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ORIGINAL ARTICLE

Daikenchuto significantly improves stool consistency and lower gastrointestinal symptoms in patients with chronic constipation

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Abstract

Background and Aim: A number of basic and clinical studies have confirmed that the traditional Japanese herbal medicine, Daikenchutou (DKT) has a pharmacological effect on cholinergic and serotonergic mechanisms with a favorable safety profile and an improving effect on lower gastrointestinal (GI) symptoms including abdominal pain or bloating. The purpose of this study is to evaluate the efficacy and safety of DKT on chronic constipation.
Methods: This multicenter, randomized, placebo-controlled, double-blinded clinical trial enrolled 67 patients with chronic constipation fulfilling Rome III criteria. After a 2-week observation period, 63 patients with persistent symptoms were finally randomized to a 4-week course of treatment with DKT or placebo. The primary endpoint consisted of a global assessment of overall treatment effect (OTE), while the secondary endpoints consisted of improvements in stool consistency, spontaneous bowel movements, lower GI symptoms related to constipation, and quality of life. Factors associated with OTE were also investigated.
Results: After 4 weeks administration of DKT, OTE was significantly higher than placebo. No side effects were observed. Significant improvement in stool consistency and lower GI symptoms was observed in the DKT group. The improvements in lower GI symptoms as well as stool consistency were associated with OTE. OTE was higher in patients with greater improvement in lower GI symptoms with mental component summary scores close to normal before treatment.
Conclusion: DKT was effective and safe in treating chronic constipation, especially in patients having symptoms related to constipation with no impaired mental component summary score.

Introduction

Chronic constipation is considered one of the most frequent gastrointestinal (GI) symptoms encountered in daily clinical practice[1–3] and is associated with adverse implications for patients' quality of life and economic well-being.[4] Management of chronic constipation involves improving not only abnormal bowel movements but also constipation-related symptoms, such as abdominal bloating and abdominal pain.[5] Although there are several available laxatives that improve bowel movements,[6] the effectiveness of these laxatives in improving constipation-related symptoms has not been clarified. Constipation-related symptoms, such as abdominal bloating, are frequently observed in Asian patients with lower GI motility dysfunction.[6] However, there are no definitive evidence-based useful treatment options.

The traditional Japanese herbal medicine, Daikenchuto (DKT) consists of mixed DKT extracts powder and Japanese Pharmacopeia (JP) koi (maltose powder) in a ratio of 1.25:10 (wt/wt). DKT extract powder is a mixture of dried extracts of *Zingiberis rhizoma* (JP processed ginger), *Panax ginseng* (JP ginseng radix), and *Zanthoxyli fructus* (JP pepper) in a ratio of 5:3:2 by weight, respectively.[7] So far, DKT has been used clinically mainly for the management and prevention of postoperative adhesive bowel obstruction.[8–12] To summarize the results of previous several basic studies to date, DKT is considered to promote acetylcholine release from intrinsic cholinergic nerve endings via 5-HT_3 and 5-HT_4 receptors,[10–13] by blocking potassium channel subfamily K member 9 (KCNK9) channels[14] and by releasing calcitonin gene-related peptide,[15] which cause intestinal contractions.

There are many factors that can cause abdominal bloating, and representative factors include visceral hypersensitivity to intestinal distension and excessive distension of the colon due to excessive production of abdominal gas caused by constipation.[16,17] One clinical study in healthy adults has reported a significant reduction in small intestinal transit time after 5 days of administration of DKT.[18] Similar results have also been reported in several animal experiments using dogs and pigs.[19] Recently, two interesting animal studies have been reported on the effects of DKT on visceral perception.[20,21] These results suggest that DKT may successfully treat abdominal bloating or pain commonly observed in patients with chronic constipation.

Although the efficacy of DKT for treating chronic constipation has been reported,[22] the level of evidence is low because the study was a single-armed trial with a small sample size that was performed in a single institution. Therefore, we conducted a multicenter, randomized, placebo-controlled, double-blind clinical trial to evaluate the safety and effectiveness of DKT for patients with chronic constipation with complaints of abdominal bloating.

Materials and methods

Patient selection. Patients with either constipation-predominant irritable bowel syndrome (IBS) or functional constipation fulfilling Rome III criteria, aged 18–75 years, in addition, who were required to have chronic constipation to the extent that they could discontinue laxative use, including on-demand use, during the 6-week study period and to report abdominal bloating. At least 1 week prior to study enrollment, all patients were instructed not to use medications used to treat abnormal bowel movements. Patients were instructed to keep their usual lifestyle throughout the study period and to inform the investigators of any changes in their habits. Exclusion criteria included either patients with evidence of organic diseases that could cause GI symptoms, those who had received any medication for IBS or functional constipation within 7 days before or during the study period, or those with metabolic or systemic diseases affecting the digestive system, including diabetes mellitus. Written informed consent was obtained from all participants. This study was approved by the ethics committee of our hospital (approval number 2343), complied with the tenets of the Declaration of Helsinki, and was registered in the University Hospital Medical Information Network (UMIN registration ID: UMIN000020570). All authors reviewed the study data and approved the final version of the manuscript.

Randomization and study design. After 2 weeks of observation, patients were enrolled in the 4-week, randomized, placebo-controlled, double-blinded clinical trial. Consecutively numbered opaque envelopes containing computer-generated allocations were used for concealment. The attending physicians were blinded to the patients' symptom assessments associated with the medication. The study flowchart is shown in Figure 1. All patients with chronic constipation underwent blood tests, ultrasonography, and colonoscopy to exclude organic diseases as necessary. Patients were randomized to receive either DKT (15 g three times per day after meals) or placebo for a treatment period of 4 weeks. Patients were instructed to keep a diary of constipation-related symptoms and stools. Patients returned to the clinic after 4 weeks of treatment to complete a questionnaire regarding the overall treatment efficacy (OTE). For safety, patients continued to be monitored by telephone for 7–10 days after the end of treatment.

Details of questionnaires. During the observation and treatment periods, patients completed a previously validated questionnaire about lower GI symptoms related to constipation, such as abdominal pain, abdominal bloating, strain, and sensation of incomplete evacuation. Symptom scores were evaluated on a 7-grade Likert scale (0 = none, 1 = extremely rare, 2 = rare, 3 = a few, 4 = sometimes, 5 = often, 6 = always) according to the previous studies.[23,24] At the second visit, the health status was assessed using the acute (1-week recall) version of the Short Form-8 health-related quality of life survey (SF-8),[25] which consists of a physical component summary and a mental component summary.[26] At the third visit, the global assessment of OTE was evaluated using a self-administered questionnaire that rated the OTE since the start of treatment as extremely improved (=3 points), improved (=2 points), slightly improved (=1 point), not changed (=0 point), slightly aggravated (=−1 point), aggravated (=−2 points), or extremely aggravated (=−3 points), as previously reported.[27] Patients kept a diary of the number of spontaneous bowel movements (SBM), stool consistency as assessed by the Bristol Stool Form Scale, and lower GI symptoms, such as abdominal pain, abdominal bloating, strain, and sensation of incomplete evacuation. All questionnaires were completed by the study participants themselves and mailed to the data center.

Outcome measures. The primary efficacy endpoint was the global assessment of OTE. Secondary endpoints included a time course of changes in stool consistency, SBM, and lower GI symptoms related to constipation as well as improvement degree in these parameters. Symptom scores at pretreatment, 2 weeks posttreatment, and 4 weeks posttreatment for each eligible patient were the average of the symptom scores for the previous 1 week at each time point. The degree of improvement (Δ) was calculated by the following formula: improvement degree (Δ) = (average of the scores for the 7 days prior to the fourth week of treatment) − (average of the scores for the 7 days prior to treatment).

Clinical factors related to OTE were further investigated. Constipation-related parameters examined for correlation with the OTE were as follows: SBM, stool consistency, abdominal pain score, abdominal bloating score, straining score, and sensation of incomplete evacuation score as indicators of improvement in parameters after treatment. SF-8 mental component summary score and SF-8 physical component summary score were set as pretreatment parameters associated with OTE.

In addition, the same investigation (correlation between the above-mentioned constipation-related parameters and the OTE) was conducted by restricting the subject to the DKT group.

Sample size calculation. Based on a previous study,[28] the significance level (α) was set at 5%, the statistical power ($1 - \beta$) was set at 80%, and the number of patients required per group

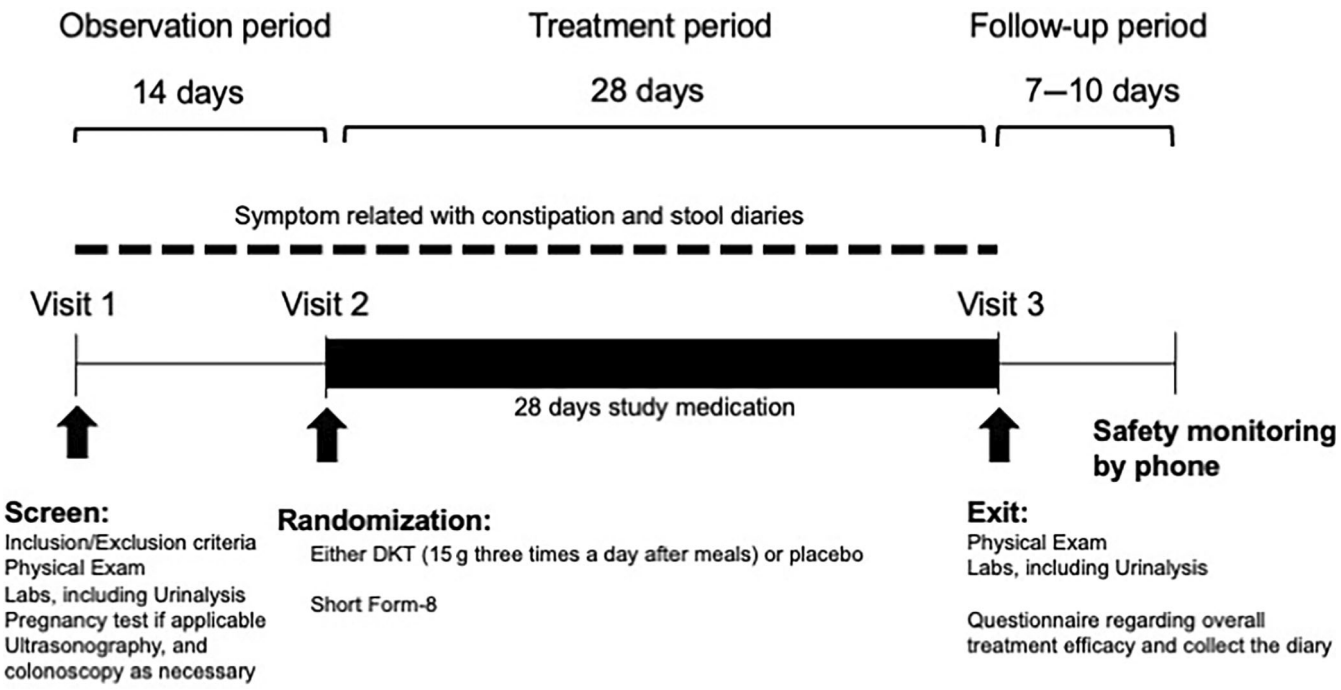

Figure 1 Study timeline.

was calculated. Assuming a discontinuation/dropout rate of 20%, we required 55 patients in each group.

Statistical analysis. Data are presented as mean ± SD. The Student's *t*-test was used to compare the means of two independent groups. The Chi-square test with Yates' correction or Fisher's exact test was used for comparison of categorical data. Each participant's improvement degree (Δ) for stool consistency, SBM, and lower GI symptoms related to constipation were calculated before and after treatment, and the median scores for the two treatment groups were compared against one another using Wilcoxon's rank sum test. The therapeutic response in each group was evaluated on the basis of stool consistency, SBM, and lower GI symptoms related to constipation using Wilcoxon's signed-rank test. The Spearman test was used to evaluate correlations between the OTE and clinical parameters. In all analyses,

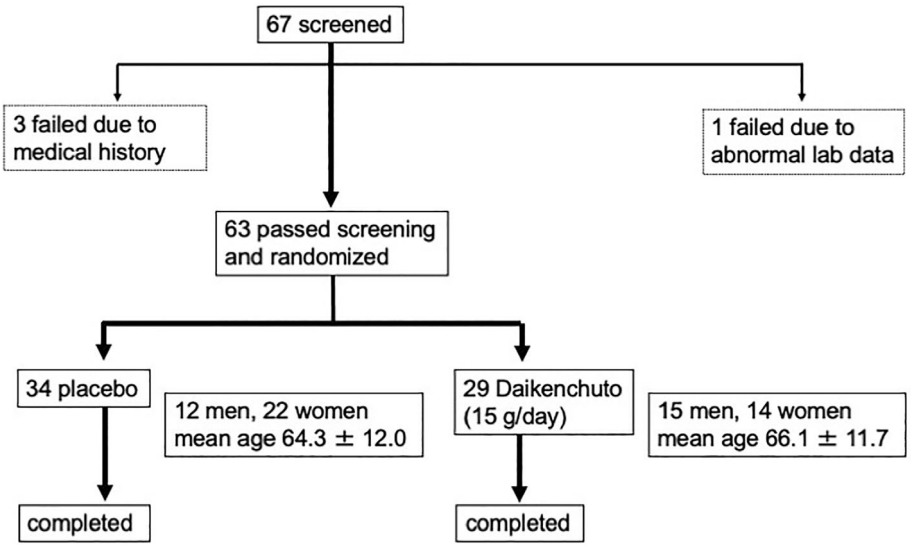

Figure 2 Enrolment and randomization of study participants.

Table 1 Clinical characteristics of the included patients at baseline

	DKT ($n = 29$)	Placebo ($n = 34$)
Sex (men/women)	15/14	12/22
Age (years old)	66.1 ± 11.7	64.3 ± 12.0
Body mass index (kg/m^2)	23.2 ± 2.5	22.8 ± 3.2
Duration of constipation symptoms (years) (median [range])	2.1 (0.5–30)	1.9 (0.7–35)
Mean number of complete spontaneous bowel movement per day	0.9 ± 0.2	0.7 ± 0.4
Bristol stool form	2.7 ± 0.5	3.1 ± 0.3
Abdominal pain score	4.2 ± 0.8	4.9 ± 0.7
Abdominal bloating score	4.0 ± 1.2	3.0 ± 0.9
Straining score	4.9 ± 0.7	4.8 ± 0.5
Feeling of incomplete bowel evacuation score	4.2 ± 0.3	4.3 ± 0.2

Data are expressed as the mean ± SD. Each score represents the average of the scores for the 7 days prior to treatment.
DKT, Daikenchuto.

$P < 0.05$ was considered significant. All statistical analyses were performed using the SPSS statistical package version 17.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics of enrolled patients at baseline. Sixty-seven patients with chronic constipation were screened for study eligibility, and a final total of 63 were randomized. Twenty-nine patients (15 men, 14 women; mean age: 66.1 ± 11.7 years) were assigned to the DKT group, while 34 patients (12 men, 22 women; mean age: 64.3 ± 12.0 years) were assigned to the placebo group (Fig. 2). Table 1 shows the baseline clinical characteristics of the two groups. The median duration of constipation symptoms for all eligible patients was 2 years (range: 0.5–35 years). At baseline for all eligible patients, the mean number of SBM per day was 0.7 ± 0.3, Bristol Stool Form Scale was 2.9 ± 1.0, abdominal pain score was 4.5 ± 0.6, abdominal bloating score was 3.5 ± 1.1, straining score was 4.6 ± 0.9, and feeling of incomplete bowel evacuation score was 4.0 ± 0.2, respectively.

Primary efficacy endpoint: Global assessment of OTE. No significant treatment-related side effects were observed throughout the treatment and observation periods. The OTE after 4 weeks of administration of DKT was significantly higher than that of the placebo group (1.7 ± 1.2 *vs* 1.0 ± 1.2, $P = 0.021$; Fig. 3a).

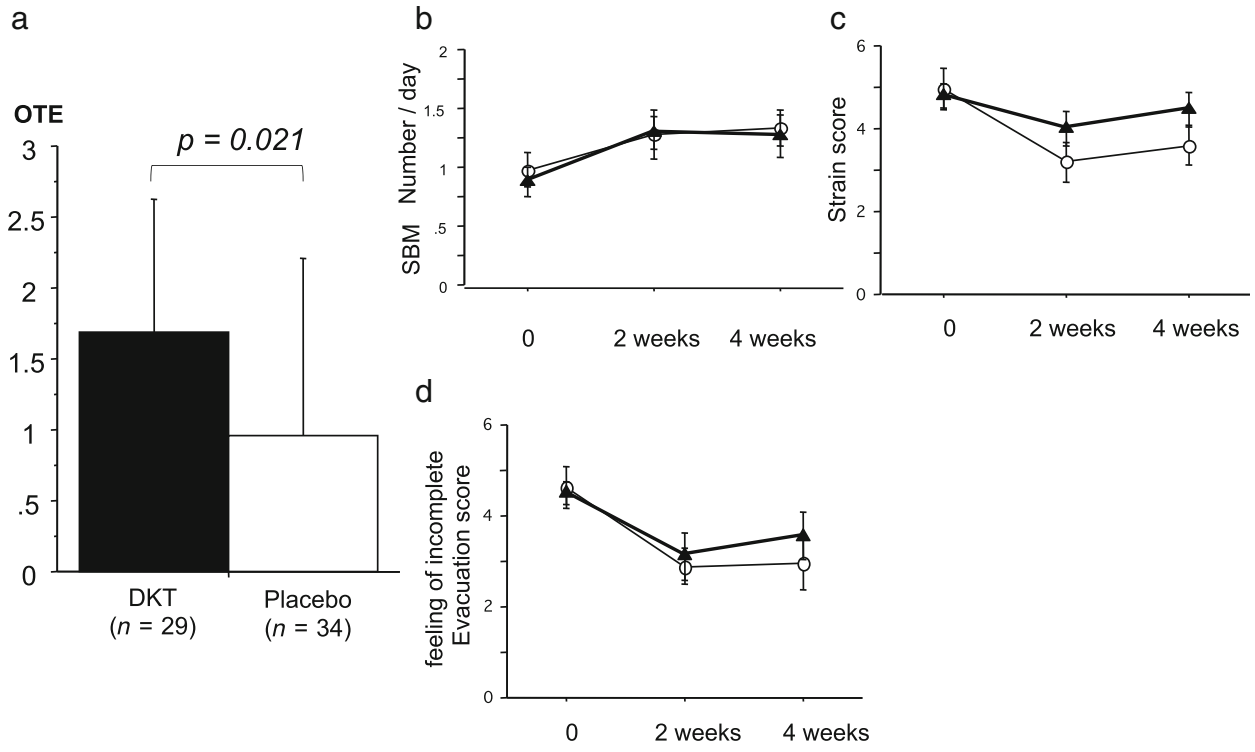

Figure 3 (a) Primary endpoint: global assessment of overall treatment efficacy (OTE). After 4 weeks of treatment, the OTE was significantly higher in the daikenchuto (DKT) group compared with that in the control group. (b–d) Time course of changes in parameters: (b) spontaneous bowel movement, (c) strain score, (d) feeling of incomplete evacuation score. —○—, DKT; —▲—, placebo.

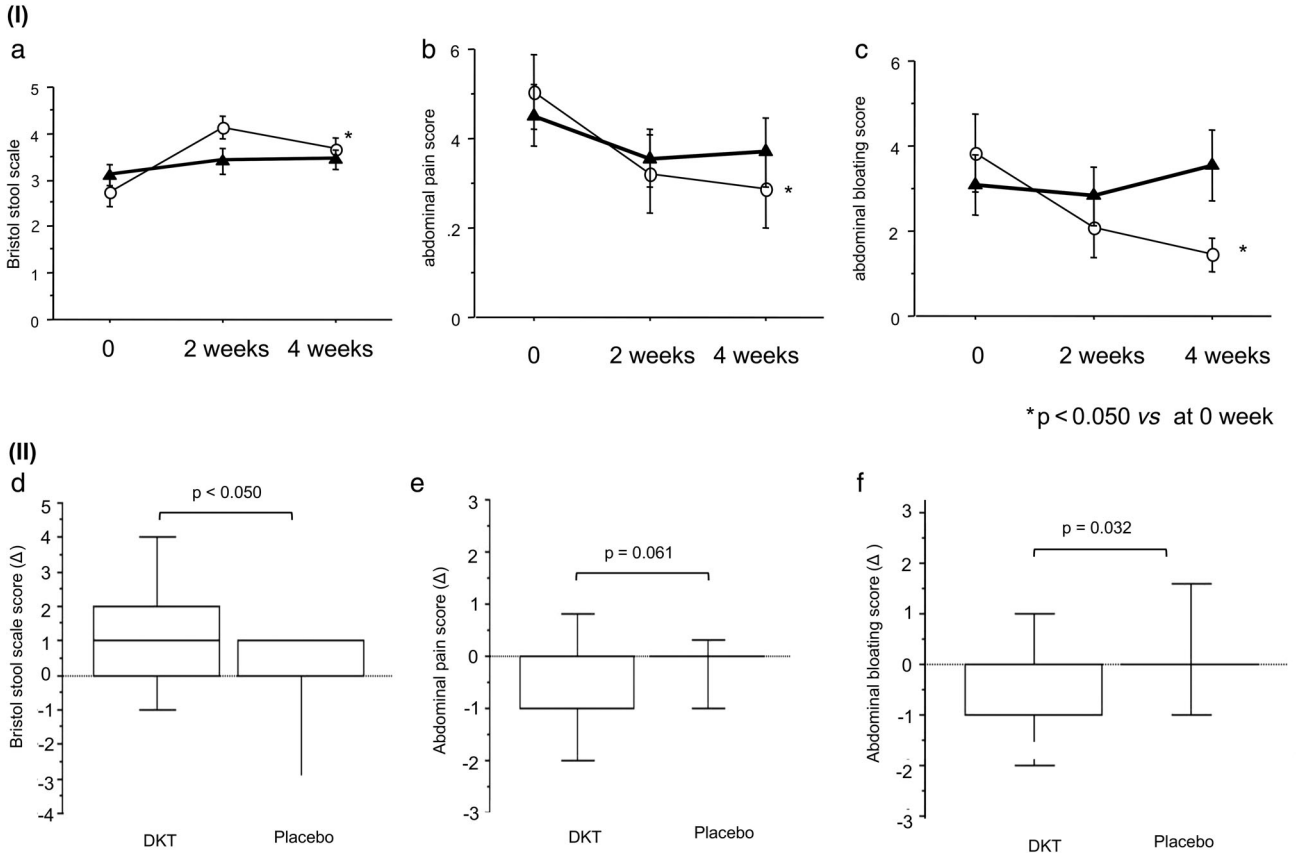

Figure 4 Secondary endpoints (stool consistency, number of bowel movements, and lower gastrointestinal symptoms related to constipation). (I) Time course of changes in parameters (a: Bristol stool scale, b: abdominal pain score, c: abdominal bloating score). (II) Improvement degree of parameters (d: Bristol stool scale, e: abdominal pain score, f: abdominal bloating score). *$P < 0.050$ *versus* baseline. Lower gastrointestinal symptoms related to constipation included abdominal pain, abdominal bloating, strain, and sensation of incomplete evacuation. Stool consistency was evaluated by the Bristol Stool Form Scale. The daikenchuto (DKT) group showed significant improvements in stool consistency and lower GI symptoms related to constipation, while the control group showed no improvements in these outcome measures. DKT tended to improve the number of bowel movements, but this change was not significant. —○—, DKT; —▲—, placebo.

Table 2 Factors related to the overall treatment efficacy in all eligible patients

Parameters	Correlation coefficient	95% confidence interval	*P* value
Number of spontaneous bowel movement	0.295	0.021–0.528	0.036
Stool consistency	0.528	0.305–0.696	<0.001
Abdominal pain scores	0.450	0.199–0.646	0.008
Abdominal bloating scores	0.523	0.287–0.700	<0.001
Straining scores	0.342	0.127–0.604	0.045
Feeling of incomplete bowel evacuation scores	0.398	0.137–0.607	0.035
SF-8 mental component summary scores	0.168	0.128–0.437	0.265
SF-8 physical component summary scores	0.212	0.084–0.473	0.158

Stool consistency is assessed by the Bristol Stool Form Scale.

Secondary efficacy endpoints

Improvements in stool consistency evaluated by the Bristol Stool Form Scale, number of SBM, and lower GI symptoms related to constipation. The lower GI symptoms such as abdominal pain and abdominal bloating, and stool consistency were significantly improved in the DKT group, whereas these parameters were not improved in the placebo group (Fig. 4). There were no significant improvements in SBM, strain, and feeling of incomplete evacuation (Fig. 3b–d).

As shown in Figure 4d–f, theΔabdominal bloating score was significantly higher in the DKT group than in the placebo group (-0.60 ± 1.08 in DKT *vs* 0.07 ± 0.84 in placebo, $P = 0.032$), and theΔabdominal pain score was tended to be higher in the DKT group than in placebo group (-0.59 ± 0.97 in DKT *vs* -0.13 ± 0.67 in placebo, $P = 0.063$), while there were no significant differences in ΔSBM, Δstraining score, and Δfeeling of incomplete evacuation score (Fig. 3b–d).

Table 3 Factors related to the overall treatment efficacy only in the Daikenchuto group

Parameters	Correlation coefficient	95% confidence interval	*P* value
Number of spontaneous bowel movement	−0.032	−0.438 to 0.385	0.887
Stool consistency	0.568	0.224 to 0.787	0.025
Abdominal pain scores	0.517	0.133 to 0.766	0.011
Abdominal bloating scores	0.686	0.382 to 0.856	0.002
Straining scores	0.483	0.089 to 0.747	0.018
Feeling of incomplete bowel evacuation scores	0.421	0.011 to 0.710	0.045
SF-8 mental component summary scores	0.499	0.098 to 0.760	0.017
SF-8 physical component summary scores	0.103	−0.503 to 0.333	0.052

Stool consistency is assessed by the Bristol Stool Form Scale.

Factors related to the OTE in all eligible patients. Table 2 shows the correlation between OTE and the degree of improvement in clinical parameters related to constipation. The OTE correlated with the degree of improvement in stool consistency ($r = 0.528$, $P < 0.001$), abdominal pain score ($r = 0.450$, $P = 0.008$), and abdominal bloating score ($r = 0.523$, $P < 0.001$).

Factors related to the OTE only in the DKT group. Table 3 shows the correlation between the OTE and the degree of improvement in clinical parameters related to constipation for the DKT group only. The OTE correlated with the degree of improvement in stool consistency ($r = 0.568$, $P = 0.025$), abdominal pain score ($r = 0.517$, $P = 0.011$), abdominal bloating score ($r = 0.686$, $P = 0.002$), straining score ($r = 0.483$, $P = 0.018$), sensation of incomplete evacuation score ($r = 0.421$, $P = 0.045$), and SF-8 mental component summary scores ($r = 0.499$, $P = 0.017$).

Discussion

This multicenter, randomized, placebo-controlled, double-blinded clinical trial shows two important results. First, administration of DKT for 4 weeks resulted in a significantly higher OTE than placebo treatment. Second, the effectiveness of DKT was more pronounced in patients with greater improvement in lower GI symptoms scores and with no impaired SF-8 mental component summary scores before treatment.

DKT has been reported to be effective in treating the symptoms of constipation in certain cases, such as patients with Parkinson's disease, pregnant women, and patients with stroke.[29–31] In addition, several studies have reported that DKT significantly improves constipation and abdominal bloating and/or pain.[22,32,33] However, although these studies suggest that DKT significantly improves constipation and constipation-rated symptoms, the level of evidence is low because each study had a small sample size and did not have a double-blinded placebo-controlled design. Therefore, the present study is considered the first report from the Asian region to scientifically demonstrate the efficacy of DKT in improving OTE and constipation-related symptoms, and the factors associated with OTE in patients with chronic constipation.

Animal experiments suggest that DKT promotes GI motility via four main mechanisms of action. The first mechanism by which DKT activates GI motility is activation of TRPA1 channels, the second is activation of TRPV1 channels, and the third is promotion of motilin secretion from motilin-secreting cells.[18,34] In addition, it has recently been shown that hydroxy-α sanshool, a component of DKT, is absorbed and reaches the colon via the blood and has motility-enhancing effects by blocking KCNK9 channels in the enteric nervous system and Cajal interneurons.[14] The ingredients responsible for these hyperkinetic effects are said to be prickly ash (hydroxy-α sanshool) and ginger ([6]-shogoal). Although we did not evaluate the medicinal effects of each crude ingredient of DKT in the present study, we believe that these mechanisms may be partially responsible for our results.

Abdominal bloating is characterized by symptoms of trapped gas, abdominal pressure, and fullness, and is frequently present in patients with IBS or functional constipation. Patients with lower GI functional disorders in Asian countries reportedly have a high prevalence of abdominal bloating; Gwee et al. reported that abdominal bloating is present in 26% of patients with lower GI functional disorders in low-frequency areas, and in 83% of cases in high-frequency areas.[6] Although many patients with lower GI functional disorders experience abdominal bloating, this symptom is difficult to treat.[35] Abdominal bloating can occur for a variety of reasons, including food intolerance, previous infections that have disrupted the gut microbiota, disrupted visceral sensation, delayed intestinal transit, and abnormal reflux of visceral fluid.[16] The success of DKT in the treatment of abdominal bloating in the present randomized controlled trial may be attributed to two interesting pharmacological effects reported in previous basic studies. The first is the improvement of GI motility via TRIPV1, TRIPA1, or motilin,[14,18,34] and the second is the possible improvement in visceral hypersensitivity due to its anti-inflammatory effects[21] and antagonistic effects on 5-HT_{3A} receptors in peripheral nerves.[36] Further study is necessary to clarify how these mechanisms of action of DKT affect abdominal bloating in humans.

The present study found that the OTE was significantly associated with not only the degree of change in stool consistency but also the degree of changes in the abdominal pain score and abdominal bloating score. We believe that these results are valuable in reconfirming the importance of assessing not only stool consistency and bowel movement frequency, but also constipation-related symptoms in the treatment of chronic constipation. The present study also showed that DKT was particularly effective for patients with a high abdominal bloating score whose mental quality of life was not impaired. Although more detailed pathophysiological studies are needed, the present results suggest that DKT may be effective in treating abdominal distension that is not caused by psychological stress. We believe that our results will be clinically useful in identifying patients with abdominal bloating who will benefit from DKT.

Currently, there are many Western medicine treatment options for chronic constipation, including traditional laxatives as well as new pharmacologic treatments, such as secretagogues (lubiprostone and linaclotide) and a bile acid transporter inhibitor

(elobixibat). These Western medicines are effective in alleviating the symptoms of chronic constipation, but some are expensive and their long-term effectiveness is still controversial. The European and French guidelines for the treatment of chronic constipation consider the use of complementary and alternative therapies, including herbal therapy. However, the French guidelines state that in the absence of reliable studies of herbal therapies, it is impossible to give a definite opinion on their efficacy. The European guidelines also conclude that the level of evidence for the efficacy of herbal therapies is low or very low, and the recommendations are weak because of the lack of high-quality studies and the difficulty in comparing products with unclear compositions.[37] Traditional Japanese herbal medicines consist of several components, and in recent years, some extracts of these herbal medicines have been found to be effective in managing constipation and related symptoms. Considering the diversity of pathological conditions of functional GI disorders, including chronic constipation,[38] the multiple mechanisms of action of traditional Japanese herbal medicines in contrast to Western medicines may make them useful as candidate therapeutic agents.

The present study has several limitations. First, no pathological evaluation, such as assessment of colonic transit time, was performed. However, recent reports from Asian countries have shown that the Bristol Stool Form Scale and colonic transit time are related, suggesting that the Bristol Stool Form Scale used in the present study is a suitable alternative indicator.[39] Second, rectal evacuation disorder was not completely ruled out by anorectal function testing. However, rectal evacuation disorders were excluded based on a detailed interview and physical examination at the initial visit in accordance with previous reports.[40] Third, the constipation type of IBS and functional constipation may coexist. However, because it is difficult to completely distinguish between the two conditions in clinical practice, we believe that the present study represented the real-world clinical situation.

In conclusion, in this multicenter, randomized, placebo-controlled, double-blinded clinical trial, DKT is proven to be effective and safe for patients with chronic constipation, not only improving stool consistency but also improving various kinds of lower GI symptoms related to constipation simultaneously. Furthermore, DKT was found to be effective in improving abdominal bloating and other constipation-related lower GI symptoms in patients with chronic constipation, where psychological factors were less involved.

Data availability statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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