Original Article

Effects of flaxseed supplementation on functional constipation and quality of life in a Chinese population: A randomized trial

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Background and Objectives: This prospective, randomized, controlled study aimed to evaluate the effects of flaxseed supplementation on functional constipation and quality of life in adult men and women in China. **Methods and Study Design:** 90 subjects with functional constipation diagnosed by the Rome IV criteria were enrolled. Subjects were randomly assigned to receive either 50 g/day flaxseed flour with meals (n=60) or 15 mL/day of a lactulose solution on an empty stomach (n=30) every morning for 4 weeks. Wexner constipation scores, stool consistency according to the Bristol Stool Form Scale, and bowel habits (frequency of bowel movements/week, the time spent on defecation) were the primary outcomes. The change in Patient Assessment of Constipation Quality of Life score was the secondary outcome. **Results:** After 4 weeks, the bowel habits in both groups were significantly improved. The median Wexner constipation score decreased from 14 to 6.5 in the flaxseed group (p<0.001) and from 15 to 9 in the lactulose group (p<0.001). The median defecation frequency per week increased significantly (2 to 7 for flaxseed and 2 to 6 for lactulose, p<0.001 for both groups). The Patient Assessment of Constipation Quality of Life score decreased significantly (−1.34 and −0.66 for flaxseed and lactulose, respectively; p<0.001 for both groups). **Conclusions:** Flaxseed flour is somewhat more effective at increasing defecation frequency than lactulose, improving bowel movements and promoting life quality of subjects with chronic functional constipation in the Chinese population.

Key Words: flaxseed, lactulose, Chinese, functional constipation

INTRODUCTION

Functional constipation is a functional bowel disease associated with persistent difficulty in defecation, a reduced number of bowel movements, and incomplete bowel movements.[1] It has become a common disorder in both developed and developing countries. The prevalence of chronic constipation in the general population ranges from 15% to 25%,[2,3] affecting individuals regardless of age or sex. Changes in dietary patterns contribute to the increase in functional constipation.[4] In recent years, living standards in China have improved. The consumption of meat, eggs, and milk has increased while consumption of grains, vegetables, and fruits decreased in China. From 1982 to 2012, the intake of cereal dropped from 502.0 g to 276.4 g while the intake of livestock and poultry meat increased from 46.2 g to 110.3 g.[5]

Functional constipation can also be influenced by psychological and social factors.[6] Functional constipation increases with age[2] and can cause anxiety, discomfort, and even intestinal obstruction,[7] leading to a decline in a patient's quality of life.[2] The diagnosis of functional constipation is normally performed according to the Rome IV Criteria for Functional Gastrointestinal Disorders.[8] Treatments for functional constipation include drugs, surgery, and psychological behavioral interventions.[3,9,10] All these treatments have limitations because of their side effects or because they are efficacious for only a short time.[11] Flax is an important oilseed crop, and flaxseed is a major source of α-linolenic acid (18:3; n-3) and the richest food source of lignans.[12] The beneficial effects of flaxseed include lowering of blood pressure and blood glucose levels, promoting apoptosis in colorectal tumor cells; additionally, flaxseed can have anti-inflammatory and anti-viral properties.[13-17] Flaxseed is also a good source of soluble and insoluble fiber and has been used for centuries in China and globally as a traditional medicine to treat constipation.[13] Flaxseed exists in several forms including whole seed, ground seed, and partially

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defatted flaxseed meal. The highest content of dietary fiber among the common forms of flaxseed is found in partially defatted flaxseed meal.[18] Several studies have shown that flaxseed has similar laxative properties in healthy[19,20] and constipated individuals.[21] However, to our knowledge, there have been no randomized controlled trials testing the efficacy of flaxseed supplementation in subjects with functional constipation.

The present study was designed to investigate the effects of flaxseed supplementation on the frequency of bowel movements per week, time spent on defecation, Wexner scores (a measure of fecal incontinence), and quality of life in subjects with functional constipation. The aim was to understand the advantages of dietary treatment and to explore a comprehensive, effective, safe and convenient method for treating functional constipation.

METHODS

Subjects

A total of 198 subjects from the Gastroenterology Outpatient Clinic in Huadong Hospital, Shanghai, China, and in local community health centers, were screened for eligibility to participate in the trial. Subjects could be male or female, had to be between 40 and 70 years of age, had to have functional constipation according to Rome IV criteria diagnosed by a research gastroenterology physician, and had to have lived in Shanghai for at least 6 months with no plans to leave in the next 6 months. The Rome IV criteria for diagnosing functional constipation include ≥2 of the following: straining during ≥25% of defecations; lumpy or hard stools for ≥25% of defecations; sensation of incomplete evacuation for ≥25% of defecations; sensation of anorectal obstruction/blockage for ≥25% of defecations; manual maneuvers to facilitate ≥25% of defecations (e.g., digital evacuation or support of the pelvic floor); and fewer than three spontaneous bowel movements per week. These criteria must be fulfilled for the previous 3 months with symptom onset at least 6 months prior to diagnosis. The subjects were asked to refrain from making any major lifestyle changes. Subjects were required to discontinue laxative or other cathartic drug treatment at least one week before the trial, with the exception of enema. All subjects were enrolled between December 2017 and April 2018. All subjects provided signed informed consent; were willing to comply with all of the requirements and procedures; and agreed not to participate in another interventional clinical research study during the present study. Exclusion criteria were severe non-gastrointestinal diseases (severe renal, liver, heart, pituitary, thyroid or mental disorders); pelvic floor dysfunction; abdominal or pelvic surgery before the screening visit; any other gastrointestinal disorders including inflammatory bowel disease, chronic pancreatitis, or lactose intolerance; regularly taking probiotic or prebiotic supplements; and antibiotic use during the month preceding the study.

The study was approved by the independent Ethics Committee of Huadong Hospital Affiliated with Fudan University and conducted in accordance with the Declaration of Helsinki (2017KO66). The trial was pre-registered ISRCTN: ChiCTR1800014882 (http://www.chictr.org.cn/com/25/hvshowproject.aspx?id=12943).

Management of study subjects

Study staff used WeChat and telephone calls to communicate with study subjects and to determine adherence to study procedures. WeChat is a Chinese multi-purpose messaging and social media application developed by Tencent (Shenzhen, China) and first released in 2011 (https://weixin.qq.com/). It supports sending of voice messages, web links, pictures, text, and files. By 2016, WeChat was used by more than 94% of smartphone users in China. Because of the high coverage and comprehensive functions of WeChat, subjects in our trial were contacted and managed mainly through WeChat. After the subjects were enrolled in the study, they were contacted by telephone. After that, study staff added subjects as WeChat friends and formed three chat groups for observation during the treatment. One or two study staff managed each group. Telephone contact was used for those subjects who did not use smart phones or WeChat.

Treatment

Subjects were randomly assigned (2:1 flaxseed: lactulose) by the investigators to two groups according to a computer-generated randomization schedule. Subjects randomized to the lactulose group (n=30) received 15 mL of oral lactulose solution (66.7 g per 100-mL bottle; from Beijing Hanml Pharm. Co. Ltd.) on an empty stomach every morning for 4 weeks. In parallel, subjects randomized to the flaxseed flour group (n=60) received 50 g of flaxseed flour daily. Subjects were instructed to use a hot liquid such as water, milk, soy milk and rice congee, and mix in the flaxseed flour or to mix flaxseed flour with rice or wheat flour to make a pie according to subjects' preferences. The flaxseed flour used in the study was ground brown flax seed from TAFOODs in Canada and supplied by Suzhou Huidong Biotechnology Co. Ltd. All subjects were asked not to change their daily habits, including exercise.

Study measures

At screening, all subjects underwent comprehensive evaluations, including screening of medical history, and had height, body weight, BMI, and blood pressure measured. These measures were taken at baseline and at 2 and 4 weeks. The oral lactulose solution and flaxseed flour were provided at baseline and at week 2.

Primary endpoint

The constipation of all subjects was assessed by Wexner scores.[22] Eight variables were included in the scoring system: frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per attempt, assistance for defecation, unsuccessful attempts for evacuation per 24 hours, and duration of constipation. Scores ranging from 0 to 4 (with the exception of "assistance for defecation", the score for which ranges from 0 to 2) were derived. The global score was obtained by adding the individual scores. Stool form and consistency were assessed using the Bristol Stool Form Scale (BSFS).[23]

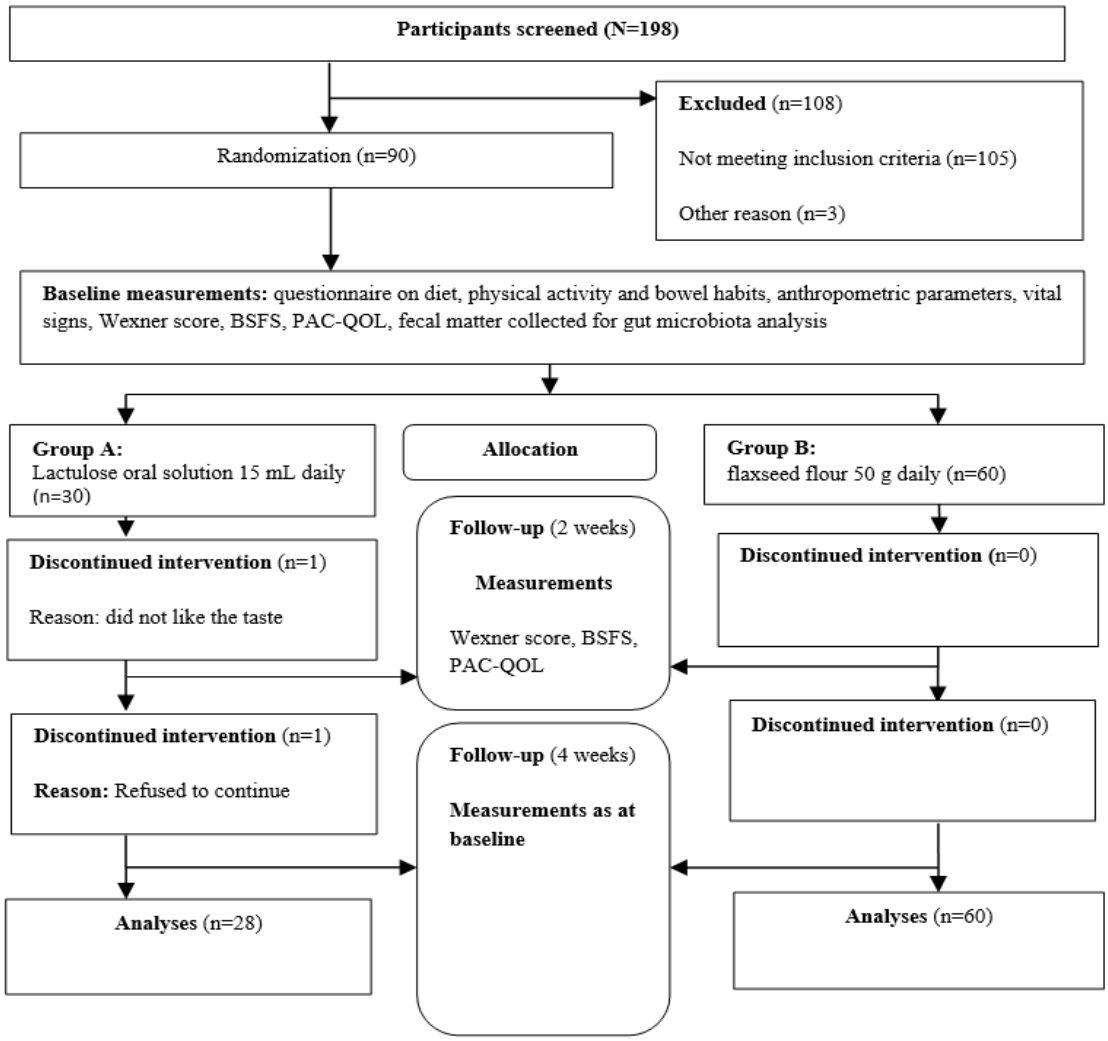

Figure 1. Study flow chart of the flaxseed intervention trial on constipation. BSFS, Bristol Stool Form Scale; PAC-QOL, Patient Assessment of Constipation Quality of Life.

Secondary endpoint

The Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire24 was used to assess the change in quality of life as a secondary outcome of the study. This test was shown to have good reliability and validity.25 The PAC-QOL scale consists of 28 items: physical discomfort (items 1-4), psychosocial discomfort (items 5-12), worry and anxiety (items 13-23), and satisfaction (items 24-28). The patient's quality of life was investigated using a 5-level score. Various discomforts are given 0-4 points from "completely no" to "extremely". The total score is the average score of all items, and the higher the score, the lower the quality of life.

Additionally, endpoints such as change from baseline in bowel habits (e.g. frequency of bowel movements/week, the time spent on defecation, abdominal fullness and abdominal bloating, and treatment satisfaction) were assessed.

Statistical analysis

Assuming the same effect of flaxseed and lactulose, an estimated sample size of 90 patients (including a reasonable drop-out rate), randomized 2:1 (flaxseed: lactulose), would provide ≥90% power to detect differences between groups at a significance level of 5%. Data were entered using Epidata 3.1 (The EpiData Association, Denmark).[26] SPSS version 22.0 (IBM, Armonk, NY) was used for the statistical analyses.

The normality of data was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are reported as means ± standard deviation (SD), and non-normally distributed variables are reported as medians (interquartile range [IQR]). Categorical variables are reported as percent values. Comparisons of two means (lactulose and flaxseed groups) of normally distributed data were performed using the Student's t test. The Mann-Whitney U-test was used for data that were not normally distributed. The Chi-square test was used for categorical variables. A p value <0.05 was considered to be statistically significant.

RESULTS

Of the 198 subjects screened, 90 were enrolled in the study, provided written informed consent, and were randomly assigned to either the flaxseed or lactulose group. Of these 90 subjects, 88 completed the study. Two subjects receiving the lactulose solution discontinued the study because one could not tolerate the taste of the solution and the other felt that the symptoms of constipation were not a serious problem and that there was no need for intervention. A flow chart of the study is shown in Figure 1.

Table 1. Baseline characteristics of participants.

Variables	Lactulose (n=30)	Flaxseed (n=60)	*p* value
Age (years)†	53.5±8.8	52.7±8.7	0.671§
Sex (male/female)	4/26	6/54	0.918¶
BMI (kg/m^2)†	23.1±2.7	23.1±2.6	0.999§
History of constipation (%)			0.167¶
1–<5 years	20.0	31.6	
5–<10 years	23.0	16.7	
10–<20 years	33.3	25.0	
≥20 years	23.7	26.7	
Regular exercise (times/week)‡	2.0 (1.0, 4.3)	3.0 (1.0, 5.0)	0.484††
Water consumption (mL/day)‡	1000 (800, 1500)	1150 (1000, 1500)	0.560††
Vegetables (g/day)‡	300 (225, 400)	300 (263, 400)	0.662††
Fruit (g/day)‡	200 (100, 150)	200 (100, 300)	0.460††
Whole grains (times/week)‡	2.0 (1.0, 3.5)	2.0 (1.0, 3.0)	0.804††
Spicy food (times/week)‡	0.50 (0.0, 1.8)	1.0 (0.0, 2.0)	0.505††
Fried food (times/week)‡	1.0 (0.0, 1.3)	1.0 (0.0, 2.0)	0.591††
Soft drinks (times/week)‡	1.0 (0.0, 2.0)	1.0 (0.0, 1.4)	0.201††

†Mean±SD; ‡Median (IQR); §Student's t test; ¶Chi-Square test; ††Mann-Whitney U-test.

Characteristics of the study population are shown in Table 1. The study population was predominantly female (87% in the lactulose group and 90% in the flaxseed group) and had a BMI in the normal range. There were no significant differences between the lactulose and the flaxseed flour groups with respect to sex, age, history of constipation, frequency of exercise, and dietary habits.

During the 4 weeks of treatment, the study subjects consumed more than 95% of the prescribed doses of lactulose solution and flaxseed flour. None of the subjects reported adverse events during the treatment period.

The severity of constipation at baseline and after 4 weeks of treatment was assessed by Wexner score (Table 2). The lactulose and flaxseed flour groups both had a statistically significantly lower Wexner score at the end of treatment. In the lactulose group the score improved from 15 to 9 and in the flaxseed flour group it improved from 14 to 6.5. However, the flaxseed flour group had a significantly bigger improvement in bowel movement difficulty, abdominal pain, and failure of evacuation than the lactulose group.

The median frequency of bowel movement/week changed from 2 to 6 in the lactulose group and from 2 to 7 in the flaxseed group, which represented a statistically significant difference between the groups (Table 2). Both groups also showed a significant reduction in the median duration of bowel movement, from 20 to 10 minutes in the lactulose group and from 20 to 5 minutes in the flaxseed group.

Bristol stool form scores were used to determine stool type (Figure 2). At baseline, >78% of subjects reported hard stools. However, after 4 weeks of treatment, the proportion of subjects reporting hard stools was 25% and 3.3%, respectively, for the lactulose and the flaxseed flour groups. Subjects with normal stool type at 4 weeks increased to 53.6% in the lactulose group and to 86.7% in the flaxseed group. Whereas none of the subjects reported watery stool at baseline, 21.4% of subjects in the lactulose group and 10% in the flaxseed group did at 4 weeks.
Quality of life was assessed by PAC-QOL score (Table 2). In both groups, there was a significant reduction in median score for all the parameters that were assessed. The reduction in median score for physical comfort, psychosocial comfort, and worries and concerns was similar for lactulose and flaxseed treatment. There was a greater reduction in the satisfaction and PAC-QOL scores in the

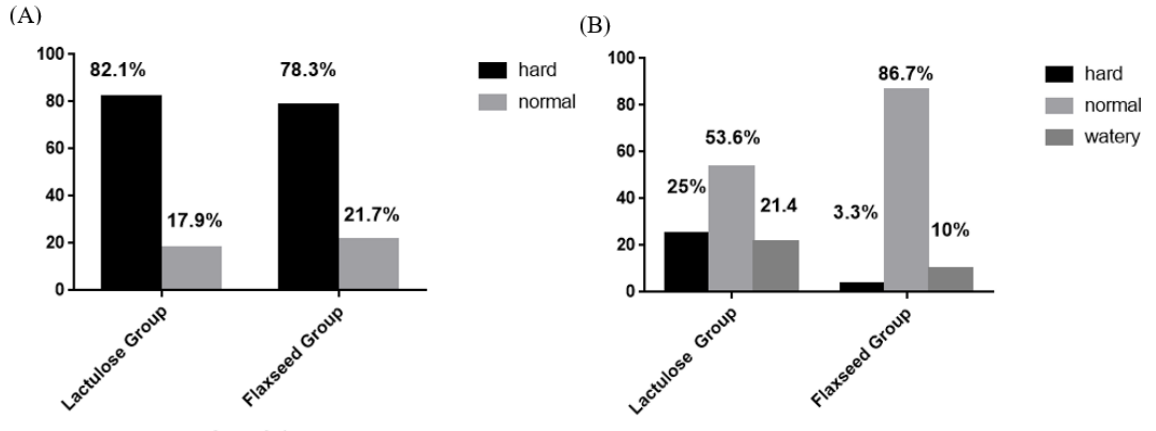

Figure 2. Stool type at baseline and 4 weeks. Bristol stool form scores for the lactulose (n=30) and flaxseed (n=60) groups are shown at baseline (A) and 4 weeks (B). The change in stool type between baseline and 4 weeks was significantly different between the lactulose and flaxseed groups (Chi-Square test, $p<0.05$).

Table 2. Constipation assessment at baseline and 4 weeks.

Variables	Lactulose (n=28)				Lactulose vs flaxseed (change from baseline)
	Baseline†	4 weeks†	Change from baseline	*p*-value‡	*p*-value‡
Wexner scores					
Bowel movement					
Frequency	1.0 (1.0, 2.0)	0.0 (0.0, 0.5)	1.0 (0.0, 1.0)	<0.001	
Difficulty	2.0 (2.0, 4.0)	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)	<0.001	
Completeness	3.0 (3.0, 4.0)	1.0 (1.0, 2.5)	1.0 (0.0, 2.0)	<0.001	
Abdominal pain	1.0 (0.0, 2.0)	1.0 (0.0, 1.5)	0.0 (0.0, 1.0)	0.373	
Minutes in lavatory per attempt	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	1.0 (0.0, 1.0)	0.010	
Assistance	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.029	
Failure of evacuation	1.0 (1.0, 1.0)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.092	
Duration of constipation	3.0 (2.0, 4.0)	3.0 (2.0, 3.5)	0.0 (0.0, 1.0)	0.254	
Overall score	15.0 (13.0, 16.0)	9.0 (7.0, 11.5)	5.0 (3.0, 7.0)	<0.01	
Bowel movement frequency and duration per attempt					
Frequency of bowel movements (BMS/week)	2.0 (1.0, 2.0)	6.0 (2.5, 7.0)	4.0 (1.5, 5.0)	<0.001	
Duration of bowel movements (min)	20.0 (10.0, 30.0)	10.0 (5,0 15.0)	10.0 (5.0, 13.0)	<0.001	
PAC-QOL scores and subscores					
Physical discomfort	1.25 (0.71, 2.17)	0.67 (0.50, 0.91)	0.50 (0.17, 1.0)	0.001	
Psychosocial discomfort	1.83 (1.17, 2.08)	0.50 (0.21, 1.17)	1.08 (0.50, 1.67)	<0.001	
Worries and concerns	2.00 (1.33, 2.75)	0.92 (0.50, 1.30)	1.09 (0.21, 1.79)	<0.001	
Satisfaction	3.75 (3.00, 4.00)	2.00 (1.00, 3.00)	1.25 (0.25, 2.50)	<0.001	
PAC-QOL scores	1.86 (1.61, 2.39)	0.93 (0.63, 1.36)	0.66 (0.30, 1.43)	<0.001	
	Flaxseed (n=60)				
Wexner scores					
Bowel movement					
Frequency	1.0 (0.0, 1.0)	0.0 (0.0, 0.0)	1.0 (0.0, 1.0)	<0.001	0.708
Difficulty	2.0 (2.0, 3.0)	1.0 (0.0, 1.0)	2.0 (1.0, 2.0)	<0.001	0.027
Completeness	3.0 (2.0, 3.8)	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)	<0.001	0.501
Abdominal pain	2.0 (1.0, 2.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	<0.001	0.005
Minutes in lavatory per attempt	2.0 (1.0, 2.0)	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	<0.001	0.070
Assistance	2.0 (0.0, 2.0)	0.0 (0.0, 0.0)	1.0 (0.0, 1.8)	<0.001	0.060
Failure of evacuation	1.0 (1.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	<0.001	0.026
Duration of constipation	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	0.0 (0.0, 0.0)	0.582	0.508
Overall score	14.0 (11.0, 16.0)	6.5 (5.0, 9.0)	7.0 (4.0, 9.0)	<0.001	0.017
Bowel movement frequency and duration per attempt					
Frequency of bowel movements (BMS/week)	2.0 (1.0, 2.8)	7.0 (6.0, 7.0)	5.0 (4.0, 5.0)	<0.001	0.028
Duration of bowel movements (min)	20.0 (10.0, 20.0)	5.0 (5.0, 10.0)	10.0 (5.0, 15.0)	<0.001	0.413
PAC-QOL scores and subscores					
Physical discomfort	1.33 (0.83, 1.75)	0.42 (0.17, 0.83)	0.79 (0.29, 1.42)	0.001	0.189
Psychosocial discomfort	1.50 (1.17, 2.00)	0.33 (0.00, 0.95)	1.00 (0.66, 1.67)	<0.001	0.843
Worries and concerns	1.92 (1.17, 2.50)	0.50 (0.17, 1.00)	1.17 (0.54, 1.84)	<0.001	0.536
Satisfaction	3.25 (3.00, 3.75)	1.67 (1.17, 2.13)	1.79 (1.25, 2.00)	<0.001	0.040
PAC-QOL scores	1.73 (1.52, 2.33)	0.46 (0.35, 1.41)	1.34 (1.00, 1.66)	<0.001	0.004

†Median (IQR); ‡Mann-Whitney U-test.

flaxseed group than in the lactulose group.

DISCUSSION

Constipation is a common health problem that may be related to dietary habits. Increasing standards of living have led to lower intakes of grains, fruits, and vegetables and more frequent problems with constipation. Flaxseed is rich in dietary fiber and can be used to increase dietary fiber intake. Fifty grams of flaxseed contain 13.3 g of dietary fiber, which corresponds to about 50% of the recommended daily intake according to Chinese dietary reference intakes.[27] In addition, the lipid content of flaxseed has also been shown to be an effective treatment for constipation; this has been attributed to its lubricating and stool-softening properties.[28] The majority of the subjects in this study supplemented with flaxseed flour suffered from functional constipation for more than 10 years and had tried various treatments including lactulose. None of these treatments led to satisfactory improvements. The results from this study showed that subjects taking flaxseed flour had less difficulty with bowel movements, less abdominal pain, and less failure of evacuation than the group taking lactulose. The increase in frequency of bowel movements per week was significantly higher with flaxseed flour than with lactulose. However, whereas the difference between lactulose and flaxseed flour was sta-

tistically significant, the clinical relevance of this difference may be limited (six bowel movements per week with lactulose and seven with flaxseed flour). Subjects in both treatment groups reported a reduction in hard stools. The flaxseed flour group had a higher proportion of normal stools than the lactulose group and a smaller proportion of watery stools. The PAC-QOL score reduction was also significantly larger in the flaxseed flour group than in the lactulose group, mostly because of a greater improvement in satisfaction.

The control group in this study was administered lactulose, which is a laxative commonly used to treat functional constipation. Lactulose is a synthetic disaccharide that is resistant to breakdown in the stomach and the small intestine. In the colon, bacteria such as *Lactobacillus acidophilus* and *L. bifidus* metabolize lactulose into mild acids.[29] These acids facilitate water retention, increase peristalsis, and lead to easier evacuation of the bowels.[30] However, this metabolism of lactulose can lead to considerable production of gases including carbon monoxide, methane, and hydrogen.[31] The resulting lactulose side effects include abdominal pain, bloating, and flatus.[32-34] These lactulose properties may be the cause of the higher proportion of watery stools and lower improvement in satisfaction in the lactulose group than the flaxseed flour group that were observed in this study.

Our study is limited by the relatively small number of participants and the fact that all subjects were recruited from a single city in China, limiting the generalizability of the results. Furthermore, we did not analyze any confounding variables such as smoking, alcohol consumption, or sleeping patterns. However, in the subjects we enrolled, we showed that flaxseed, a natural and healthy functional food that is enriched in α-linolenic acid, lignans, and other biologically active substances, is a safe, effective, and convenient treatment for chronic constipation with few side effects. Compliance with the study protocol was very good in the flaxseed flour group. Flaxseed flour can be consumed in a variety of ways and is easy to add to the diet. This fact may have contributed to the very good compliance and indicates that flaxseed supplementation can have appeal in a wider population. Future studies that include a larger number of subjects with a more diverse clinical and cultural background will contribute to a better understanding of the health benefits of flaxseed.

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AUTHOR DISCLOSURES

The authors declare that they have no competing interests.

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