



Evaluating Walnut-Fig Syrup as an Innovative Herbal Medicine for Functional Constipation in the Elderly: A Randomized Controlled Clinical Trial

Saeed Joudikhajeh^{1,2}, Bitā Sepehri³, Robab Mehdizadeh Esfanjani⁴, Hossein Rezaeizadeh⁵, Yunes Ranjbar⁶, Mostafa Araj-Khodaei^{7*}

Abstract

Objectives: Functional constipation (FC), or chronic idiopathic constipation, is one of the most common chronic disorders with no specific cause. Although FC is not associated with the progress of severe disease or additional mortality, it significantly decreases the patients' quality of life. While several medications are available to treat constipation, there is no adequate treatment response in most cases. Herbal remedies are one of the most widely used options for FC.

Materials and Methods: In this double-blind controlled trial, all patients, researchers, and analysts were unaware of the ingredients contained in the drugs, as well as the assigned groups. We recruited a total of 90 elderly patients diagnosed with FC according to the Rome IV diagnostic criteria for irritable bowel syndrome (IBS). Patients were divided into two equal groups (n=45 in each) receiving fig-walnut syrup and lactulose syrup. Then, CBC-FBS-TSH-CR-NA-K-CA tests were taken from all patients, and the developed syrups (walnut-fig or lactulose) were prescribed to patients (15 cc half an hour before bedtime).

Results: While 43 (95.6%) patients responded to treatment in the intervention group, 41 (91.1%) patients responded to treatment in the conventional treatment group. There was no statistically significant difference between the two groups in terms of response to treatment ($P = 0.677$).

Conclusions: The results showed that the oral syrups developed in this study improved FC in the elderly and had no side effects.

Keywords: Walnut, Fig, Aging, Functional constipation, Traditional medicine

Introduction

Traditional Persian medicine (TPM) is one of the most ancient forms of traditional medicine with a universal outlook on human health and disease. TPM scholars consider constipation as the beginning of numerous human disorders (1,2). According to Avicenna's theory, four aptitudes, *ha'zeme* (digestive), *ja'zebeh* (absorptive), *ma'sekheh* (retentive), and, *da'feh* (propulsive), are elaborate in the process of absorption and digestion of the ingested food (3,4). Functional constipation (FC), or chronic idiopathic constipation, is one of the most common chronic disorders (5). Because physical activities cannot improve symptoms, FC is known as a functional gastrointestinal disorder (5,6).

The most causes of constipation include a change in routine and daily diet, consumption of insufficient fluids and fiber, and lack of exercise (7). Some important symptoms are straining to pass the motion, bloating, hard and dry stools that may be painful to pass, reduced frequency of defecation, sitting on the toilet for much

longer than usual, and a sense of incomplete emptying of bowels (7,8).

Fiber consumption is a proper strategy for the improvement and treatment of constipation (9). There are two broad types of fiber, including insoluble and soluble. Insoluble fiber enhances bulk to the feces, helping it to move more quickly through the bowel. Rich sources of insoluble fiber are found in wheat bran, whole-grain bread, and cereals (9,10). Soluble fiber helps to soften the feces. Rich sources of soluble fiber comprise vegetables, legumes, and fruits (10). Constipation can occur as a result of high-fiber diet if insufficient water is consumed (11).

Findings revealed that constipation is more common in the elderly due to several factors, including reduced intestinal muscle contractions and dependence on regular medications (12). Some medical problems, such as slow transit, anal fissure, obstruction, hernia, abdominal or gynecological surgery, irritable bowel syndrome (IBS), endocrine system problems, tumors, and diseases of the central nervous system can be caused by FC (12,13).

Received 4 February 2022, Accepted 10 August 2022, Available online 7 October 2022

¹Student Research Committee, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran. ²Department of Persian Medicine, Faculty of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. ³Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. ⁴Neurosciences Research Center, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran. ⁵Department of Persian Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran. ⁶Baharan Private Clinic Research Team, Tabriz, Iran. ⁷Research Center for Integrative Medicine in Aging, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran.

*Corresponding Author: Mostafa Araj-Khodaei, Tel: +989128382094, Email: mostafaa33@gmail.com



Key Messages

- ▶ According to this, constipation has many complications, including fecal incontinence, hemorrhoid prolapse, anal fissure, rectal prolapse, uterus and bladder, intestinal obstruction, agitation in patients with dementia, reduction in the quality of life of the elderly, and urinary retention. The solution to the mentioned problems has fewer side effects and is more compatible with the temperament of the elderly. Also, its acceptance is more than that of chemical drugs due to its good taste, and in addition to treating the problem of constipation, it also strengthens the strength of the elderly.

Urinary incontinence, hemorrhoids, rectal prolapse, fecal incontinence, and fecal impaction are essential complications of chronic constipation (13,14). The consequences of constipation can be considerable. In vulnerable older people who are frail, extreme straining can initiate a syncopal episode, cerebral ischemia, or coronary problems (15). Less acutely, constipation leading to fecal impaction can present with nausea, pain, anorexia, and be associated with functional decline (16). In some cases, constipation is caused by more serious illnesses and events, including tumors and systemic diseases.

Emollient laxative glycerin suppositories are rectal laxatives for relieving mild to moderate constipation (17). Bulking agents such as ispaghula are applicable in gastrointestinal motility disorders (18). Osmotic laxatives such as lactulose and polyethylene glycol are effective in the elderly, but have an unpleasant taste (19).

The drugs to treat constipation might have poor therapeutic response or side effects. In addition, the preparation of these drugs requires a high cost, which in some cases makes them difficult to access. Herbal remedies have long been popular for overcoming these limitations and problems. In most cases, cheap and affordable herbal medicines have good effectiveness and no side effects. So, they can easily replace common medicines in the treatment of constipation.

Figs and walnuts are examples of plant fruits with exceptional properties proven to cure several diseases. Walnuts contain other nutritional characteristics such as vitamin E and melatonin compounds with potent antioxidant activity (20,21). The ingestion of walnuts has been revealed to increase the antioxidant capacity of blood and protect against disease elements (20,21). Moreover, figs contain vitamins, cellulose, minerals, and amino acids with high levels of water and fiber.

Previous studies reported that consumption of fig could reduce colonic transit time and increase fecal weight in animals (22). Also, *Ficus carica* paste showed anti-constipation activity in rats (23). Similarly, walnuts have healing properties for constipation. According to the evidence, walnuts showed laxative properties and improved constipation (24,25).

As far as the researchers of this study investigated, despite several published articles on the anti-constipation properties of figs and walnuts, no experimental work has evaluated the anti-constipation activity of fig-walnut mixture so far. Accordingly, this study aimed to evaluate the effectiveness of fig-walnut mixture on improving FC in elderly people.

Materials and Methods

This double-blind randomized clinical trial was approved by Tabriz University of Medical Sciences, Iran (ethics code: IR.TBZMED.REC.1399.161). All patients, researchers, and analysts were unaware of the ingredients contained in the drugs and the assigned groups.

According to the Rome IV Diagnostic Criteria for IBS, we recruited a total of 90 elderly patients diagnosed with FC referred to the gastrointestinal clinic of Imam Reza hospital in Tabriz (Iran) from September 9, 2020 to February 2, 2021. Patients were divided into two equal groups (n=45 in each) receiving fig-walnut syrup and lactulose syrup. Then, CBC-FBS-TSH-CR-NA-K-CA tests were taken from all patients, and the developed syrups (walnut-fig or lactulose) were prescribed to patients (15 cc half an hour before bedtime). The inclusion criteria were as follows: 1. Presence of at least 2 of the following for at least 3 months: Hard or bullet-like stools in more than 25% of cases, Forcing in more than 25% of cases, Sensation of anorectal blockage or cramp in more than 25% of cases, the need for manual maneuvers to facilitate excretion in more than 25% of cases, Spontaneous bowel, Feeling of incomplete emptying in more than 25% of cases, and movements less than 3 times a week. The exclusion criteria were reluctance of the elderly, drug intolerance, possible side effects of the drug (nausea, vomiting, severe abdominal pain and allergic side effects, etc), history of allergy to figs and walnuts, recent surgery, limited mobility, Alzheimer's, recent surgery and history of diabetes, IBS, gastrointestinal obstruction, gastrointestinal inflammation, spinal cord injuries, Parkinson's, systemic lupus erythematosus, hypothyroidism, hyperparathyroidism, and serious psychiatric disorders.

Study Design and Participants

In this study, a total of 90 patients were randomly assigned into two equal groups (n=45) of conventional treatment and herbal treatment groups. The drug was prepared similar to lactulose in terms of appearance. Each patient consumed 15 cc of syrup at night, one hour before bedtime.

Firstly, a gastroenterologist visited the patients. Then, the questionnaire was completed by a PhD student in traditional medicine. The study aims were explained to all participants prior to inclusion and an informed consent was obtained. Next, the necessary clinical tests, including CBC-FBS-TSH-CR-NA-K-CA were obtained from all participants. In case of a malignant tumor suspicion, the patient was referred for colonoscopy at the discretion of a

gastroenterologist.

At the beginning of the visit, we recorded the patients' information, including name, age, sex, and height, and selected the patients based on the inclusion criteria. Then, using interviews, examinations, and questionnaires, information was collected before and after prescribing drugs in case and control groups. The duration of treatment was four weeks and the information was obtained from the patients at the time of admission, second week, and fourth week. Then, the information was entered into SPSS software (version 17) and statistical analysis was performed. Efficacy analysis (improved or unimproved) was performed using a randomly enrolled treatment intent model for all patients. Information on defecation, fecal incontinence, oily drainage from the anus, stool retention pain intensity, stool hardness, and drug intake was collected.

Sample Size

In this study, elderly patients diagnosed with FC referred to gastrointestinal clinic of Imam Reza hospital in Tabriz, Iran were included according to the Rome IV diagnostic criteria for FC. The sample size was calculated using G*Power software (version 3.0.10) to compare the mean in the community. The sample size was calculated as 42

subjects in each group. Finally, to ensure the sufficient sample size, 45 patients were included in each group (Figure 1).

Statistical Method

For statistical analysis, mean and standard deviation, *t* test, χ^2 test, repeated measures analysis of variance (ANOVA), and Fisher exact test (significance level: 5%) were used. Data was expressed as mean \pm SD or percentage. Since the study was double-blind, the patients and researchers were unaware of the contents of the drugs and the assigned groups. In other words, if the patients did not meet the mentioned criteria within two weeks, they were considered as improved.

Results

In the case group, the median age of patients was 62.5-70 years, the minimum age was 60 years, and the maximum age was 80 years. The median age of patients in the common treatment group was 65 years with a mid-quartile range 61-70.5, the minimum age was 60 years, and the maximum age was 83 years. There was no statistically significant difference between the two groups in terms of age ($P = 0.341$). Also, there was no significant difference between the two groups in terms of gender, education,

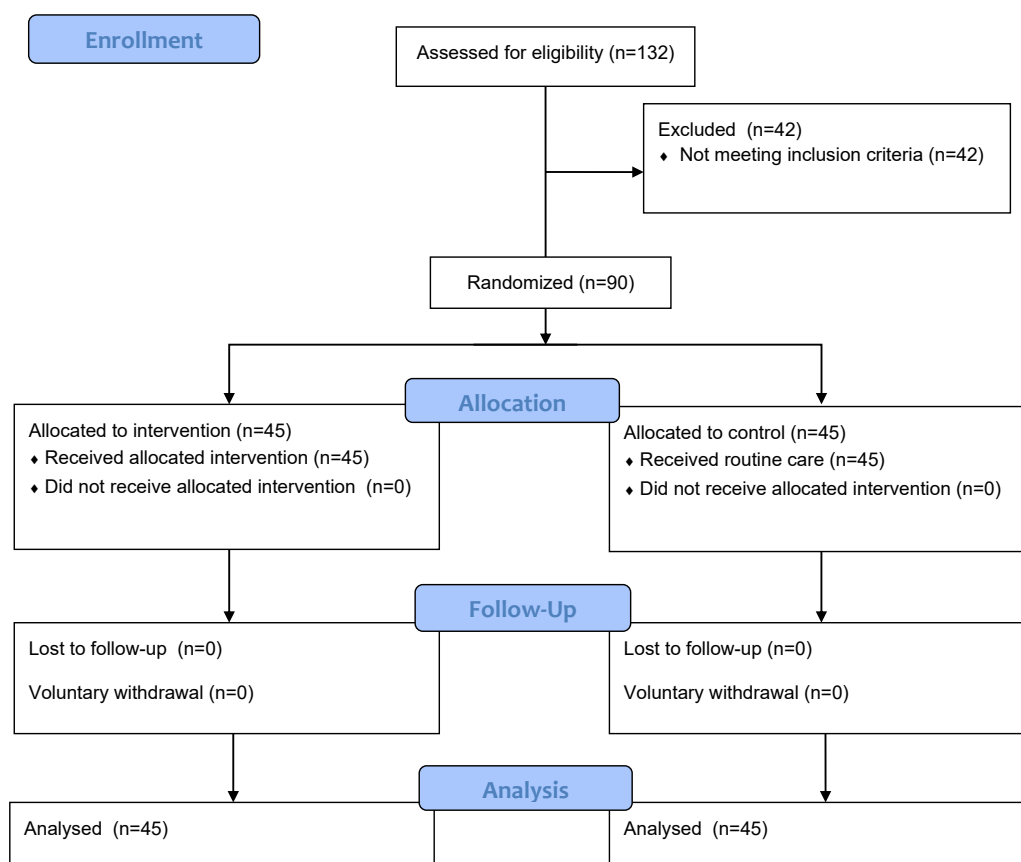


Figure 1. Flowchart of the Study.

Table 1. Distribution and frequency percentage of individual variables

Variable	Status	Common Treatment Group (n = 45)	Case Group (n=45)	P Value
		No. (%)	No. %	
Gender	Male	8 (17.8)	9 (20)	0.788 ^a
	Female	37 (82)	36 (80)	
Education level	High school	40 (88.9)	39 (86.7)	0.755 ^b
	Diploma	3 (6.7)	2 (4.4)	
	Associate degree	1 (2.2)	2 (4.4)	
	Bachelor's degree	1 (2.2)	0 (0)	
	Higher than a bachelor's degree	0 (0)	2 (4.4)	
Jobs	Housewife	35 (77.8)	34 (75.6)	0.390 ^b
	Freelancer	3 (6.7)	7 (15.6)	
	Employee	2 (4.4)	2 (4.4)	
	Other	5 (11.1)	2 (4.4)	
Marital status	Single	2 (4.4)	1 (2.2)	1
	Married	43 (95.6)	44 (97.8)	
Number of children	No children	3 (6.7)	3 (6.7)	0.519 ^b
	1	4 (8.9)	6 (13.3)	
	2	3 (6.7)	7 (15.6)	
	3 and more	35 (77.8)	29 (64.4)	
Location	City	44 (97.8)	45 (100)	1 ^b
	Village	1 (2.2)	0 (0)	
Underlying disease*	No	37 (82.2)	37 (82.2)	1 ^a
	Yes	8 (17.8)	8 (17.8)	
Medication use**	No	34 (75.6)	37 (82.2)	0.438 ^a
	Yes	11 (24.4)	8 (17.8)	

* The existing underlying diseases were not among the diseases causing constipation.

** Medications are a group of drugs that are not involved in the development or treatment of constipation.

^a Chi-square test; ^b Fisher exact test.

occupation, status of children, number of children, place of residence, presence of underlying diseases, and the used drugs ($P \geq 0.05$) (Table 1).

Regarding response to treatment, 43 (95.6%) patients in the case group and 41 (91.1%) patients in the conventional treatment group responded to treatment, indicating no significant difference between the two groups ($P = 0.677$) (Table 2).

There was no statistically significant difference between the two groups in terms of the duration of response to treatment ($P = 0.242$). The duration of response to treatment was higher in the case group (34.9% within 3 days in case vs. 16.3% within 2 days in control). In the common treatment group, the highest response to treatment was 2 days in 24.4% of patients (Table 3).

As shown in Table 3, two patients in the case group and four patients in the common treatment group did not respond to treatment. Figure 2 compares the treatment duration between the two groups.

Duration of actual treatment period in the case group, with a median of 3 days and interquartile range (3-5) days,

the lowest duration time was 1 day and the maximum was 8 days. In the lactulose group with a median of 4 days and interquartile range (2.5-6.5) days, a minimum of 2 days and a maximum of 27 days of treatment was observed. There was no significant difference between the two groups in terms of treatment period ($P = 0.222$) (Table 4).

Regarding laboratory factors, there was no statistically significant difference between the two groups in any of the laboratory factors except for TSH ($P \geq 0.05$) (Table 5). In addition, no side effects were observed in any group.

Discussion

The results of this study showed that the mixture of figs and walnuts can be an effective drug in improving FC. Walnuts are a great source of probiotics that help to maintain healthy gut function. A study showed that daily consumption of walnuts (43 g/d) enhanced probiotics (1). Another study showed that probiotics can increase bowel frequency and improve stool quality. Therefore, walnuts can reduce the risk of constipation by improving the frequency of stools (2). Dietary fiber is another major nutrient that helps

Table 2. Comparison of Response to Treatment Between the Two Groups

Group (n=45)	No response to treatment	Response to treatment	P Value ^a
	No (%)	No (%)	
Case	2 (4.4)	43 (95.6)	0.677
Conventional treatment	4 (8.9)	41 (91.1)	

^a Fisher exact test.

Table 3. Comparison of the Duration of Response to Treatment (Week)

Week	Common Treatment Group (n = 45)	Case Group (n=45)	P Value ^a
1	33 (73.3)	40 (88.9)	0.242
2	6 (13.3)	3(6.7)	
3	0 (0)	0 (0)	
4	2 (4.4)	0 (0)	

^a Fisher exact test.

control constipation. Studies showed that consuming high-fiber foods can increase the frequency of stools and soften stool consistency (100 g of walnut contains 6.7 g of fiber) (3). Another study showed that dietary fiber intake may increase the frequency of stools in patients with constipation (4). Regular walnut intake can reduce the chance of constipation by increasing magnesium intake. Studies showed that magnesium deficiency may increase the risk of constipation by reducing the frequency of stools (5). High levels of polyunsaturated fatty acids in walnuts improve stool output. Polyunsaturated fats are a very important nutrient in combating constipation, and they can affect the immunity, inflammation, and motility of the gastrointestinal tract. Lubiprostone, a prostaglandin E1 derivative, is approved for the treatment of irritable bowel syndrome and chronic idiopathic constipation (6).

In a study, fig treatment significantly reduced colon transit time (stool movement increased from 2.1 to 3.7 per week) and significantly improved stool type (Bristol stool scale improved from 1.9 to 3) and abdominal discomfort (7). In summary, taking figs for four months is a useful treatment for alleviating the symptoms of IBS and may be a useful first-line treatment option (8). One study reported that after one week of ingesting flaxseed and figs, defecation frequency increased, but retention posture,

large stool volume, pain during urination, and stool consistency decreased. Also, the prepared flax and fig caplets reduced the severity of constipation (9). In another study, fig improved the symptoms of FC due to its high-fiber content. Moreover, the number of defecations was increased, the time needed for defecation was shortened, and abdominal pain, unpleasant burden of defecation, and feeling of incomplete defecation were improved (10).

Numerous studies have been performed on the medicinal properties of figs and walnuts, some of which are related to constipation (26). Finding revealed that FC could improve most of the constipation symptoms in the patients suffering from FC (27). A study indicated that consumption of FC increased stool weight and decreased segmental colonic transit time (28). Fecal number, water content and weight, and histological parameters such as mucin areas and thickness in the distal colon were enhanced in rats after consuming fig fruit. Fig treatment may be a beneficial preventive and therapeutic strategy for chronic constipation (29). A randomized double-blind study showed that *F. carica* paste may have valuable effects in patients suffering from constipation (30). The severity of FC significantly reduced after consumption of *Linum* and *Ficus* (31). Evidence revealed that dysbiosis of gut microbiota might contribute to FC and IBS (32). On the other hand, some nuts, such as walnuts, can affect the amount of microbiota. Therefore, the consumption of walnuts can indirectly affect FC (33).

Overall, our results showed that the mixture of figs and walnuts was effective in treating FC in the elderly people. Other features of the developed drug in this study included a pleasant taste, safe use, and low cost. Future studies with larger sample sizes are recommended to confirm our results.

Table 4. Comparison of the Changes in the Duration of Response to Treatment Between the Two Groups

Response to Treatment	Conventional (n = 45) Median (Interquartile)	Case (n=45) Median (Interquartile)	P Value ^a
Number of day	4 (2.5-6.5)	3 (3-5)	0.222

^a Mann-Whitney U test.

Table 5. Comparison of the Laboratory Factors Between the Two Groups

Tests	Conventional (n = 45) Median (Interquartile)	Case (N = 45) Median (Interquartile)	P Value
Hb	13.63 ± 1.3 ^c	13.75 ± 1.46 ^c	0.682 ^a
FBS	99 (106 – 93)	99 (105–93)	0.961 ^b
Ca	9.65 ± 0.54 ^c	9.71 ± 0.57 ^c	0.644 ^a
Na	140 (143–38)	140 (143–138)	0.756 ^b
K	4.2 (4.4–3.9)	4.3 (4.8–3.9)	0.133 ^b
Cr	1.01 (1.01–0.85)	1.1 (1.1–0.85)	0.588 ^b
TSH	2.37 (3.45–1.5)	2 (2.65–1.3)	0.043 ^b

^a Independent samples t test.

^b Mann-Whitney U test.

^c Mean ± SD.

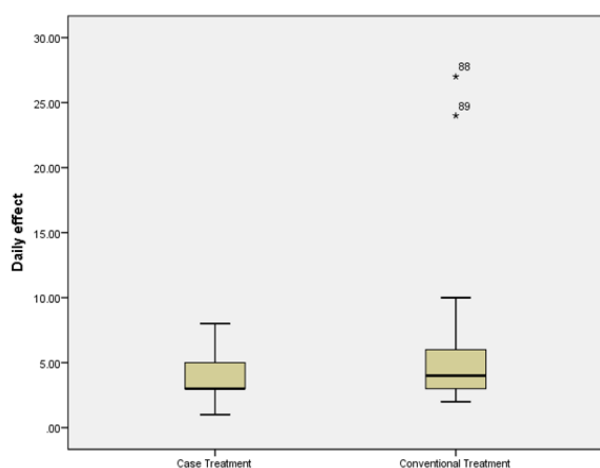


Figure 2. Comparison of the Changes in the Duration of Response to Treatment

Conclusions

In this study, we developed an herbal medicine that was effective in improving constipation in the elderly people. Although figs and walnuts were introduced as medicinal plants effective in constipation in previous studies, their combined use as an oral syrup was introduced for the first time in this study. Our findings confirmed that fig-walnut syrup can be the best alternative for conventional medicines to treat constipation. However, similar studies in all age groups and larger sample sizes are required. If similar results are achieved, the fig-walnut syrup can be introduced as an effective herbal medicine for FC. The effectiveness of the drug developed in this study on all age groups can be an interesting topic for future studies.

Authors' Contribution

Conceptualization: MA, HR

Methodology: MA, BS

Validation: BS

Formal Analysis: RM

Investigation: SJ, YR

Writing—Original Draft Preparation: All authors

Writing—Review and Editing: All authors

Supervision: MA

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

This study was approved by Tabriz University of Medical Sciences, Iran (ethics code: IR.TBZMED.REC.1399.161) and registered at the Iranian Registry of Clinical Trials website (identifier: IRCT20200714048108N1; <https://www.irct.ir/trial/50369>).

Financial Support

This work was supported by Tabriz University of Medical Sciences, Iran (grant number 63427).

References

1. Zeinalian M, Eshaghi M, Naji H, Marandi SMM, Asgary S. Constipation in Iranian-Islamic Traditional Medicine: The Origin of Diseases. *Health Scope*. 2018;7(1):e64017.

2. Taheri-Targhi S, Gjedde A, Araj-Khodaei M, et al. Avicenna (980–1037 CE) and his early description and classification of dementia. *Journal of Alzheimer's Disease*. 2019;71(4):1093-1098.
3. Nimrouzi M, Zarshenas MM. Holistic approach to functional constipation: Perspective of traditional Persian medicine. *Chin J Integr Med*. 2019;25(11):867-872. doi:10.1007/s11655-015-2302-3
4. Ghafouri RR, Araj-Khodaei M, Targhi ST, et al. First report of a disease by rhazes 10 centuries ago. *Int J Prev Med*. 2019;10:6. doi:10.4103/ijpvm.IJPVM_216_17
5. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. *Gastroenterology*. 2016;S0016-5085(16)00222-5. doi:10.1053/j.gastro.2016.02.031
6. Serra J, Pohl D, Azpiroz F, et al. European society of neurogastroenterology and motility guidelines on functional constipation in adults. *Neurogastroenterol Motil*. 2020;32(2):e13762.
7. Yu T, Zheng Y-P, Tan J-C, Xiong W-J, Wang Y, Lin L. Effects of prebiotics and synbiotics on functional constipation. *Am J Med Sci*. 2017;353(3):282-292.
8. Nag A, Martin SA, Mladi D, Olayinka-Amao O, Purser M, Vekaria RM. The humanistic and economic burden of chronic idiopathic constipation in the USA: a systematic literature review. *Clin Exp Gastroenterol*. 2020;13:255-265. doi:10.2147/CEG.S239205.
9. Huh JW, Park YA, Sohn SK, et al. Effect of yogurt enriched water-soluble fiber on functional constipation. *Journal of the Korean Society of Coloproctology*. 2007;23(5):312-320.
10. Pires J, Guerreiro CS, Carolino E. Effect of soluble fiber in elderly with constipation. *Clinical Nutrition ESPEN*. 2020;40:636. doi:10.1016/j.clnesp.2020.09.693
11. Yurtdaş G, Acar-Tek N, Akbulut G, et al. Risk factors for constipation in adults: a cross-sectional study. *J Am Coll Nutr*. 2020;39(8):713-719.
12. Bouras EP, Tangalos EG. Chronic constipation in the elderly. *Gastroenterol Clin North Am*. 2009;38(3):463-480. doi:10.1016/j.gtc.2009.06.001
13. Stark ME. Challenging problems presenting as constipation. *Am J Gastroenterol*. 1999;94(3):567-574.
14. Rajindrajith S, Ranathunga N, Jayawickrama N, van Dijk M, Benniga MA, Devanarayana NM. Behavioral and emotional problems in adolescents with constipation and their association with quality of life. *PloS One*. 2020;15(10):e0239092.
15. Young RW. The problem of fecal impaction in the aged. *J Am Geriatr Soc*. 1973;21(8):383. doi:10.1111/j.1532-5415.1973.tb01245.x
16. Gandell D, Straus SE, Bundookwala M, Tsui V, Alibhai SMH. Treatment of constipation in older people. *CMAJ*. 2013;185(8):663-670. doi:10.1503/cmaj.120819
17. Frizelle F, Barclay M. Constipation in adults. *BMJ Clin Evid*. 2007;2007:0413.
18. Dettmar PW, Sykes J. A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Curr Med Res Opin*. 1998;14(4):227-233. doi:10.1185/03007999809113363
19. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation. *Int J Clin Pract*. 2010;64(7):944-955. doi:10.1111/j.1742-1241.2010.02397.x
20. Tapsell LC. Health benefits of walnut consumption. Paper presented at: VI International Walnut Symposium; 30 April 2010; Melbourne, Australia.
21. Ros E, Núñez I, Pérez-Heras A, et al. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation*. 2004;109(13):1609-

1614. doi:10.1161/01.CIR.0000124477.91474.FF
22. Oh HG, Lee HY, Seo MY, 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(4):275-281. doi:10.5625/lar.2011.27.4.275
 23. Lee HY, Kim JH, Jeung HW, et al. Effects of *Ficus carica* paste on loperamide-induced constipation in rats. *Food Chem Toxicol.* 2012;50(3-4):895-902. doi:10.1016/j.fct.2011.12.001
 24. Spender J. The Therapeutics of Constipation. *Br Med J.* 1870;2(516):568.
 25. Onawumi O, Faboya O, Ayoola PB. Chemical evaluation and nutritive values of African walnut leaf (*Plukenetia conophora* Mull. arg.). *International Journal of Herbal Medicine.* 2013;1(3):122-126.
 26. Badgujar SB, Patel VV, Bandivdekar AH, Mahajan RT. Traditional uses, phytochemistry and pharmacology of *Ficus carica*: A review. *Pharm Biol.* 2014;52(11):1487-1503.
 27. Kim S-Y, Back H, Oh M-R, et al. Effect of *Ficus carica* on Functional Constipation. *FASEB J.* 2010;24(S1):lb348-lb348. doi:10.1096/fasebj.24.1_supplement.lb348
 28. Oh HG, Lee HY, Seo MY, 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(4):275-281. doi:10.5625/lar.2011.27.4.275
 29. Lee H-Y, Kim J-H, Jeung H-W, et al. Effects of *Ficus carica* paste on loperamide-induced constipation in rats. *Food Chem Toxicol.* 2012;50(3):895-902. doi:10.1016/j.fct.2011.12.001
 30. Baek HI, Ha KC, Kim HM, et al. Randomized, double-blind, placebo-controlled trial of *Ficus carica* paste for the management of functional constipation. *Asia Pac J Clin Nutr.* 2016;25(3):487-496. doi:10.6133/apjcn.092015.06
 31. Tofighi Z, Golabi M, Toliyat T, Naseri M, Yassa N. Formulation and Evaluation of an Iranian Traditional Dosage Form Containing Linum and Ficus for Improvement of Functional Constipation. *Jundishapur Journal of Natural Pharmaceutical Products.* 2017;12(4):e40069.
 32. Ohkusa T, Koido S, Nishikawa Y, Sato N. Gut Microbiota and Chronic Constipation: A Review and Update. *Front Med (Lausanne).* 2019;6:19. doi:10.3389/fmed.2019.00019
 33. Bamberger C, Rossmeyer A, Lechner K, et al. A Walnut-Enriched Diet Affects Gut Microbiome in Healthy Caucasian Subjects: A Randomized, Controlled Trial. *Nutrients.* 2018;10(2):244. doi:10.3390/nu10020244

Copyright © 2022 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.