolapse and anal fistula, suspected organ diseases such as cancer in the gastrointestinal tract, serious systemic complications (liver, kidney, heart, blood, or...
metabolic disorders), and severe mental illness were excluded.

**Medication**

DKT (Tsumura & Co., Tokyo, Japan) was orally administered to patients at 15 g/day before each meal for 28 days. Concomitant drugs such as prokinetics, IBS medications, anticholinergic, laxatives, anti-diarrheals, antiflatulents, and Kampo medicines were prohibited during the study period. However, laxatives such as picosulfate and bisacodyl and anti-diarrheal like loperamide were considered to be used as rescue drugs. Antipsychotics, antidepressants, mood stabilizers, anxiolytics, sleeping pills, and dementia treatments were used during the observation period in a fixed dose and administration method. If patients had taken prohibited concomitant drugs or DKT before the start of the study, a 2-week withdrawal period was established before DKT administration.

**Anorectal manometry**

Anorectal manometry was performed using a one-channel pressure transducer (Starlet GMMS-100PC-X, Star Medical Co., Tokyo, Japan). Patients were placed in a left lateral recumbent position with 90 degrees of hip flexion. After calibrating the device to 0 using atmospheric pressure, the catheter was inserted into the patient’s anus with the pressure sensor positioned on the patient’s dorsal side. The first author of this study evaluated MRP, which is defined as the maximum value of the pressure curve, by pulling the catheter at 1 mm per second (rapid pull-through technique) using an automated pulling device. The author then reinserted the catheter and pulled it out manually and stopped every 5 mm (station pull-through technique), causing the patient to have voluntarily anorectal contraction(s) for approximately 3 seconds. This maximum squeeze value represented the MSP. After the completion of the examination, the atmospheric pressure position and the length of the anal canal were manually entered, and an automatic analysis was performed using Anorect Mi.dll.

**Bowel diary**

During the study period, patients recorded their daily bowel movements, FI, and stool form (BSFS) in a diary from the baseline up to 30 days. Frequency of bowel movements and FI was calculated using the average values at the time of evaluation, and fecal properties were evaluated using a median value in consideration of patients who showed repeated cases of hard and soft stools.

**Evaluation**

Changes in NRS, CCIS, FIQLS, and internal anorectal pressure MRP and MSP at 2 weeks and 4 weeks were compared with the baseline. The number of bowel movements, frequency of FI, and changes in stool form (BSFS) were evaluated using patient bowel diaries. The safety of DKT was evaluated by adverse events, abnormal changes in clinical test variables, and side effects.

**Statistical analysis**

The efficacy of DKT was evaluated at varying endpoints, that is, at baseline, 2 weeks, and 4 weeks after using the Wilcoxon signed-rank test with a two-sided risk rate of 5%.

The correlation analysis of each endpoint was obtained by the change in value from the baseline using Spearman’s correlation coefficient with a 95% confidence interval (Fisher’s z-transformation). All analyses were conducted using SAS 9.4 software (SAS Institute Japan Co., Ltd.) and R Version 3.4.1 (The R Development Core Team).

**Ethics**

This study was registered in Japan Registry of Clinical Trials (jRCT) and received approval from Hiroshima University Clinical Research Review Committee (Approval code: CRB6180006) prior to the start of the study (UMIN 000030252, https://www.umin.ac.jp/ctr/index.htm). This study was conducted in accordance to the Declaration of Helsinki and complied with the study protocols and Ethical Guidelines for Medical and Health Research Involving Human Subjects.

**Results**

**Patients**

In total, 21 patients were enrolled in this study. One patient withdrew after 2 weeks at his/her own request. There were 4 males and 17 females who participated in this study, and the average age was 88 years old (73 to 98 years old), the average body mass index (BMI) was 21.4 (15.8 to 27.3), and the average MMSE score was 17.7 (11 to 30) (Table 1). As rescue drugs, picosulfate and bisacodyl were used several times in three patients who had constipation for more than 3 days. Loperamide was not used in any case.

**Abdominal symptoms**

The results of abdominal symptoms using NRS are shown in Figure 2. Improvement in abdominal pain was noted at 2 weeks after, with the baseline score being 1.8 ± 1.5 and 2 weeks after being 1.3 ± 1.1 (p < 0.01) and 0.9 ± 0.6 (p < 0.01) after 4 weeks. Abdominal bloating also showed improvement, with the baseline being 1.9 ± 1.3, 1.2 ± 1.0 (p < 0.01) after 2 weeks, and 0.9 ± 0.5 (p < 0.01) after 4 weeks.

**FI severity**

The results of CCIS are shown in Table 2. Total score, leakage of solid stool, and leakage of liquid stool improved
Figure 2. Time course of abdominal symptoms. Abdominal pain and bloating in patients were evaluated at baseline (0 week), 2 weeks, and 4 weeks after DKT administration. Data is shown as mean ± S.D.; *P  <  0.05, **P  < 0.005 vs. baseline control by the Wilcoxon rank-sum test.

Table 1. Patient Characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number (sex)</td>
<td>21 (4 males, 17 females)</td>
</tr>
<tr>
<td>Age (range)</td>
<td>88 ± 6.1 ³ (73 to 98)</td>
</tr>
<tr>
<td>BMI</td>
<td>21.4 ± 3.2 ³</td>
</tr>
<tr>
<td>MMSE</td>
<td>17.7 ± 6.1 ³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients with the following comorbid disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Brain disease</td>
</tr>
<tr>
<td>Mental disease</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients with the following surgical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocecal resection</td>
</tr>
<tr>
<td>Hysterectomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

All 21 patients in this study had some kind of comorbid disease. BMI, body mass index (kg/m²); MMSE, Mini-Mental State Examination. #: Data is shown as mean ± S.D.

after 2 weeks (p < 0.01) and continued after 4 weeks of DKT administration. Consequently, pad use and lifestyle alteration improved after 4 weeks (p < 0.05).

Quality of life

Table 3 shows the result of FIQLS. The total score improved after 2 weeks (p < 0.01) and continued after 4 weeks.

Anorectal manometry

MRP demonstrated significant improvements at 2 weeks (p < 0.01), and this improvement continued even after 4 weeks (p < 0.01). There was no significant difference in MSP, yet it showed a tendency for improvement (p = 0.058) (Figure 3).

Patient bowel diary

No significant differences were noted as regard to the
number of bowel movements, stool properties (BSFS), or frequency of FI. Two out of three patients with hard stool at the beginning of this present study ameliorated their defecation status to normal. On the other hand, in two out of three patients with watery stool, their stool condition changed to normal or hard. Further, in 11 out of 13 patients with normal stool, their conditions remain unchanged in the duration of this present study. However, it was unclear whether DKT has influenced stool condition because of the small number of participants. Eleven (52.4%) patients did not have FI during the study period.

Table 2. Time Course of Fecal Incontinence Severity.

<table>
<thead>
<tr>
<th></th>
<th>0 week</th>
<th>2 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>1.9 ± 1.3</td>
<td>1.2 ± 1.0 **</td>
<td>0.9 ± 0.5 **</td>
</tr>
<tr>
<td></td>
<td>(0.004)</td>
<td>(0.004)</td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>2.3 ± 1.4</td>
<td>1.1 ± 1.4 **</td>
<td>1.0 ± 1.4 *</td>
</tr>
<tr>
<td></td>
<td>(0.004)</td>
<td>(0.005)</td>
<td></td>
</tr>
<tr>
<td>Gas</td>
<td>1.9 ± 1.7</td>
<td>1.4 ± 1.6</td>
<td>1.4 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>(0.118)</td>
<td>(0.324)</td>
<td></td>
</tr>
<tr>
<td>Wears pad</td>
<td>3.8 ± 0.7</td>
<td>3.3 ± 1.3</td>
<td>3.0 ± 1.6 *</td>
</tr>
<tr>
<td></td>
<td>(0.125)</td>
<td>(0.031)</td>
<td></td>
</tr>
<tr>
<td>Lifestyle alteration</td>
<td>1.8 ± 1.5</td>
<td>1.3 ± 1.1 **</td>
<td>0.9 ± 0.6 *</td>
</tr>
<tr>
<td></td>
<td>(0.004)</td>
<td>(0.008)</td>
<td></td>
</tr>
<tr>
<td>Total CCIS</td>
<td>12.1 ± 5.1</td>
<td>8.2 ± 4.9 **</td>
<td>7.7 ± 5.3 **</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.0001)</td>
<td>(0.0002)</td>
<td></td>
</tr>
</tbody>
</table>

Cleveland Clinic Incontinence Score (CCIS) was evaluated before (0 week) DKT administration and 2 and 4 weeks after DKT administration. Data is shown as mean ± S.D. *p < 0.05, **p < 0.005 significance versus 0 week by the Wilcoxon signed-rank test, respectively. The parentheses show p-value.

Correlation

No correlation was observed between each endpoint in NRS, CCIS, FIQLS, MRP, MSP, BSFS, and change in frequency of FI.

Safety and adverse events

Patients showed good tolerance, exhibiting a compliance rate of 96.1% at 2 weeks and 95.2% at 4 weeks. There were no clear adverse reactions, abnormal blood test values, or side effects during the study period.

Discussion

This is the first prospective study to examine the efficacy and safety of DKT in elderly patients with FI. Our study demonstrated that DKT can be safely administered to elderly patients to alleviate abdominal pain and bloating, improve CCIS and FIQLS, and increase anorectal pressure which was noted at 2 weeks of administration, thus suggesting an early improvement of FI and QOL.

Defecation disorders in elderly people are difficult to treat

Table 3. Time Course of the QOL of Patients with Fecal Incontinence.

<table>
<thead>
<tr>
<th></th>
<th>0 week</th>
<th>2 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FIQLS</td>
<td>3.25 ± 0.76</td>
<td>3.49 ± 0.71 *</td>
<td>3.54 ± 0.67 *</td>
</tr>
<tr>
<td></td>
<td>(0.008)</td>
<td>(0.016)</td>
<td></td>
</tr>
</tbody>
</table>

Fecal Incontinence Quality of Life Scale (FIQLS) was evaluated before (0 week) DKT administration and 2 and 4 weeks after DKT administration. Data is shown as mean ± S.D. *P < 0.05 significance versus 0 week by the Wilcoxon signed-rank test. The parentheses show P-value.
because oftentimes constipation and FI occur simultaneously due to the decline of various functions with age. Elderly patients are prone to develop constipation from reduced anal function owing to a muscle weakness in puborectalis and levator ani muscle and physical inactivity caused by weakened limbs and trunk, in addition to a lack of water intake and dietary fiber. If constipation continues, a reduced rectal sensation and urge to defecate progresses, which aggravates the disorder. Furthermore, age plays a key role in developing passive FI by a declining internal anal sphincter, and the use of laxatives can loosen feces that may cause FI[28].

When considering the optimal treatment for elderly patients with FI, it is ideal for patients to avoid any invasive treatment such as surgery. It is also ideal to have a treatment that is affordable, normalizes stool form, improves colorectal function, and is easily administered to patients with impaired comprehension or loss of motivation, which is required for biofeedback.

In this study, DKT alleviated abdominal pain and bloating. These findings are consistent with previous reports by Horiiuchi et al.[29] and Yuki et al.[30] that demonstrated the reduction of abdominal bloating in patients with chronic constipation. There are some conflicting reports on fecal form and frequency. In a prospective, randomized study evaluating an intestinal motility effect of DKT in patients after total gastrectomy reported by Akamaru et al.[31], optimization of BSFS and consistency of defecation were improved. Also, reports mainly from Japan indicate that DKT increased the frequency of bowel movements regardless of dose and improved constipation in patients[32]. On the other hand, in a randomized study conducted by Iturrino et al.[22] that generally examined women with chronic constipation, no improvement in bowel frequency or constipation was observed regardless of the dose. The disparity in results from other reports is derived from a difference in patient age and BMI. In another report, plasma concentration of hydroxy-alpha-sanshool, one of the main components of DKT, was affected by age and BMI, but there was minimal ethnic difference between Japanese and US participants[33]. DKT is preferably indicated in “ones that show physical weakness, cold abdomen, impaired gastrointestinal function, stagnation of fluid and gas, abdominal pain, bloating, and flatulence.” According to a report by Arita et al.[34] which evaluated the possible DKT responders in post-stroke patients with constipation, DKT was effective in patients with severe constipation and high gas volume. In this study, we have included patients with abdominal pain and bloating as well as presence of FI in our inclusion criteria. This may have positively affected the study outcomes.

The decrease in anorectal pressure with age has been determined to be the cause of passive FI, which mainly occurs due to decreased internal anal sphincter function. MRP significantly decreases with age, and this has a great influence on FI in elderly people[35]. In recent reports[22,23], DKT demonstrated an increase in MRP, and similar findings were demonstrated in this study. An increase in MRP is considered to be one of the reasons for improving FI. Barak et al. reported that topical α-agonist oxymetazoline increased MRP by 25.2% compared to that at baseline (mean, 33.8 mmHg), resulting in an improvement in mean FI episodes in patients with spinal cord injury[36]. Abe et al.[23] reported an increase in MSP with DKT, yet our study only showed a tendency for this. One of the factors that explains our finding was the participants enrolled in this study consisted of elderly people with lower cognitive function; therefore, it is possible that the people did not make a sufficient effort during squeeze contraction.

In a report of DKT on rectal function, Iwai et al. conducted a study on DKT in ten children with severe constipation that demonstrated lowered rectal-anal sensory threshold and improvement in rectal reservoir function[21]. Iturrino et al.[22] reported that DKT at 15 g/day improved first sensation and gas by the evaluation of anorectal sensory threshold using barostat. The enteric nervous system senses external pressure developed in the colon, anus, and rectum, and among the external sensor molecules is the TRP group, such as TRPV1 and TRPA1. DKT contains abundant TRP-stimulating components, including hydroxy-alpha-sanshool, [6]-shogaol, and [6]-gingerol[37,38], which stimulate TRP molecules expressed in the colon and anus and possibly contribute to maintaining external sensor function and muscle contraction. In terms of pathology, one can consider that physical inactivity from aging leads to a continuous lack of external stimulation of the colon and anus, which results in the formation and progression of FI. Although it is within the realm of speculation, some effect of DKT may contribute to the chemical stimulation of external sensors in the colon and anus.

In this study, we could not observe any correlation between the frequency of FI and each endpoint. This may indicate that multiple actions of DKT could affect the pathological condition of FI. Several hypotheses can be made for the mechanism of action of DKT: (1) Hydroxy-alpha-sanshool, the main component of DKT, goes into the bloodstream[39,40] and stimulates KCNK9 molecules expressed on enteric nerves, and interstitial cells of Cajal that control intestinal motility, therefore increasing the reaction of the nerves and cells, resulting in the contraction of internal anal sphincter[41,42]. (2) DKT contains abundant TRP-stimulating compounds including hydroxy-alpha-sanshool, [6]-shogaol, and [6]-gingerol[37]. These compounds may play a role in modulating TRPV1 and TRPA1 molecules which work as external sensors and contribute to the contraction of internal anal sphincter. (3) Processed ginger compounds such as [6]-shogaol and [6]-gingerol are known to inhibit cyclooxygenase-2 enzyme activity and the production
of its metabolite PGE2[43], with the same being shown by DKT[44]. In consideration of the previous hypotheses, the following may be limited to pathological conditions that include inflammatory factors, but we could argue that DKT may improve FI by increasing MRP enabling stool retention in the rectum and promoting water absorption leading to stool solidification, which results in enhancement of anorectal sensation threshold.

This single site, open-label, single-arm study targeting elderly Japanese has limitations, that is, having a short observation period and small number of cases. Further international, multi-center, double-blind comparative studies are expected in the future.

In conclusion, DKT improves MRP and is expected to have therapeutic effects on patients with FI. It also demonstrates its effect on improving QOL in patients with abdominal symptoms and is considered to be a safe and appropriate treatment for elderly people with FI.

Acknowledgements
We would like to thank Dr. Motoaki Koizumi, Dr. Masamichi Noguchi, Mr. Tomohiro Uwajima of Tsumura & Co., and Mr. Satoshi Shimono and Ms. Ayuko Sadamitsu from Gion Ushita Hospital. We would also like to thank all of our medical and administrative staff members for their contributions in making this study possible.

Conflicts of Interest
This study received funding from Tsumura & Co.

Author Contributions
Kazufumi Shimazutus
a. Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data
b. Drafting the article or revising it critically for important intellectual content.
c. Final approval of the version to be published.
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Yusuke Watadani
a. Substantial contributions to acquisition of data and analysis and interpretation of data
b. Revising it critically for important intellectual content
c. Final approval of the version to be published
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Hiroki Oghe
a. Substantial contributions to conception and design
b. Drafting the article
c. Final approval of the version to be published
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

c. Final approval of the version to be published
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Approval by Institutional Review Board (IRB)
Name of the IRB: Hiroshima University Clinical Research Review Committee
Approval code: CRB6180006

References
15. Kono T, Kanematsu T, Kitajima M. Exodus of Kampo, traditional


