Original Article

Randomized, double-blind, placebo-controlled trial of Ficus carica paste for the management of functional constipation

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Background and Objectives: Constipation affects up to 20% of the world's population. The aim of this study was to investigate whether supplementation with *Ficus carica* paste could be used to treat constipation in Korean subjects with functional constipation. **Methods and Study Design:** We conducted a randomized, double-blind, placebo-controlled trial. Subjects with functional constipation were orally supplemented with either *F. carica* paste (n=40) or placebo (n=40) for 8 weeks. We measured the efficacy and safety of *F. carica* paste. Primary outcomes (colon transit time) and secondary outcomes (questionnaire related to defecation) were compared before and after the 8-week intervention period. **Results:** *F. carica* paste supplementation was associated with a significant reduction in colon transit time and a significant improvement in stool type and abdominal discomfort compared with the placebo. Blood parameters and clinical findings for organ toxicity remained within normal ranges. **Conclusion:** These results suggest that *F. carica* paste may have beneficial effects in subjects suffering from constipation.

Key Words: *Ficus carica*, constipation, defecation, colonic transit time, clinical trials

INTRODUCTION

Functional constipation, also known as chronic idiopathic constipation, is a common gastrointestinal complaint in clinical practice and affects 9.2% of Koreans.[1] Patients suffer from abdominal discomfort, bloating, lumpy/hard stools, and incomplete defecation without a clear anatomical or physiological cause, but do not meet the criteria for irritable bowel syndrome.[2] Several underlying mechanisms have been implicated in the pathophysiology of functional constipation, which remains poorly understood. As a consequence, there is no specific therapy available for the treatment of functional constipation.[3] Well established therapeutic approaches include behavioral interventions and use of laxatives,[4,5] but these do not always bring satisfactory relief. Thus, alternative treatments with long-term efficacy are necessary to manage functional constipation.

Ficus carica L., a fruit tree that is native to Asia and belongs to the family Moraceae, is now distributed worldwide. *F. carica* L. contains minerals, vitamins, dietary fiber, amino acids, and several bioactive compounds such as flavonoids, polyphenols, and anthocyanins.[6-9] *F. carica* L. is traditionally used for its medicinal benefits in laxative, cardiovascular, respiratory, antispasmodic, and anti-inflammatory remedies.[10] Experimental studies have reported the beneficial effects of *F. carica* L. in the treatment of hyperglycemia,[11,12] hypercholesterolemia,[13] hyperlipidemia,[14] platelet aggregation,[15] liver damage,[16]

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and viral infection.[17] Recently, we reported the laxative effects of *F. carica* L. using loperamide-induced constipation in rat (*F. carica* paste 0, 1, 6, and 30 g/kg) and beagle models (*F. carica* paste 12 g/kg daily).[18,19] After feeding animals *F. carica* paste for three to four weeks, we observed increases in mucin production and peristaltic movement, which ultimately led to shortened colonic transit time and increased fecal quantity.

Based on encouraging results from animal studies, we hypothesized that *F. carica* paste might prove useful for the treatment of human functional constipation patients in a clinical trial. We designed a randomized, double-blind, placebo-controlled clinical trial using Korean subjects with functional constipation defined according to the Rome III criteria.[2]

METHODS

Subjects and ethics approval

Study subjects were recruited from the Clinical Trial Center for Functional Foods (CTCF2) in Chonbuk National University Hospital (Jeonju, Republic of Korea) between June 2013 and December 2013 through a local newspaper advertisement. A total of 109 subjects agreed to participate in the current study. Inclusion criteria for the study were: (1) age between 19 and 39 years, (2) diagnosis of functional constipation by ROME III criteria (Table 1),[2] (3) colonic transit time ≥36 h, and (4) written informed consent. Exclusion criteria included: (1) allergy or hypersensitivity to any ingredients in the test products, (2) previous history or current disease of the digestive system, cardiovascular system, and endocrine system, or any neurological disorder, (3) diagnosis of irritable bowel syndrome by ROME III criteria, (4) a history of disease that could interfere with the test products or impede their absorption, such as gastrointestinal disease or gastrointestinal surgery, (5) use of certain medications that cause alteration of bowel movements within two weeks, (6) use of antipsychotic medication within 2 months, (7) history of alcohol or substance abuse, (8) participation in any other clinical trials within the prior two months, (9) laboratory tests, or medical/psychological conditions deemed by the investigators to interfere with successful participation in the study, and (10) pregnancy or current breast feeding. All subjects provided written informed consent before entering the study. The study, which was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice by the International Conference on Harmonization (ICH GCP), was approved by the Functional Foods Institutional Review Board (FFIRB) of Chonbuk National University Hospital (FFIRB number: 2013-02-003). The protocol is registered at www.clinicaltrials.gov (NCT02138851).

Preparation of F. carica paste

F. carica paste was provided by Yeongam Green Fig Agriculture Co., Ltd. (Yeongam, Korea) and was standardized to contain 1.7% fiber. The daily dose was calculated from the results of previous animal[18,19] and pilot clinical studies. The nutritional compositions (Table 2) of *F. caria* paste samples was analyzed by the Korea Health Supplement Institute (Sungnam, Korea) and Korea Food Research Institute (Sungnam, Korea). The general composition (calories, carbohydrate, crude fat, crude protein, water, ash, sodium, fiber) of the *F. carica* paste was analyzed by analytical methods for general compositions in Korea Food Code.[20] Fiber measurements were performed using the enzymatic-gravimetric method.[21]

Total flavonoids were measured by the modified methods of Davis[22] with rutin as the standard. Total phenolic compounds were measured with the Folin-Ciocalteu reagent according to the method modified from Singleton,[23] using gallic acid as a standard. Flavonoid (gallic acid, apigenin, naringenin, luteolin, kaempferol, epicatechin, catechin, quercetin, chlorogenic acid, naringin, and rutin) analyses were performed using an Acquity UPLC system (Waters, Miliford, MA, USA) with an Acquity UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm) and a Waters Xevo TQ Triple Quadrupole tandem mass spectrometer to investigate whether *F. caria* paste also contained flavonoids.

The placebo was made with the same taste, smell and appearance without the non- laxative ingredients. The placebo supplements were composed primarily of water, sugar and modified starch.

Study design

The current study was conducted as an eight-week, randomized, double-blind, placebo-controlled clinical trial according to a computer-generated randomization schedule designed to assign subjects to the *F. carica* paste or placebo groups. Neither the investigators nor the subjects knew the randomization code or the results. Subjects attended a screening visit at which inclusion and exclusion criteria were assessed. The enrolled subjects were scheduled for their first visit, and subjects were randomly assigned to either the *F. carica* paste group (n=40) or placebo group (n=40). Subjects received either *F. carica* paste or placebo every four weeks, and all subjects were instructed to take either three *F. carica* paste packs or

Table 1. Rome III functional constipation criteria[†]

1. Must include two or more of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at least 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
   e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

[†]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Table 2. Nutritional compositions

Nutritional compositions	Contents
Calories (kcal/100g)	41.7
Carbohydrate (%)	9.1
Crude fat (%)	0.5
Crude protein (%)	1.2
Water (%)	88.8
Ash (%)	0.4
Sodium (mg/100g)	6.9
Fiber (%)	1.7
Total flavonoids (μg/g, dry)	44.0
Total phenolics compounds (μg/g, dry)	332
Flavonoids/phenols (μg/g, dry)	0.1
Gallic acid (μg/g, dry)	0.8
Apigenin (μg/g, dry)	0.3
Naringenin (μg/g, dry)	0.1
Luteolin (μg/g, dry)	0.2
Kaempferol (μg/g, dry)	0.1
Epicatechin (μg/g, dry)	7.8
Catechin (μg/g, dry)	0.2
Quercetin (μg/g, dry)	0.0
Chlorogenic acid (μg/g, dry)	0.8
Naringin (μg/g, dry)	0.1
Rutin (μg/g, dry)	2.9

General composition (calories, carbohydrate, crude fat, crude protein, water, ash, sodium, fiber): Korea Food Code.[20] Fiber measurements were performed using the enzymatic-gravimetric method.[21] Total flavonoids: as described in Davis et al[22] with rutin as the standard. Total phenolic compounds: Folin-Ciocalteu reagent as described in Singleton et al[23] using gallic acid as a standard. Flavonoids (gallic acid, apigenin, naringenin, luteolin, kaempferol, epicatechin, catechin, quercetin, chlorogenic acid, naringin, and rutin): Acquity UPLC system (Waters, Miliford, MA, USA) with an Acquity UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm) and a Waters Xevo TQ Triple Quadrupole tandem mass spectrometer.

three placebo packs per day (300 g/day) three times daily before meals for eight weeks. Subjects were asked to visit the center every four weeks for a total of four visits, which included the screening visit (screening, 0, 4, and 8 weeks). At each visit, current medication use, smoking status, and alcohol intake were investigated, and subjective symptoms for gastrointestinal adverse events were also assessed. During the eight-week intervention period, subjects were asked to continue their usual diets and activity and were asked not to take any other functional foods or dietary supplements. Colonic transit time, questionnaires related to defecation, biochemical parameters, anthropometric, and vital signs were assessed before and after the intervention period for both groups. Every fourth week, the subjects were asked to report any adverse events or any changes in training, lifestyle, or eating patterns and to assess pack compliance. Compliance was assessed by the number of returned packs. Subjects whose compliance with the *F. carica* paste or placebo treatment was ≤70% of the total dose were considered to have dropped out.

Study outcomes

The primary outcome was colonic transit time. The colonic transit time (CTT) was measured in all subjects before and after the 8-week intervention period using the colonic transit time method described by Metcalf et al.[24] Subjects ingested a once-daily series of three distinctive Colomark™ capsules at the same time each day for three consecutive days. Each capsule contained 20 radiopaque markers shaped like rings. Subjects then received abdominal X-rays 24 h after the ingestion of the final capsule. The colonic transit time was calculated as the sum of the markers detected on X-ray. The sum of the markers detected in the X-ray was multiplied by 1.2, resulting in CTT expressed in hours. Spinal processes and imaginary lines from the fifth lumbar vertebra to the right pelvic outlet and the left iliac crest served as landmarks defining projection zones of right, left, and rectosigmoid colon.[25]

The secondary outcome was constipation-related symptoms. Questionnaires addressing the frequency of defecation, defecation time, stool type, abdominal pain/discomfort, effort required for evacuation, sensation of incomplete evacuation, stool amount per defecation, and satisfactory relief were administered at every visit. Stool consistency was investigated using the Bristol stool form chart on a scale from 1-7,[26] where 1 denotes separate hard lumps, like nuts; 2, sausage-shaped but lumpy; 3, like a sausage or snake but with cracks on the surface; 4, like a sausage or snake, smooth and soft; 5, soft blobs with clear-cut edges; 6, fluffy pieces with ragged edges, a mushy stool; 7, watery, no solid pieces. An average score close to the three-point mode indicates normal stool. Abdominal discomfort scores were evaluated using a scale of 1-5 as follows: score 1, very low; score 2, low; score 3, average; score 4, high; score 5, very high. A higher score indicates severe abdominal pain.

Safety and dietary measures

Safety assessments included an electrocardiogram (ECG), and laboratory tests (WBCs, RBCs, haemoglobin, hematocrit, platelets, total bilirubin, alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), glucose, total protein, albumin, blood urea nitrogen (BUN), creatinine, creatine kinase, lactate dehydrogenase (LDH), Na, K, Cl, Ca, and P) before and after the 8-week intervention period. Blood pressure and pulse were assessed at every visit. Anthropometrics were assessed before and after the 8-week intervention period. Height and weight were measured using the same machine during the study period. Body Mass Index (BMI, kg/m^2) was calculated by dividing the weight (kg) by the square of the height (m).

All participants completed a dietary record at each visit during the intervention period in order to evaluate energy intake and diet quality. Dietary intake data were analyzed by a dietitian using CAN-pro 4.0 software (The Korea Nutrition Society, Seoul, Korea).

Statistical analysis

Statistical analysis was performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). The intent-to-treat (ITT) population included all randomized subjects who received *F. carica* paste/placebo and attended at least one study visit after the start of the intervention. The analysis of efficacy and safety was performed in the ITT

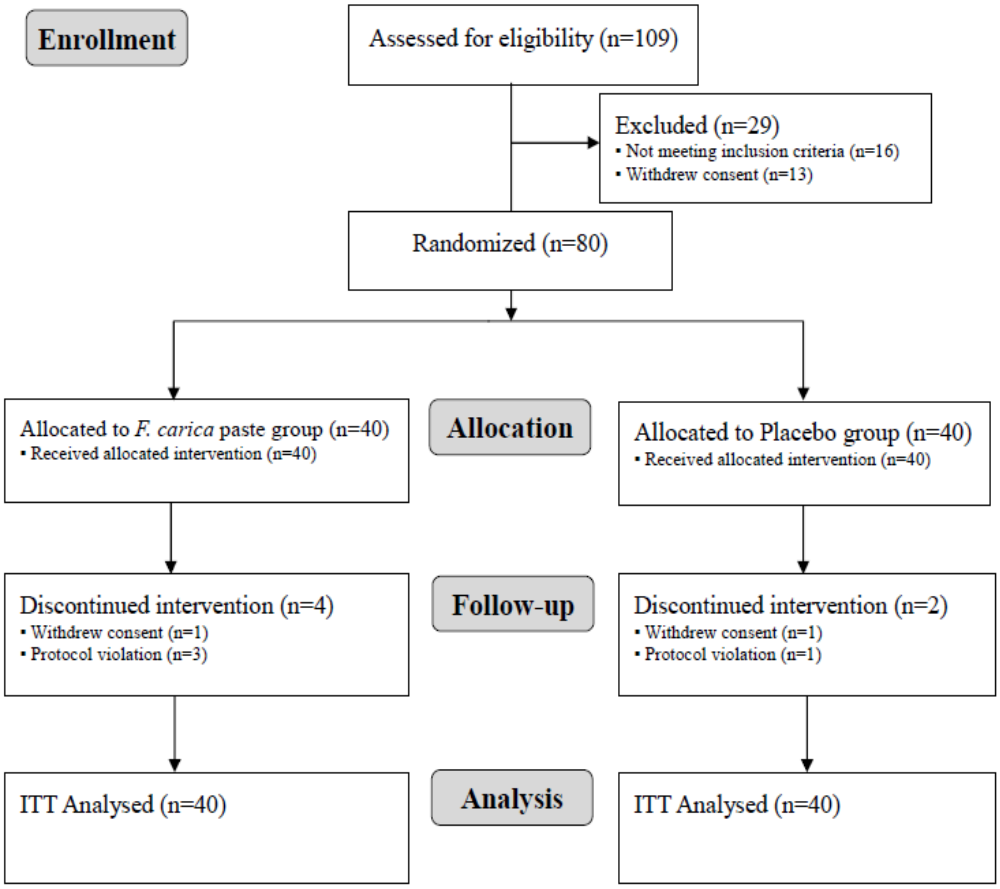

Figure 1. Flow chart for the study subjects. Number of study participants enrolled, allocated, followed, and analyzed, shown using the CONSORT 2010 Flow Diagram.

population.

Data are shown as mean and standard deviations (SD). The sample size was statistically determined to obtain a power of 80% with an alpha of 0.05. In order to demonstrate effects on colonic transit time, which was calculated to be a 5 h reduction with a standard deviation of 8 h, a sample size of 64 subjects (32 in the *F. carica* paste group and 32 in the placebo group) was required. Assuming a 20% loss to follow-up, we set the total sample size at 80. The two groups were equal in size in order to obtain the greatest statistical power. General characteristics differing between the *F. carica* paste and placebo groups were analyzed by an independent *t*-test or a chi-square test. The significance of differences within or between groups was tested by a linear mixed-effect model and paired *t*-tests of the mean. The chi-square test was performed to determine differences in frequencies of categorized variables between groups. A value of $p<0.05$ was considered statistically significant.

RESULTS

General subject characteristics

The sampling and trial profiles are summarized in Figure 1 for the subjects who completed the study. A total of 109 subjects were screened. Twenty-nine subjects were excluded from the current analysis because they did not meet all of the inclusion criteria or withdrew consent. The remaining 80 subjects were divided equally and randomly into the *F. carica* paste or placebo groups. Four subjects from the *F. carica* paste group and two subjects from the placebo group failed to complete the study. Two subjects voluntarily withdrew consent for personal reasons. Four subjects discontinued treatment because of protocol violation. As a result, 74 subjects (*F. carica* paste group=36 and placebo group=38) remained.

General characteristics of the subjects are shown in Table 3. There were no significant differences between groups in baseline characteristics such as age, sex, height, weight, body mass index, alcohol intake, and smoking status.

Colonic transit time

There was no difference in the overall colonic transit time at 24 h in the two groups at baseline (Table 4 and Figure 2). After 8 weeks of supplementation, mean colonic transit times were significantly decreased in both the placebo (76% reduction) and *F. carica* paste (61% reduction) groups. Of note, there were significant treatment effects on colonic transit time in subjects receiving *F. carica* paste ($p=0.030$). Colon transit time was significantly improved in the *F. carica* paste group compared with the placebo group ($p=0.045$).

Constipation-related symptoms

F. carica paste supplementation was associated with beneficial effects on stool consistency as evaluated by Bristol score ($p=0.024$) and abdominal discomfort ($p=0.012$) compared with the placebo (Table 5). However, *F. carica* paste had no significant treatment effects on frequency of defecation, defecation time, abdominal pain, effort for

Table 3. Demographic characteristics of study subjects

	Placebo group (n=40)	*F. carica* paste group (n=40)	Total (n=80)	*p*-value†
Age (years)	24.7±4.5	23.3±3.4	24.0±4.1	0.123
Sex (M/F)	4/36	5/35	9/71	>0.999‡
Height (cm)	164±5.8	165±6.7	165±6.2	0.302
Weight (kg)	56.3±7.1	59.4±10.4	57.8±9.0	0.125
BMI (kg/m^2)	21.0±2.4	21.7±3.0	21.3±2.7	0.258
Alcohol drinker (Yes/No)	27/13	26/14	53/27	0.813‡
Unit/week	2.0±2.4	1.8±1.6	1.9±2.0	0.605
Smoker (Yes/No)	2/38	2/38	4/76	>0.999‡
A piece/day	6.5±5.0	6.5±5.0	6.5±4.0	>0.999

M: male; F: female; BMI: body mass index.
Data are presented as mean±SD.
†Analyzed by independent *t*-tests and the *p*-value represents the comparison to the placebo group.
‡Analyzed by Chi-square tests (Fisher's exact test) and the *p*-value represents the comparison to the placebo group.

Table 4. Colon transit time

	Placebo group (n=40)				*F. carica* paste group (n=40)				*p*-value§
	Baseline	8 week	Change†	*p*-value‡	Baseline	8 week	Change†	*p*-value‡	
CTT (h)	61.6±10.9	46.7±16.3	-15.0±17.7	<0.0001	63.7±10.1	38.7±20.3	-24.5±22.4	<0.0001	0.030

CTT: colon transit time.
Data are presented as the mean±SD.
†Change = 8 week – Baseline.
‡Analyzed by paired *t*-test between baseline and 8 weeks in each group.
§Analyzed by linear mixed-effect model and the *p*-value represents the comparison to the placebo group.

evacuation, sensation of incomplete evacuation, stool amount per defecation, or satisfactory relief.

Safety and dietary measures

Safety was assessed by assessing adverse events, electrocardiograms, laboratory tests (hematology, biochemistry, and urinalysis), vital signs, and anthropometric parameters (data not shown). At each visit, information about symptoms or adverse events was recorded, but no serious adverse events were reported during the 8-week study period. The results of the safety assessments were in the normal range, and no subjects withdrew because of adverse events. In addition, no significant differences in dietary intake (calorie, carbohydrate, protein, fat, and fiber) were observed between the groups during the intervention period (Table 6).

DISCUSSION

Our study is the first randomized, placebo-controlled, double-blind clinical trial to evaluate the safety and efficacy of *F. carica* paste for the treatment of functional constipation patients. After 8 weeks of supplementation, we observed a statistically significant reduction in colonic transit time, as demonstrated by a decrease in the number of radio-opaque markers remaining in the gastrointestinal tract. A significant increase in Bristol score and a significant reduction in abdominal discomfort were also observed. Our results are consistent with those of our previous animal studies showing that *F. carica* paste accelerates colonic transit and improves bowel function.[18,19] In addition, our study subjects did not report any specific adverse events, unlike patients using currently prescribed laxatives.

The acceleration of colonic transit due to *F. carica* paste may be associated with loosened stool consistency. Using the Bristol stool score, we observed an increase in score from 1.9±0.7 to 3.03±0.82 in the *F. carica* paste group, while the Bristol stool score changed from 2.2±0.7 to 2.8±0.8 in the placebo group (p=0.024). Low scale scores (score 1 or 2) mean harder stool, while higher values (score 3 or 4) indicate a normal stool consistency. Given that a minor change in Bristol score from 2 to 3 may represent a significant acceleration in the colonic transit and improvement in the subjective symptoms of constipation patients,[27] *F. carica* paste may increase colonic transit by loosening stool consistency. Regarding the effect of *F. carica* paste on colonic transit, we previously observed that *F. carica* paste maintained the thickness of the distal colon and areas of crypt epithelial cells in loperamide-treated rats.[18] These histological findings reveal that *F. carica* paste preserves the intestinal area responsible for mucin secretion against loperamide treatment. In addition, we observed increases in the water content of the stool and intestinal tension associated with *F. carica* paste treatment. These findings are all related to loosened stool consistency and increased colonic transit. Similar findings were also observed in beagles, in which constipation was induced by a high protein diet.[19] Acceleration of colonic transit through enhanced intestinal tension and colonic secretion may deliver stool from the proximal colon to the distal colon more rapidly, leading to defecation with greater ease and less straining.

F. carica paste had no significant treatment effects on constipation related symptom parameters except for abdominal discomfort. Volunteers in the present study were not actively seeking treatment for their condition and thus

Table 5. Questionnaire related to defecation

	Placebo group (n=40)				*F. carica* paste group (n=40)				*p*-value[§]
	Baseline	8 week	Change[†]	*p*-value[‡]	Baseline	8 week	Change[†]	*p*-value[‡]	
Frequency of defecation per week	2.2±0.8	3.4±1.4	1.2±1.5	<0.0001	2.1±0.7	3.7±2.1	1.6±2	<0.0001	0.346
Defecation time (min)	11.0±5.5	6.3±3.7	-4.9±4.8	<0.0001	11.4±6.4	6.3±3.6	-5.4±4.9	<0.0001	0.700
Bristol score	2.2±0.7	2.8±0.8	0.7±1	0.001	1.9±0.7	3.0±0.8	1.1±0.9	<0.0001	0.024
Abdominal pain	3.2±0.6	3.0±0.8	-0.2±0.8	0.061	3.0±0.7	2.6±0.5	-0.3±0.5	0.001	0.518
Abdominal discomfort	3.5±0.6	3.1±0.7	-0.3±0.8	0.007	3.6±0.7	2.8±0.7	-0.8±0.8	<0.0001	0.012
Effort for evacuation	3.1±1.0	2.4±0.8	-0.8±1.2	0.012	3.3±1.0	2.3±0.7	-0.9±1	<0.0001	0.467
Sensation of incomplete evacuation	2.1±0.6	2.8±0.7	0.7±0.9	<0.0001	2.1±0.8	2.9±0.9	0.8±0.9	<0.0001	0.513
Stool amounts per defecation	2.4±0.8	2.5±0.7	0.1±0.9	0.744	2.3±0.9	2.7±0.9	0.3±1	0.033	0.167
Satisfactory relief	-	3.3±0.8	-	-	-	3.4±0.8	-	-	

Data are presented as the mean±SD.
[†]Change = 8 week – Baseline.
[‡]Analyzed by paired *t*-test between baseline and 8 weeks in each group.
[§]Analyzed by linear mixed-effect model and the *p*-value represents the comparison to the placebo group.

Table 6. Dietary intake

	Placebo group (n=40)				*F. carica* paste group (n=40)				*p*-value[§]
	Baseline	8 week	Change[†]	*p*-value[‡]	Baseline	8 week	Change[†]	*p*-value[‡]	
Calorie (kcal)	1499±499	1415±565	-9.0±518	0.389	1385±401	1366±537	37.6±396	0.801	0.801
Carbohydrate (g)	217±69.5	203±83.3	-6.5±69.8	0.258	186±60.1	196±72.3	18.6±54.4	0.355	0.143
Fat (g)	44.3±19.2	43.2±24.5	1.7±25.0	0.796	46.4±17.8	41.1±22.7	-3.9±24.6	0.179	0.469
Protein (g)	54.4±22.6	52.4±24.8	0.8±27.4	0.666	53.9±18.2	50.6±24.1	-1.6±21.8	0.36	0.829
Fiber (g)	13.3±5.2	12.1±5.9	-0.8±6.3	0.244	10.5±3.9	10.9±5.2	0.7±4.3	0.637	0.217

Data are presented as the mean±SD.
[†]Change=8 week–Baseline.
[‡]Analyzed by paired *t*-test between baseline and 8 weeks in each group.
[§]Analyzed by linear mixed-effect model and the *p*-value represents the comparison to the placebo group.

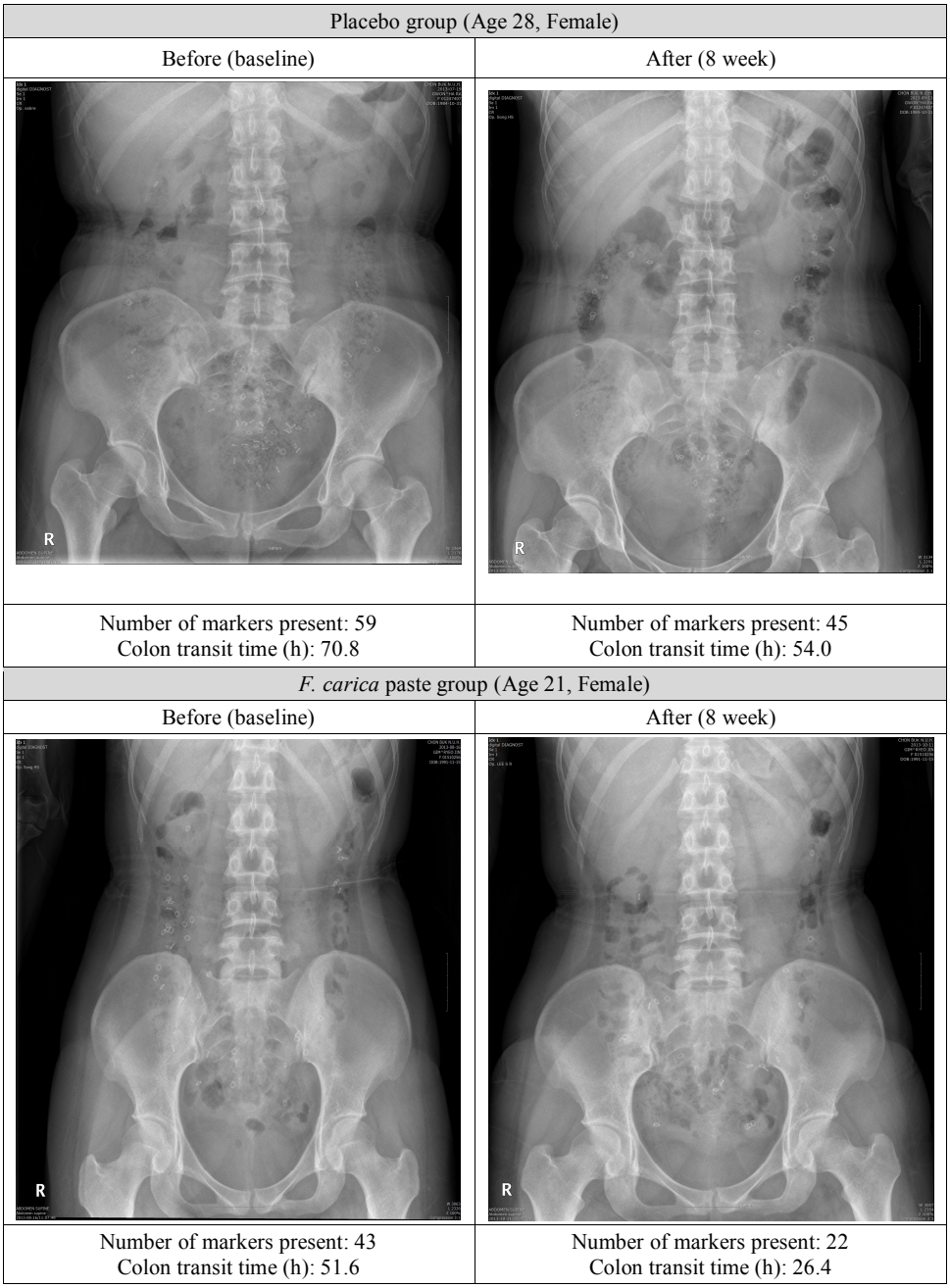

Figure 2. Representative abdominal X-rays data at baseline and 8 week in a subject from *F. carica* paste or placebo group.

could be considered to have relatively mild constipation, also reflected by their low Bristol scores at baseline (2.2±0.7 and 1.9±0.7 in placebo and *F. carica* paste groups, respectively). These relatively low Bristol scores may have contributed partly to the failure to achieve statistical significance.

From a mechanistic point of view, the beneficial effects of *F. carica* paste on constipation are most likely related to its composition. As shown in Table 2 and also reported by several previous studies,[6-9] *F. carica* contains high amounts of cellulose, phenols, flavonoids, and anthocyanins, which are reported to have laxative effects. These bioactive substances may stimulate chloride channel or serotonergic signaling, which in turn stimulate colonic secretion of water, electrolytes, and mucin.[28-32] In addition, differences in fiber may affect colonic transit time. Specifically, the concentration of fiber in *F. carica* was 5.1 g. Fiber appears to shorten CTT, primarily because of enhanced bowel movement and mucin secretion.[33] Fiber can also decrease colonic mucinase activity to increase the mucin content.[34] Indeed, many reports have shown the favorable effects of dietary fiber on constipation. Alternatively, some component of *F. carica* may have a direct effect on smooth muscle, which increases intestinal motility. This hypothesis was supported by our previous study.[18] *F. carica* paste increased peristalsis and intestinal tension in a dose-dependent manner. However, Gilani et al[15] reported an antispasmodic effect of *F. carica*. These opposite conclusions may result from differences in the nutritional composition of test materials and the experimental design. We used an ethanol extract of fresh *F. carica* fruit, whereas Gilani et al used a water extract of dried *F. carica* fruit. Phytochemical analysis reveals plenty of alkaloids, flavonoids, coumarins, saponins, and terpenes in water extracts. However, as shown in Table 2, the *F. carica* paste used in this study contains different

bioactive substances such as gallic acid, apigenin, naringenin, luteolin, kaempferol, epicatechin, catechin, quercetin, chlorogenic acid, naringin, and rutin. Differences in the geographical area of cultivation of *F. carica* (Pakistan vs Korea) might also result in different nutritional compositions. In addition, Gilani et al observed the antispasmodic activity of *F. carica* in K^+-induced sustained contraction of isolated rabbit jejunum, whereas we observed spasmodic activities using isolated stable rat ileum.

Three aspects of this study should be reported as potential limitations in drawing broader conclusions. First, the study sample was mainly female. The greater inclusion of female patients is due to the higher prevalence of functional constipation in woman,[35] which seems to be associated with cultural factors.[36] Therefore, these results should be applied with caution to the general population of functional constipation patients. Second, because this study was a placebo-controlled study, psychological and behavioral placebo responses should be considered. Spiller[37] analyzed 25 randomized, controlled studies of irritable bowel syndrome and found that median placebo response was 47%, which is three times the size of the difference between drug and placebo response. The minimum length of any clinical trial should be 3 months, because the placebo effect takes approximately 3 months to tail off. In this study, subjects who received the placebo also improved colonic transit, stool consistency, and constipation-related symptoms. Nevertheless, *F. carica* paste was superior to the placebo in achieving a therapeutic response. Third, the sample size was powered to detect changes in primary outcome (colonic transit). The final sample size might be underpowered to detect more significant differences in secondary outcome (constipation-related symptoms). This may be reflected in statistical insignificance for some measures.

Traditional dietary patterns in East Asian countries are characterized by high intake of rice, fermented foods, and vegetables. However, this dietary pattern has recently rapidly changed to be more similar to that of Western countries, with a high intake of bread and meat. This change may contribute to the increased prevalence of gastrointestinal motility disorders including functional constipation in the Korean population. Indeed, a recent population-based study performed in a Korean community shows that the prevalence is 16.5% for self-reported constipation, 9.2% for functional constipation, and 3.9% for constipation-predominant irritable bowel syndrome.[1] At present, other than laxatives, there is no approved gut motility-stimulating agent for constipation. Our study demonstrates that *F. carica* paste is effective for accelerating colonic transit without noticeable side effects. Therefore, *F. carica* paste can be used to manage patients with slow transit and functional constipation.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Jun DW, Park HY, Lee OY, Lee HL, Yoon BC, Choi HS et al. A population-based study on bowel habits in a Korean community: prevalence of functional constipation and self-reported constipation. Dig Dis Sci. 2006;51:1471-7. doi: 10.1007/s10620-006-9087-3.
2. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130:1480-91. doi: 10.1053/j.gastro.2005.11.061.
3. Rajindrajith S, Devanarayana NM, Benninga MA. Review article: faecal incontinence in children: epidemiology, pathophysiology, clinical evaluation and management. Aliment Pharmacol Ther. 2013;37:37-48. doi: 10.1111/apt.12103.
4. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics. 2011;128:753-61. doi: 10.1542/peds.2011-0179.
5. Whitehead WE, di Lorenzo C, Leroi AM, Porrett T, Rao SS. Conservative and behavioural management of constipation. Neurogastroenterol Motil. 2009;21(Suppl 2):55-61. doi: 10.1111/j.1365-2982.2009.01404.x.
6. Oliveira AP, Valentao P, Pereira JA, Silva BM, Tavares F, Andrade PB. *Ficus carica* L.: metabolic and biological screening. Food Chem Toxicol. 2009;47:2841-6. doi: 10.1016/j.fct.2009.09.004.
7. Solomon A, Golubowicz S, Yablowicz Z, Grossman S, Bergman M, Gottlieb HE, Altman A, Kerem Z, Flaishman MA. Antioxidant activities and anthocyanin content of fresh fruits of common fig (*Ficus carica* L.). J Agric Food Chem. 2006;54:7717-23. doi: 10.1021/jf060497h.
8. Vinson JA, Zubik L, Bose P, Samman N, Proch J. Dried fruits: excellent in vitro and in vivo antioxidants. J Am Coll Nutr. 2005;24:44-50.
9. Vaya J, Mahmood S. Flavonoid content in leaf extracts of the fig (*Ficus carica* L.), carob (Ceratonia siliqua L.) and pistachio (Pistacia lentiscus L.). Biofactors. 2006;28:169-75.
10. Guarrera PM. Traditional phytotherapy in Central Italy (Marche, Abruzzo, and Latium). Fitoterapia. 2005;76:1-25. doi: 10.1016/j.fitote.2004.09.006.
11. Perez C, Canal JR, Torres MD. Experimental diabetes treated with *ficus carica* extract: effect on oxidative stress parameters. Acta Diabetol. 2003;40:3-8. doi: 10.1007/s00059 20300001.
12. Perez C, Dominguez E, Canal JR, Campillo JE, Torres MD. Hypoglycaemic activity of an aqueous extract from *ficus carica* (fig tree) leaves in streptozotocin diabetic rats. Pharm Biol. 2000;38:181-6. doi: 10.1076/1388-0209(200007)3831-SFT181.
13. Canal JR, Torres MD, Romero A, Perez C. A chloroform extract obtained from a decoction of *Ficus carica* leaves improves the cholesterolaemic status of rats with streptozotocin-induced diabetes. Acta Physiol Hung. 2000; 87:71-6. doi: 10.1556/APhysiol.87.2000.1.8.
14. Perez C, Canal JR, Campillo JE, Romero A, Torres MD. Hypotriglyceridaemic activity of *Ficus carica* leaves in experimental hypertriglyceridaemic rats. Phytother Res. 1999;13:188-91. doi: 10.1002/(SICI)1099-1573(199905)13:3<188::AID-PTR411>3.0.CO;2-P.
15. Gilani AH, Mehmood MH, Janbaz KH, Khan AU, Saeed SA. Ethnopharmacological studies on antispasmodic and antiplatelet activities of *Ficus carica*. J Ethnopharmacol. 2008;119:1-5. doi: 10.1016/j.jep.2008.05.040.

16. Saoudi M, El Feki A. Protective role of *Ficus carica* stem extract against hepatic oxidative damage induced by methanol in male wistar rats. Evid Based Complement Alternat Med. 2012;2012:150458. doi: 10.1155/2012/150458.
17. Camero M, Marinaro M, Lovero A, Elia G, Losurdo M, Buonavoglia C, Tempesta M. *In vitro* antiviral activity of *Ficus carica* latex against caprine herpesvirus-1. Nat Prod Res. 2014:28:2031-5. doi: 10.1080/14786419.2014.918120.
18. Lee HY, Kim JH, Jeung HW, Lee CU, Kim DS, Li B et al. Effects of *Ficus carica* paste on loperamide-induced constipation in rats. Food Chem Toxicol. 2012;50:895-902. doi: 10.1016/j.fct.2011.12.001.
19. Oh HG, Lee HY, Seo MY, Kang YR, Kim JH, Park JW et al. Effects of *Ficus carica* paste on constipation induced by a high-protein feed and movement restriction in beagles. Lab Anim Res. 2011;27:275-81. doi: 10.5625/lar.2011.27.4.275.
20. Ministry of Food and Drug Safety (Korea). Korea Food Code. 2014/10/21 [cited 2014/12/31]; Available from: http://fse.foodnara.go.kr/residue/RS/jsp/menu_02_01_01.jsp. (In Korean)
21. AOAC. Official Methods of Analysis. Washington DC, USA: Association of Official Analytical Chemists; 2000.
22. Davis WB. Determination of flavonones in citrus fruits. Anal Chem. 1947;19:476-77.
23. Singleton VL, Orthofer R, Lamuela-Raventos, RM. Analysis of total phenols and other oxidation substrates and antioxidant by means of Folin-Ciocalteu reagent. Methods Enzymol. 1999;299:152-78.
24. Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. Gastroenterology. 1987;92:40-7.
25. Arhan P, Devroede G, Jehannin B, Lanza M, Faverdin C, Dornic C et al. Segmental colonic transit time. Dis Colon Rectum. 1981;24:625-9.
26. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-4. doi: 10.3109/00365529709011203.
27. Deiteren A, Camilleri M, Bharucha AE, Burton D, McKinzie S, Rao AS, Zinsmeister AR. Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. Neurogastroenterol Motil. 2010;22:415-23, e95. doi: 10.1111/j.1365-2982.2009.01441.x.
28. Andresen V, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology. 2007;133:761-8. doi: 10.1053/j.gastro.2007.06.067.
29. El-Salhy M, Gundersen D, Ostgaard H, Lomholt-Beck B, Hatlebakk JG, Hausken T. Low densities of serotonin and peptide YY cells in the colon of patients with irritable bowel syndrome. Dig Dis Sci. 2012;57:873-8. doi: 10.1007/s10620-011-1948-8.
30. Manabe N, Camilleri M, Rao A, Wong BS, Burton D, Busciglio I, Zinsmeister AR, Haruma K. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol. 2010; 298:G970-5. doi: 10.1152/ajpgi.00043.2010.
31. Wapnir RA, Teichberg S. Regulation mechanisms of intestinal secretion: implications in nutrient absorption. J Nutr Biochem. 2002;13:190-9.
32. Wu D, Wang X, Zhou J, Yuan J, Cui B, An R, Hu Z. Traditional Chinese formula, lubricating gut pill, improves loperamide-induced rat constipation involved in enhance of Cl^- secretion across distal colonic epithelium. J Ethnopharmacol. 2010;130:347-53. doi: 10.1016/j.jep.2010.05.018.
33. Jeon JR, Choi JH. Lactic acid fermentation of germinated barley fiber and proliferative function of colonic epithelial cells in loperamide-induced rats. J Med Food. 2010;13:950-60. doi: 10.1089/jmf.2009.1307.
34. Shiau SY, Chang GW. Effects of dietary fiber on fecal mucinase and β-glucuronidase activity in rats. J Nutr. 1983; 113:138-44.
35. Klaschik E, Nauck F, Ostgathe C. Constipation--modern laxative therapy. Support Care Cancer. 2003;11:679-85. doi: 10.1007/s00520-003-0525-x.
36. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99:750-9. doi: 10.1111/j.1572-0241.2004.04114.x.
37. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. Am J Med. 1999;107:91S-7S.

Original Article

Randomized, double-blind, placebo-controlled trial of Ficus carica paste for the management of functional constipation

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无花果酱对于功能性便秘管理的随机、双盲与安慰剂对照试验

背景和目的：便秘影响到世界人口的 20%。这项研究目的是探讨无花果酱是否可以用于韩国功能性便秘患者的治疗。**方法与研究设计：**我们进行了一项随机、双盲与安慰剂对照试验。功能性便秘患者摄入无花果酱（n=40）或安慰剂（n=40）8 周。测定无花果酱的疗效和安全性并且比较 8 周前后干预的主要疗效（结肠转运时间）和次要疗效（涉及到排便的调查问卷）。**结果：**与安慰剂组比较，无花果酱能显著减少结肠转运时间，改善粪便类型和腹部不适。血液和器官毒性的临床参数均保持在正常范围以内。**结论：**这些结果表明无花果酱可能对便秘患者产生有益的影响。

关键词：无花果、便秘、排便、结肠转运时间、临床试验