TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 6, Issue 4, Autumn 2021

Original Research

# The Effect of an Aloe-Based Polyherbal Formulation in Adults with Functional Constipation: A Randomized, Double-Blind, Placebo-Controlled, Six-Months Clinical Follow-up Trial

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**Received:** 3 Mar 2021 **Revised:** 6 Oct 2021 **Accepted:** 11 Oct 2021

**Abstract**

ion. *"Ayarij-e-Faiqra (AF)"* is a polyherbal formula that has been recommended by Persian Medicine as an efficent purgative agent . The purpose of this study was to evaluate the effect of AF on functional constipation using a double-blind, placebo-controlled clinical trial. According to the Rome III classification, 79 adults with functional constipation were included in this trial. The diagnostic criteria were according to the Rome III classification. Patients with constipation symptoms who referred to the traditional medicine clinic of Shahid Beheshti University of Medical Sciences from April 2014 to September 2016 were randomly allocated to the AF and placebo groups. The AF and placebo groups received AF and placebo for three months, respectively and followed up for another three months. During the study, the treatment efficacy was assessed by a questionnaire. AF treatment significantly decreased most of the symptoms by 84% at the end of the first month ($p < 0.05$) and by 90% at the end of the third month in comparison to placbo group

**Citation:** Ghayour Razmgah GR, Hosseini SM, Hajimehdipoor H, Saberi Firoozi M, Kashafroodi H, Ghahremani Z, Sadeghi SMH, Choopani R. **The Effect of an Aloe-Based Polyherbal Formulation in Adults with Functional Constipation: A Randomized, Double-Blind, Placebo-Controlled, Six-Months Clinical Follow-up Trial.** Trad Integr Med 2021;6(4):298-310.

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($p < 0.001$). However, three months after the end of the intervention, the frequency of constipation symptoms in both groups was not statistically significant. Based on the satisfaction questionnaire, the treatment satisfaction score during the intervention was increased to 9 in the AF group, but no significant difference was found between the two groups three months after the intervention ($p > 0.005$). Although AF could be beneficial for treating functional constipation without significant side effects, changing patients' lifestyles has great importance in this process.

**Keywords:** Functional constipation; Iranian polyherbal formulation; *Ayarij-e-Faiqra*; Rome III; Persian medicine

## Introduction

One of the most common functional gastrointestinal problems around the world is functional constipation (FC), with an estimated prevalence of 16-35.5% [1]. This disorder is generally characterized by persistent difficult, infrequent, or incomplete defecation. The incidence of constipation increases with age. Severe constipation can cause hemorrhoids, anal fissure, colon cancer, hepatic encephalopathy, and poor life quality in patients [2,3].

It is recommended that lifestyle measures such as sufficient hydration, non-strenuous exercise, increased natural fiber intake, and dedicated time to have a bowel movement can prevent constipation [1]. Then, the use of laxatives (osmotic, stimulant, surfactants, and other prokinetic agents) for the treatment of constipation is also recommended [4]. The frequent use of laxatives may cause many adverse reactions, increase medical expenses, and waste healthcare resources [2].

Recently, several drugs, including osmotic laxatives and motility-promoting agents, have been proven to be beneficial for chronic constipation. However, patients who use these medications should encounter a more prolonged therapy duration, stronger dependence, and higher economic consequences [5].

The potential therapeutic capacities of traditional and complementary medicine in public health and the needs to develop national instructions for this type of medicine has been affirmed by World Health Organization (WHO) [6].

Persian Medicine (PM) recommends purgation as one of the easiest and most effective ways to clear waste humors from the body. Purgative remedies, as systemic agents, treat constipation and expel the waste humor from vessels, membranes, and the body [7].

*'Ayarij-e-Faiqra'* (AF) is a polyherbal remedy that has been used as a remedy for many diseases, and it is an important polyherbal formula in PM. The main ingredient of AF is Aloe dried juice, which has laxative activity [7]. It is believed that other species in AF formulation help to decrease Aloe side effects or have synergistic effects, to establish the effect of AF formulation as a powerful laxative agent with the most negligible side effects [7]. In this investigation, the effect of AF on FC was evaluated and compared with placebo in a double-blind, placebo-con trolled clinical study.

## Materials and Methods

*Drug preparation*

AF was prepared according to the instructions of "*Qarabadin Kabir*" textbook [8] in Traditional Persian Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The protocol included the combination of *Cinnamomum verum* J.Presl bark, *Pistacia lentiscus* L. oleo gum resin, *Cinnamomum cassia* (L.) J.Presl bark, *Asarum europaeum* L. rhizome, *Commiphora gileadensis* (L.) C.Chr. fruit and wood, *Nardostachys jatamansi* (D.Don) DC. rhizome, *Crocus sativus* L. stigma, and *Aloe vera* (L.) Burm.f. juice (1:1:1:1:1:1:1:0.14:7.14). All the components were powdered, sieved, mixed, and packed into 500 mg hard gelatin capsules. The placebo was prepared from corn starch using capsules of the same color and size.

*Inclusion and exclusion criteria*

Inclusion criteria were age 18-50 years, the ability to participate in the whole study, the absence of significant behavioral disorders, speaking in understandable language, completion of the consent form, and having at least six months of constipation, according to Rome III criteria [9,10]. All patients signed informed written consent before any intervention.

According to Rome III, FC was diagnosed based on the following criterias: straining at stool, lumpy or hard stools, incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecation at least 25% with no sign of irritable bowel syndrome (IBS). All mentioned symptoms should be started at least six months ago [3]. Moreover, two symptoms including fewer than three defecations per week and loose stool without laxatives use should rarely be happened during the last three months.

Exclusion criteria included patients who did not meet any of the above listed inclusion criteria in addition to allergy to herbal medicines, diagnosis of obstructive constipation by a gastroenterologist based on history or colon transit, consumption of drugs that cause constipation in the last month (anticholinergic drugs, tricyclic antidepressants, calcium channel blockers, anti-Parkinson's drugs, sympathomimetics, antipsychotics, diuretics, iron supplements, anti-inflammatory drugs, hormonal drugs), abuse narcotics, stimulants, cannabis, alcohol and pseudo-opiates, illnesses affecting constipation (Parkinson's disease, multiple sclerosis, stroke, hypothyroidism, tumor, immunodeficiency, diabetes, liver or kidney failure, inflammatory bowel disease, pregnancy or lactation, history of major abdominal surgery), warning signs (weight loss or anemia), gastrointestinal complications that impede the continuation of the study (confirmed by both gastroenterologist and researcher), unpredictable complications that lead to intolerance to the drug or placebo such as idiosyncratic disease (in consultation with a gastroenterologist and researcher), secondary constipation due to some diseases and medications, unwillingness to continue the study.

*Intervention*

The study was a double-blind and randomized

controlled clinical trial on adult patients who referred to the traditional medicine clinic of Shahid Beheshti University of Medical Sciences from April 2014 to September 2016. Subsequently, the patients qualified for randomization into treatment or placebo groups. The sample size was selected according to previous studies (n = 80 patient) [11]. Accordingly, 43 ptients were assigned to the drug group and 36 to the placebo group. Both participants and researchers were blinded to treatments allocation. The drug and placebo were packed into same package and labeled with one of the two codes allocated to the drug or placebo. A number of key codes were assigned for drug and placebo packages and kept secure by an independent pharmacist. Then, each patient having inclusion criteria received a specific number. The daily dose of the drug was 1-2 capsules, was swallowed 30 min before bedtime with warm water, for three months. Each patient was planned to recieve one capsule every night. But the dose of drug was increased to two capsules per day if they had not enough bowel movements. In addition, the patients could use a laxative, a tablet (C-lax) containing senna leaf, in intolerant constipation.

The placebo group also received treatment in a similar manner (the daily dose of the drug was 1-2 capsules, which were swallowed 30 min before bedtime with warm water for three months. Each patient was planned to recieve one capsule every night). It was recommended to have dinner 2.5 h before taking the medication. Patients were referred to the clinic every month at the end of one, two, and three months, and three months after the end of the interposition) to control the signs, complications and receive the drug.

The Medical Ethics Committee of Shahid Beheshti University of Medical Sciences has approved this study (Ethical code: IR.SBMU.REC.1392.766; IRCT Id: IRCT20200303046677N1).

*Data analysis*

Data were analyzed by SPSS software version 22. Normal distribution of data was analyzed by Kolmogorov-Smirnov normality test. Since the normality assumptions were not satisfied, non-parametric Chi-square, McNemar Test, Fisher's exact test, unpaired t-test, Friedman and Mann-Whitney tests were used.

## Results

According to the inclusion and exclusion criteria, eighty-three patients were enrolled to participate in the present study. Four patients (two men and two women) in the placebo group withdraw prematurely due to lack of referral. Consequently seventy-nine patients randomly divided into intervention and placebo groups (Figure 1). There was no significant difference between the intervention and the placebo groups regarding age and sex of participants (Table 1).

Analysis of constipation symptoms before the intervention by Chi-square test and Fisher's exact test showed that the distribution of these symptoms were not significantly different between the drug and placebo groups (Table 2).

and after the intervention.

At the end of the second month, there was no significant difference in the sensation of incomplete evacuation between the groups, as shown in table 2. At the end of the third month, the frequency of

constipation symptoms were significant between the two groups (Table 2). Three months after the intervention, the frequency of constipation symptoms was not statistically significant between the drug and placebo groups (Table 2).

The comparison of treatment satisfaction scores (ranging from 1-10) at the end of the first, second, and third months revealed a significant difference between the two groups . However, there was no significant difference in the menationed scores between the groups three months after the end of intervention (Table 4).

Comparison of constipation symptoms between the two groups at the end of the first month indicated that the two groups were significanlty different in straining at stool, lumpy or hard stools, the sensation of anorectal obstruction, and use of manual maneuvers to facilitate defication (Table 2). However, the frequency of the sensation of incomplete evacuation, fewer than three defecations per week, and the loose stools without the use of laxatives were not statistically significant between the two groups (Table 3).

Table 2 also shows a significant difference in symptoms between the of the groups before and after the intervention.

At the end of the second month, there was no significant difference in the sensation of incomplete evacuation between the groups, as shown in Table 2. At the end of the third month, the frequency of constipation symptoms were significant between the two groups (Table 2). Three months after the intervention, the frequency of constipation symptoms was not statistically significant between the drug and placebo groups (Table 2).

The comparison of treatment satisfaction scores (ranging from 1-10) at the end of the first, second, and third months revealed a significant difference between the two groups . However, there was no significant difference in the menationed scores between the groups three months after the end of intervention (Table 4).

As indicated in Table 5, the frequency of laxative use before and after the third month of the intervention was not statistically significant between AF and placebo groups. However, at the end of the first, second, and third months, there was a statistically significant difference between the two groups. Comparison of consumption before intervention and three months after the end of the intervention within the groups was not significant (Table 5).

**Table 1.** Comparison of the prevalence of sex and age between the drug and placebo groups.

| Variable | Group | | p-value |
|---|---|---|---|
| | Placebo | AF | |
| gender (female%) | 24 (55.8 %) | 19 (52.8 %) | 0.787* |
| gender (male%) | 19 (44.2 %) | 17 (47.2 %) | |
| age (mean (SD)) | 36.93(2.22) | 35.69 (2.57) | 0.799**[ta] |

All data are statistically significant at $p < 0.05$* Chi-squared test.**Unpaired t-test

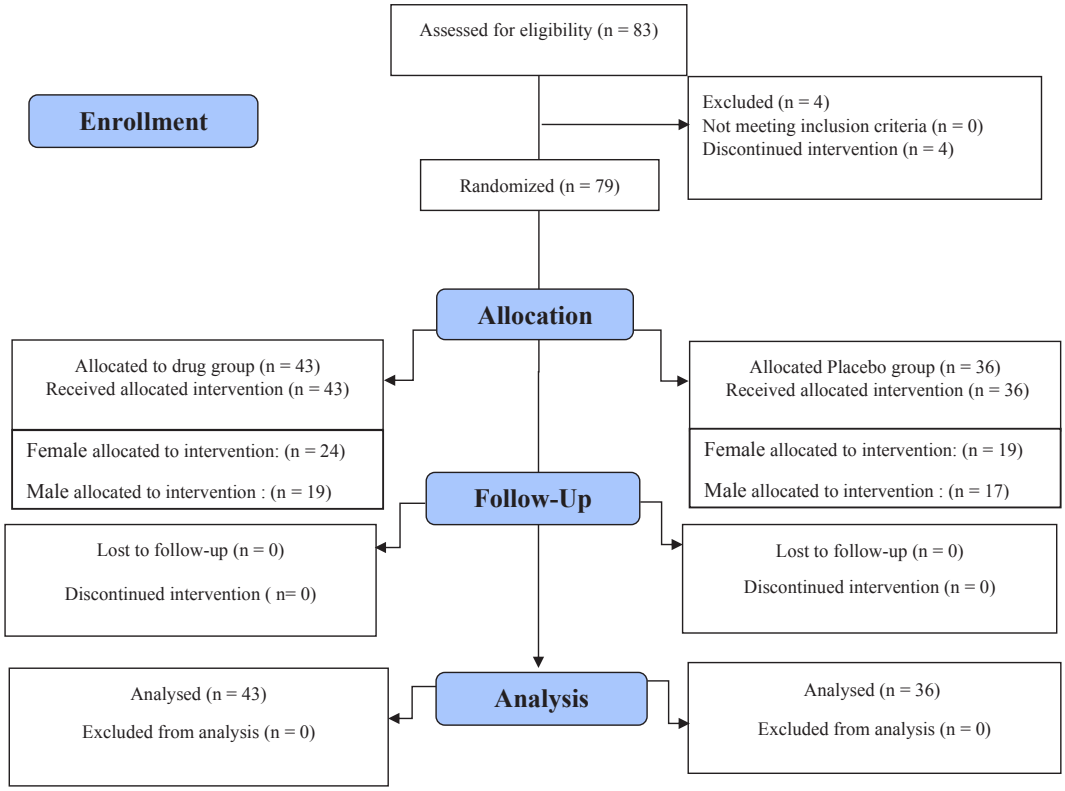


**Figure 1.** Consolidated standards of reporting trials (CONSORT) flowchart of the study.

**Table 2.** Comparison of the prevalence of variables (Diagnostic criteria of constipation) between drug and placebo groups.

| After the intervention | | | Before intervention | | | | |
|---|---|---|---|---|---|---|---|
| Time | | - | End of the first month | End of the third month | End of the second month | Three months after the end of the interven-tion | McNemar Test |
| Variable | Group | Yes N (%) | Yes N (%) | Yes N (%) | Yes N (%) | Yes N (%) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Straining | AF | 41 (95.3) | 24 (55.8) | 7 (16.3) | 13 (30.2) | 40 (93.0) | <0.001# |
| | placebo | 36 (100) | 29 (80.6) | 19 (52.8) | 30 (83.3) | 34 (94.4) | 0.031 |
| *p*-value | | 0.498* | 0.020** | <0.001** | <0.001** | 0.796** | |
| Hard stools | AF | 40 (93) | 23 (53.5) | 13 (30.2) | 10 (23.3) | 40 (93.0) | <0.001# |
| | placebo | 36 (100) | 29 (80.6) | 13 (30.2) | 25 (69.4) | 32 (88.9) | <0.001# |
| *p*-value | | 0.012** | 0.246* | 0.520** | <0.001** | <0.001** | |
| The sensation of incomplete evacuation | AF | 30 (69.8) | 21 (48.8) | 14 (32.6) | 14 (32.6) | 31 (72.1) | <0.001# |
| | placebo | 30 (83.3) | 20 (55.6) | 19 (52.8) | 28 (77.8) | 20 (55.6) | 0.727 |
| *p*-value | | 0.160** | 0.126** | <0.001** | 0.070** | 0.552** | |
| The sensation of anorectal obstruction | AF | 13 (30.2) | 5 (11.6) | 2 (4.7) | 2 (4.7) | 11 (25.6) | <0.001# |
| | placebo | 16 (44.4) | 12 (33.3) | 17 (47.2) | 13 (36.1) | 16 (44.4) | 0.250 |
| *p*-value | | 0.078** | <0.001** | <0.001** | 0.019** | 0.192** | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Manual maneuvers | AF | 23 (53.3) | 14 (32.6) | 6 (14.0) | 2 (4.7) | 26 (60.5) | <0.001# |
| | placebo | 26 (72.2) | 23 (63.9) | 24 (66.7) | 21 (58.3) | 19 (52.8) | 0.125 |
| *p*-value | | 0.492** | <0.001** | <0.001** | 0.005** | 0.088** | p-value |
| Fewer than three defecations per week | AF | 32 (74.4) | 16 (37.2) | 5 (11.6) | 3 (7.0) | 32 (74.4) | <0.001# |
| | placebo | 24 (66.7) | 19 (52.8) | 19 (52.8) | 20 (55.6) | 25 (69.4) | 0.388 |
| *p*-value | | 0.623** | <0.001** | <0.001** | 0.165** | 0.450** | |

All data are statistically significant at p < 0.05.*Chi-squared test.**Unpaired t-test.# McNemar Test

**Table 3.** The mean amount of loose stools in AF and placebo groups

| Loose stools | Group | Before intervention N (%) | End of the first month N (%) | End of the second month N (%) | End of the third month N (%) | Three months after the end of the intervention N (%) |
|---|---|---|---|---|---|---|
| Never | AF | 25(58.1) | 5(11.6) | 7(16.3) | 11(25.6) | 19(44.2) |
| | placebo | 20(55.6) | 7(19.4) | 12(33.3) | 5(13.9) | 9(25) |
| Rarely | AF | 12(27.9) | 15(34.9) | 6(14.0) | 7(16.3) | 17(39.5) |
| | placebo | 12(33.3) | 22(61.1) | 16(44.4) | 7(19.4) | 14(38.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sometimes | AF | 5(11.6) | 21(48.8) | 30(69.8) | 25(58.1) | 7 (16.3) |
| | placebo | 2(5.6) | 7(19.4) | 8(22.2) | 24(66.7) | 13(36.1) |
| Usually | AF | 1(2.3) | 2(4.7) | 0(0.0) | 0(0.0) | 0(0.0) |
| | placebo | 2(5.6) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| *p*-value | | 0.667** | 0.018** | <0.001** | 0.435** | 0.079** |

All data are statistically significant at $p < 0.05$.**Chi-square test

**Table 4.** Comparison of the satisfaction percentile between AF and placebo groups

| Time | | End of the first month | | | End of the second month | | | End of the third month | | | Three months after the end of the intervention | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Group | Percentile | | | Percentile | | | Percentile | | | Percentile | | |
| | | 25th | 50th | 75th | 25th | 50th | 75th | 25th | 50th | 75th | 25th | 50th | 75th |
| Satisfaction | AF | 6% | 7% | 8% | 7% | 8% | 9% | 8% | 8% | 9% | 2% | 3% | 4% |
| | placebo | 3% | 5% | 6% | 2% | 3% | 5% | 1% | 3% | 5% | 1% | 3% | 4% |
| *p*-value* | | < 0.001* | | | < 0.001* | | | < 0.001* | | | 0.786 | | |

All data are statistically significant in ($p < 0.05$).* Mann-Whitney U

**Table 5.** Comparison of the laxative consumption between AF and placebo groups

| Time | | Before intervention | After the intervention | | | | McNemar Test p-value |
|---|---|---|---|---|---|---|---|
| Group | | - | End of the first month | End of the second month | End of the third month | Three months after the end of the intervention | |
| | | Yes N (%) | Yes N (%) | Yes N (%) | Yes N (%) | Yes N (%) | |
| Variable | AF | 31(72.1) | 9 (20.9) | 1 (2.3) | 3 (7.0) | 30 (69.8) | 0.000# |
| | placebo | 25(69.4) | 18(50.0) | 10 (27.8) | 16 (44.4) | 25 (69.4) | 0.012# |
| *p*-value* | | 0.796 | 0.007* | 0.001* | 0.000* | 0.975 | |

All data are statistically significant in ($p < 0.05$).*Unpaired t-test .#McNemar Test

## Discussion

In this trial, which was conducted to assess the effects of AF on functional constipation, significant changes were observed in the patients who used this medication in comparison to placebo. Also, there is no considerable severe side effect to be reported. Therefore, this drug has shown significant beneficial effects on the alleviation of functional constipation symptoms with acceptable safety and effectiveness. Also, according to the Rome III questionnaire, the most common symptoms of functional constipation were significantly reduced, and the patient's satisfaction with treatment was significantly increased.

Purgation is the most simple and effective way to clear waste phlegm from body. Laxative medicines are not only used for the treatment of constipation, but also for removing the waste phlegm from different organs of the body [12]. "*Ayarij*" is a multi-component purgative agent used to treat many diseases in PM. AF is a kind of "*Ayarij*" with Aloe dried juice as the main component [8,12,13]. AF has several uses in PM; it is used for tremor relief [14], gastric ulcer [15,16], and obesity [17,18]. AF is an essential polyherbal formulation described as a purgative by Hippocrates [19]. People used aloe dried juice as a tonic, purgative, laxative, and emmenagogue in traditional medicine [17]. Anthraquinones, present in Aloe juice, are known as potent laxatives; they stimulate mucus secretion, increase intestinal water content, and intestinal peristaltic movement [20]. The aloin content of Aloe is not absorbed in the upper intestine, but can be hydrolyzed in the colon by intestinal bacteria to produce some active metabolites such as aloe-emodin-9-anthrone, which like senna, acts as a stimulant and irritant in the gastrointestinal tract [17,18,21]. Despite the laxative effects of Aloe, which have been established during different studies [21], Umadevi, et al. reported severe side effects of using this herb that discontinued drug usage by patients. Abdominal cramps, distension, diarrhea, red urine, hepatitis, dependency, or worsening of constipation were critical adverse effects, which were reported in that trial study [17] .

Moreover, the laxative effect may cause electrolyte imbalances (low potassium levels), which are frequently reported as more common side effects [17]. To improve Aloe efficiency and reduce its side effects, particularly abdominal cramps, preparing compound drugs are great choices. In PM, various plants have been added to Aloe by different formulations [18]. In a randomized, double-blind placebo-controlled trial on a polyherbal formulation, with Aloe as the main constituent, Davis, et al. demonstrated that abdominal distension was the only side effect. Therefore, some participants withdraw from the study with nausea or vomiting [20]. However in our study, the side effects were mild and there was no withdrawal rate in the drug group.

The gastroprotective effects of some plant species used in the present study have been established in several studies. For example, *Cinnamomum cassia* has anti-bacterial, an

ti-fungal, anti-*H. Pylori*, gastroprotective, and anti-inflammatory effects. This herb have been shown to be beneficial in treating gastric complaints such as diarrhea, flatulence, and vomiting, which were caused by Aloe [22,23]. Some previous evidence have pointe out *Nardostachys jatamansi* as a tonic for the brain, stomach, and liver [24].

Moreover, in some *in vivo* studies, the positive effects of *N. jatamansi* on depression, anxiety, and agitation were observed [25-28]. *Cinnamomum verum* has been traditionally used to treat dyspeptic conditions such as spasms of the gastrointestinal tract and flatulence [29].

Recent researches indicated that Pistacia lentiscus had both digestive and anti-ulcer properties in rats and also showed anti-*H. Pylori* and gastroprotective effects in patients [30,31].

According to a previous investigation, the protective effects of *Commiphora gileadensis* on stomach have been established [32].

Several studies have reported the effect of saffron on different parts of the gastrointestinal tract, especially its relaxant effect on this area [33]. The plant materials present in AF formulation have protective effects on Aloe side effects and increase efficacy of the drug [7].

In the present study, AF and placebo treatment effectively relieved the symptoms; most patients in the AF group had more satisfaction during the treatment. Three months after the intervention, satisfaction in the AF group was still higher than the placebo group. There was a decrease in the severity of all constipation symptoms in the third month. At the end of the third month, AF-treated group experienced a significant decrease (95%) in some symptoms, such as less than three times defecations per week, manual maneuvers, and sense of anorectal obstruction. In the placebo group, these symptoms were reduced in 12% of patients. In AF-treated group, symptoms such as sense of incomplete evacuation, hard stools, and straining at stool decreased to 69% at the end of the third month. These symptoms had been reduced by 7 %, 16%, and 30% in patients in the placebo group. After two months of intervention, the AF-administered patients' condition regarding the loose stools variable was more significantly improved than the placebo group. However, comparing the average laxative usage between the AF and placebo groups has shown that laxative use in both groups was significantly decreased, which may be due to the placebo effect. Some patients in both groups reported complications such as abdominal pain and slight anal itching. All reported complications were treated, and no one was excluded. During three months of follow-up after the intervention, the parameters returned to baseline. This could be happened because of the lack of a healthy lifestyle, which was not investigated in this study. Constipation is mainly related to diet and the patient's lifestyle. Regular physical exercise and higher fiber intake lead to a reduced risk of constipation even after the control of numerous factors [34]. Also, according to traditional

medicine, various lifestyle factors may influence the risk of constipation [18]. Lifestyle plays a vital role in constipation by affecting body and mind, and therefore changing the lifestyle is essential in treating constipation. Some factors, like regular physical activity, higher fiber intake, BMI, aspirin use, alcohol, and coffee affect bowel movement frequency and overall health status [35-37].

This study had some strengths and limitations. The strenghts were the design of the study as a randomized clinical trial that had a blind approach in selecting remedies, monitoring the patients, and managing the obtained data. We had a long-term (6 months) follow-up. Data were obtained from 95% of participants. The population was composed of adults with functional constipation who were diagnosed based on the fully recognized Rome III criteria. AF was a new formulation that reduced aloe complications.

Our limitations include lack of information about the patients' temperament, insufficient time for choosing treatment phase, and discontinued participation of the patients due to some difficulties of performing endoscopic and colonoscopic confirmations.

In conclusion, it was found that AF was helpful during the intervention. This formulation, due to herbal ingredients, decreased the adverse effects of Aloe. However, after the intervention, due to the lifestyle, especially dietary intake and any other medical intervention, parameters returned to pretreatment values.

## Conflicts of Interest

None declared.

## Acknowledgments

This study is a research thesis, which has been supported by the School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Iran.

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