

Formulation and Evaluation of an Iranian Traditional Dosage Form Containing *Linum* and *Ficus* for Improvement of Functional Constipation

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Abstract

Background: Constipation is a common gastrointestinal problem worldwide.

Objectives: The current study aimed to prepare a dosage form containing flaxseed and figs and evaluate the effects of this drug to treat functional constipation.

Methods: A total of 10 formulations were developed using various proportions of excipients by wet granulation method. The best formulation containing 300 mg flaxseed powder and 1200 mg figs extract (total weight of 2000 mg) was selected. After compression of caplets, evaluation tests such as general appearance, hardness, thickness, weight variation, friability, disintegration time and standardization studies were performed. During clinical study, 15 patients with functional constipation received the prepared dosage form three times daily for two weeks, and then statistical differences within the groups were compared.

Results: After the first week of experiment the increase of defecation frequency and reduction of retentive posturing, large fecal mass, pain feeling during evacuation and consistency of stool were significantly noticeable ($P < 0.05$).

Conclusions: Prepared caplets of *Linum* and *Ficus* reduced the severity of constipation in patients.

Keywords: Drug Formulation, Flaxseed, *Linum usitatissimum*, Figs, *Ficus carica*, Constipation

1. Background

Constipation is a common gastrointestinal symptom characterized by altered bowel habits, abdominal discomfort and/or difficult defecation (1). Constipation is thought to be caused by various factors such as insufficient intake of dietary fiber, emotional influence, dysfunction of the nervous system, structural abnormality, systemic disease or drug effects (2). Constipation can be the cause of severe secondary diseases resulting from enteric fermentation, inducing toxic gas, and therefore requires active prevention and proper treatment (3).

A lot of drugs are approved to treat constipation and most of them are laxatives. The mechanism of bulking agents and/or laxatives is different such as causing water retention by their osmotic effects (4), stimulating intestinal secretion (5) or directly increasing the intestinal motility (6). Unfortunately, these drugs are not so ideal in clinical use because chronic use of them, especially anthranoid laxatives, showed adverse side effects including induction of tolerance, loss of colonic motility, melanosis coli, cathartic colon and colorectal cancer (7-9).

Therefore, using dietary or medicinal fibers is well ac-

cepted as initial steps to treat constipation especially mild complaints of infrequency or hard stools (9, 10).

There are many plants in traditional Iranian medicine (TIM) used to treat constipation. Flaxseed or linseed (*Linum usitatissimum*) and fig (*Ficus carica*) are two famous plants to treat constipation in TIM (11-13).

Flaxseed is a good source of soluble and insoluble fibers (14). The dietary fiber of flaxseed significantly exhibited positive effects on constipation, shortened the start time of defecation and increased small intestine transit rate and stool frequency (15, 16). Flaxseed demonstrated laxative influence in both healthy subjects and the ones with constipation (17-19).

The fruits of *Ficus carica*, known for high fiber content, improved the symptoms of patients with functional constipation. It increased the number of bowel movements, reduced defecation time and improved abdominal pain and discomfort effort for evacuation and the sense of incomplete evacuation (20).

2. Objectives

The current study aimed to evaluate a new caplet dosage form containing combination of flaxseed and fig fruit and investigated the laxative effect of this drug in patients with constipation symptoms.

3. Methods

3.1. Plant Extraction

A 1000 g of *Ficus* fruit was macerated in hot water for 24 hours, and then the extract was filtered through a cloth membrane and lyophilized; 500 g of flaxseed was frozen at -20°C, and then grounded. The figs extract and flaxseed powder were refrigerated for subsequent use.

3.2. Preparation of Dosage Form

Caplets containing flaxseed and figs were prepared by wet granulation method. Flaxseed powder and *Ficus* extract in different doses were mixed with required quantities of excipients and achieved formulations were listed in Table 1. The blend was granulated by hand, and then the wet coherent mass was dried and the sized was reduced by passing through sieve # 20. The granules were compressed in to caplets each containing 300 mg flaxseed powder and 1200 mg figs concentrated extract and a total weight of 2000 mg on rotary caplet press (Korcher, Germany) using 15 × 10 mm punches.

Table 1. Different Formulations Prepared From Flaxseed and Figs

| Formulations | Flaxseed Powder, g | <i>Ficus</i> Extract, g | Excipients, g |
|--------------|--------------------|-------------------------|---|
| F1 | 0.31 | 1.54 | Avicel (0.15 g) |
| F2 | 0.31 | 1.54 | Lactose (0.15 g) |
| F3 | 0.31 | 1.54 | Avicel + Lactose (0.075 + 0.075 g) |
| F4 | 0.33 | 1.33 | Avicel (0.34 g) |
| F5 | 0.17 | 0.84 | Avicel + CaHPO ₃ (0.15 + 0.84 g) |
| F6 | 0.17 | 0.84 | Avicel + CaHPO ₃ + Talc (0.15 + 0.72 + 0.12 g) |
| F7 | 0.17 | 0.84 | Saccharose + Talc (0.71 + 0.125 g) |
| F8 | 0.36 | 1.46 | Cellulose (0.18 g) |
| F9 | 0.36 | 1.46 | Saccharose (0.18 g) |
| F10 | 0.31 | 1.26 | Avicel (0.43 g) |

3.3. Evaluation of Prepared Caplets

The prepared caplets were evaluated for quality control tests such as hardness, thickness, weight variation, friability and disintegration time.

3.3.1. Hardness and Friability

Hardness of caplets was determined by Monsanto hardness tester (21). Friability test was conducted by Roche Friabilator. Ten caplets were weighed and were subjected to the combined effect of attrition and shocked by utilizing a plastic chamber that revolved at 25 rpm for four minutes, dropping the caplets at distance of six inches with each revolution. Operated for 100 revolutions, the caplets were dedusted and reweighed. The percentage friability was calculated (22).

3.3.2. Thickness

The thickness and length of caplets were determined using Vernier-caliper (21). Ten caplets were selected randomly for this test and the average value was reported.

3.3.3. Weight Variation

The average weights of twenty random selected caplets were determined, and then individual caplets were compared with the average weight (23).

3.3.4. Disintegration Time

Disintegration test was conducted in accordance with Indian pharmacopeia (IP) 1996 for gastro resistant tablets. Caplets were placed in tubes and disintegration time was noted in pH 1.2 for first two hours, subsequently caplets media was changed to pH 7.4 and test was further carried out to measure disintegration time of caplets. The disintegration time for six caplets was measured, and the average time and standard deviation were calculated for each. Test was performed in triplicate (n = 3).

3.3.5. Quality Control

Standardization of caplets was performed based on mucilage contents as active ingredients of *Ficus* and *Linum*. Mucilage contents of caplets were determined according to Fedeniuk and Biliaderis method with some modifications (24). Five caplets were grinded separately and extracted overnight in 25°C water (1:20 w/v). The extracts were filtered through cheesecloth and the mucilage was precipitated by addition of three volumes of ethanol. The mucilage was collected using pre-weighed filters and dried at room temperature.

3.4. Pilot Clinical Trial

3.4.1. Study Design

It was a 14-day human pilot study. Fifteen patients with functional constipation complaints aged 22 - 53 years participated in the study. The investigators and patients were aware of the study group assignment. The study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR. TUMS. REC. 1395. 2574).

3.4.2. Patients

The diagnosis of functional constipation in patients was confirmed by a questionnaire and the patients with signs of constipation were visited by physicians to confirm and complete the criteria. The inclusion criteria were less than two defecation weekly, more than one fecal incontinence per week, retentive posturing or excessive volitional stool retention, feeling of painful or hard bowel movements, presence of a large fecal mass in the rectum or large diameter stools. These criteria were according to Rome III criteria of functional constipation (25). The exclusion criteria were consumption of fermented foods or intestinal medicines except in an emergency case.

3.4.3. Study Protocol

The patients received one prepared caplets three times daily for two weeks in September 2012. The patients were asked to fill out questionnaires about bowel activities including frequency, form, volume and consistency of defecation, pain feeling during evacuation and retentive posturing. They received instructions to choose a right score for their symptoms. These scores were measured on the pattern of visual analog scale (VAS) (26-29). Scores for average of consistency of stools were in the range between 0 (soft and comfortable) and 100 (maximum consistency imaginable for patients) and also, scores for the severity of pain during defecation were ranged between 0 (without any pain) and 100 (maximum pain imaginable for patients). All concomitant medications were recorded, only using any other laxatives was forbidden. At the end of the experiment, the filled sheets were evaluated. The study results were expressed as mean \pm standard deviation. Statistical significance was evaluated by the Student paired T-test; $P < 0.05$ was considered significant.

4. Results

Among formulations of Table 1, number 10 was selected for preparing caplets because of showing better pressing ability. The caplets were capsule shaped with an average length of 15.0 ± 0.1 mm and average thickness of $3.0 \pm$

0.1 mm. The results showed that the thickness of all formulated caplets was uniform. The average hardness of all caplet formulations was 9.0 ± 0.25 kg/cm² indicating that all caplets had adequate mechanical strength. The average weight of caplets was 2000.0 ± 0.001 mg. The accepted percentage of deviation was $\pm 5\%$ for more than 250 mg weight caplets which meant the caplets complied within the IP limit in terms of uniformity of weight. According to the United States pharmacopeia (USP), in friability test the maximum weight loss should not be more than 1% (0.8% in the current experiment). The results revealed that the caplets passed the friability test. In disintegration test, no drug release took place in the first two hours at pH 1.2, indicating no drug release in stomach. Drug release started after changing dissolution media pH to 7.4 and completed within 45 minutes. This finding demonstrated that the prepared anti-constipation formulation acted as gastro resistant caplets. The caplets were standardized based on mucilage contents as 69.3 ± 0.02 mg.

The prepared caplets containing flaxseed and figs were evaluated in patients with persistent constipation difficulties. Table 2 demonstrated the changes in defecation of patients before and after receiving caplets. The frequency of defecation versus baseline increased after the first week ($P < 0.05$); however it showed significant enhancement at the end of the second week ($P < 0.01$). Retentive posturing decreased meaningfully after the first week ($P = 0.0003$) until there was no sign of stool retention after the second week. The frequencies of large fecal mass or large diameter stools showed significant difference based on the frequency of baseline after the first and second weeks ($P = 0.036$ and 0.015 , respectively). It was noticeable that there was no variance between the results of the first and second weeks ($P = 0.343$), which meant that the prepared traditional dosage form of flaxseed and *Ficus* only needed one week to decrease fecal mass. Feeling pain during evacuation and consistency of stool showed obvious reduction after the first week of experiment ($P = 0.005$) and then the comparison of results of the first and second weeks demonstrated stronger difference ($P = 0.00002$). It meant that this dosage form was active to reduce pain and stool consistency during the experiment.

5. Discussion

In the current study a new dosage form (caplet) containing flaxseed powder and figs concentrated extract was prepared based on the traditional medicine of Iran and quality control tests were performed.

There were previous clinical reports for usage of flaxseed in treatment of constipation. Tarpila et al. (19) showed that after the period of three months treatment

Table 2. Changes in Defecation of Patients With Functional Constipation Before and After Receiving Caplets Containing Flaxseed and Figs^{a,b}

| Criteria | Before Experiment | First Week | Second Week |
|----------------------------------|-------------------|--------------------------|-------------------------|
| Frequency of defecation | 0.0 ± 0.50 | 1.0 ± 1.00 ^c | 3.0 ± 1.90 ^d |
| Frequency of retentive posturing | 5.2 ± 1.32 | 2.4 ± 1.84 ^d | 0.0 ± 0.00 ^d |
| Frequency of large fecal mass | 0.5 ± 0.53 | 0.1 ± 0.32 ^c | 0.0 ± 0.00 ^c |
| Feeling pain during evacuation | 97.0 ± 6.75 | 61.0 ± 28.1 ^d | 7.0 ± 15.7 ^d |
| Consistency of stool | 98.9 ± 3.33 | 54.4 ± 26.0 ^d | 6.7 ± 20.0 ^d |

^aValues are expressed as mean ± SD.

^bStatistical analysis was evaluated by the student paired T-test and compared with baseline (before drug intake).

^cP < 0.05,

^dP < 0.01.

with flaxseed, constipation and abdominal symptoms of patients with irritable bowel syndrome significantly reduced. Safety laboratory values were unchanged with exception of serum thiocyanate and blood cadmium. These toxic factors with 12-24 g/d flaxseed stayed within safe limits. Another study revealed that daily intake of yoghurt containing linseed reduced the severity of constipation in the elderly subjects with mild constipation (30). Cockerell et al. (31) compared the clinical effectiveness of whole linseeds, ground linseeds and no linseeds to manage constipation in patients with irritable bowel syndrome (IBS). Although linseeds may be useful to relieve IBS symptoms, there were no significant changes in stool frequency or stool consistency in any of the groups. There was only one clinical trial study on consumption of *Ficus carica* on improvement of functional constipation. It was shown that after two weeks of treatment with *F. carica*, the total colonic transit time was shortened. *Ficus carica* increased the number of bowel movements, reduced defecation time and improved abdominal pain and discomfort, the effort for evacuation and the sense of incomplete evacuation (20).

5.1. Conclusions

The clinical trial of contemporaneous consumption of flaxseed and figs in a drug was performed for the first time in the current experiment. It was found that this drug was capable to relieve symptoms of patients with functional constipation including frequency, form, volume and consistency of defecation, feeling pain during evacuation and retentive posturing.

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Footnotes

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