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Efficacy of the *Malva sylvestris* L. flowers aqueous extract for functional constipation: A placebo-controlled trial

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A B S T R A C T

Objective: To evaluate the efficacy of *Malva sylvestris* L. flowers extract for treatment of FC.
Method: Adults with FC were allocated to receive the *M. sylvestris* L. flowers aqueous extract syrup (MSL, 1 g extract/day) or placebo for four weeks. Frequency of constipation symptoms and stool forms were assessed every week. Self-reported improvement was assessed after treatment.
Results: Compared with placebo, more increase was observed in defecation frequency ($F = 18.8$, $P < 0.001$) and more decrease was observed in frequency of all constipation symptoms by MSL ($F = 16.5$ to 25.3, all P values <0.001). Also, the MSL group experienced more reduction in frequency of hard stool forms (45.4% vs. 9.1%, $P < 0.001$) and reported more improvement in all symptoms (all P values <0.01) than placebo.
Conclusion: The *M. sylvestris* L. flowers aqueous extract is efficacious and safe for the treatment of FC in adult patients. Investigating the mechanisms of action is warranted. IRCT2014031617032N1.

1. Introduction

Chronic constipation is a common gastrointestinal complaint affecting up to 20% of the adults and 30% of the children in Western countries [1,2]. In Iran, the reported prevalence of constipation ranges from 1.4% to 37% [3]. Usually, there is no clear underlying structural or biochemical abnormalities leaving the diagnosis of functional constipation (FC) or chronic idiopathic constipation [4]. The prevalence of FC ranges from 12% to 17% in Western countries [5], and from 2.4% to 11.2% in Iran [3]. It is associated with high healthcare costs [6,7] and significant impairment in quality of life [8].

Current medical treatments for FC include various laxatives (e.g. bulking and osmotic) and prokinetic agents (e.g. 5- hydroxytryptamine 3,4–receptor (ant)agonists) [9]. A number of these treatments are shown effective in the treatment of FC. However, not all patients have satisfactory response to these medications and concerns exist regarding the adverse effects as well [9]. Accordingly, a large number of patients with FC try complementary and alternative medicine (CAM) for treatment with herbal therapies among the most used CAM methods [10,11]. Several herbal medicines are proposed for the treatment of constipation, but there is lack of scientific evidence supporting their efficacy and safety [10,12–14].

The genus *Malva* L. (in the family Malvaceae) is represented by about 40 taxa worldwide. The *Malva sylvestris* L. is an annual herb with shallowly lobed leaves and purple flowers blooming at late spring. This herb is native to Europe, North Africa, and South-west

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Asia especially Iran [15,16]. There is a long history of using *M. sylvestris* L. in Iran where it is named as 'Panirak' (or 'Khobazi') and commonly used as a vegetable as well as a medicinal plant [16]. The *M. sylvestris* L. is proposed for the treatment of burn and dermal infected wounds, bronchitis, inflammations, and digestive problems including constipation [15,16]. Leaves, flowers, and aerial parts are used as laxative in human and animals [15]. Mucilages are one of the major components responsible for the therapeutic effects of *Malva,* and the Malvaceae family possesses the most abundant deposits of mucilages. These mucilages, which can be found mainly in leaves, flowers, and roots, are probably responsible for the laxative effects of the *M. sylvestris* L [15].

Although several non-pharmacological therapies are claimed to be beneficial for patients with FC, most of them lack supportive qualified evidence. The *M. sylvestris* L. is suggested for the treatment of constipation in traditional medicine documents [15]. However, to our knowledge, there is no report from a placebo-controlled trial on its application in the treatment of constipation. Accordingly, we aimed to investigate the efficacy of *M. sylvestris* L., the flowers extract, for the treatment of FC in adult patients. We hypothesized that this herbal drug would result in improvement of stool frequency and consistency, as well as improvement of constipation symptoms.

2. Methods

2.1. Participant and study setting

This study was conducted in the gastroenterology clinic of the Shariati University Hospital in Isfahan city (Iran) between December 2013 and October 2014. Inclusion criteria were age between 18 and 65 years and diagnosis of FC by a gastroenterologist based on the Rome III criteria [4]. Appropriate work-ups were done by the gastroenterologist according to the current standards [4]. Patients with active anal fissure, history of gastrointestinal surgery (except appendectomy and cholecystectomy), and pregnant/lactating women were not included into the study. Exclusion criteria were no proper consumption or preservation of the drug, using laxatives during the study, occurrence of any severe side effects, and willingness to discontinue the study for any reason. The study was approved by the Ethics Committee of the Tehran University of Medical Sciences and informed consent was obtained from patients. The study protocol was registered at the Iranian Registry of Clinical Trials [http://www.irct.ir, registration code: IRCT2014031617032N1].

2.2. Study design

2.2.1. Herbal drug preparation

The herbal medicine used in this trial was an aqueous extract of the *M. sylvestris* L. (Malvaceae; Panirak or Khobazi). Preparation of the *M. sylvestris* L. and placebo syrups was done in the Herbal Medicine Laboratory of the Shahid Beheshti School of Pharmacy (Tehran, Iran). The extract was produced from the dry flowers of the herb which has been harvested in Kerman (Iran) [17] and purchased from the local herbal medicine market (Tehran city, Iran). The herbs were approved by the Herbarium of the Shahid Beheshti School of Pharmacy.

One liter of boiled water (100^{c} degree) was added to 100 mg of dry flowers and kept in closed container in the laboratory for four hours. The solvent was then removed under vacuum at 40^{c} degree using a rotatory vacuum evaporator. Sugar solution 50% was added to the extract obtaining 50 mg of the extract in each 1 cc of the syrup. Herb-to-extract ratio was then 6:1. Placebo was prepared based on pharmacopoeia simple syrup formula including approved color additives and looked the same as the *M. sylvestris* L. syrup.

2.2.2. Allocation, medication, blinding, and compliance

The study was a placebo-controlled clinical trial with two parallel groups. Patients were alternately and equally allocated into two groups of *M. sylvestris* L. extract (MSL) and placebo and consumed 10 cc of the syrup twice daily (2–3 h after breakfast and lunch) for four weeks. Therefore, patients in the MSL group received 1 g of the extract equal to 6 g of the herb/day. This dosage of the product and duration of therapy was determined by referring to the PDR for Herbal Medicines [18]. The MSL and placebo were packed and alphabetically labeled in the same opaque and sealed bottles. Attending physician, patients, outcome assessor, and data analyzer were blinded to the study arms. A co-investigator who was not involved in patients' recruitment or allocation or in outcome assessment was aware of the drug codes and cleared it after data analysis. The gastroenterologist enrolled the patients and assigned them to their groups alternately. The outcome assessor checked patients' compliance every week by live interview or telephone call.

2.3. Measurements

Symptoms of constipation were assessed using an investigator generated questionnaire based on the Rome III criteria 4. Items evaluated the frequency of defecation as per week and frequency of hard stool, straining during defecation, sensation of incomplete evacuation, and manual maneuvers to facilitate evacuation as rated from 0 (never) to 3 (always). The Bristol stool scale was used to specify the stool form with types 1 and 2 considered as hard, 3 and 4 as normal, and 5 to 7 as loose stool forms [19,20]. Patients completed this questionnaire at baseline, week 2, and week 4 at the time of visit, and at week 1 and 3 by telephone interview. Overall improvement in each symptom was assessed (self-rated) at the end of therapy and rated from much improved to much worse. The response categories were then merged to improved, same, and worse. Side effects were assessed at weeks 2 and 4 by interview and using a checklist.

2.4. Data analyses

2.4.1. Primary and secondary outcomes

The primary outcome of the study was the changes in defecation and constipation symptoms' frequency after treatment. Changes in stool consistency, overall self-reported improvement in symptoms after treatment, and side effects were considered as the secondary outcomes.

2.4.2. Sample size calculation

Sample size was determined using the formula for repeated measures design [21] where α and β as the type I and II error rates were considered to be 5% and 20%, respectively. Minimum detectable standardized effect size (i.e. Δ) was considered to be of 0.26. Sample size was then calculated as 55 patients in each study group after about 20% drop-out rate was considered.

2.4.3. Statistical analyses

Data were analyzed using the SPSS software version 16.0 (SPSS Inc., Chicago IL., USA.). Normal distribution of quantitative data was checked with the Kolmogorov–Smirnov Test. Data are reported as mean ± standard deviation (SD) or number (%) for continuous and categorical data, respectively. Comparisons between the two groups were done with the Independent Sample t-Test, Mann–Whitney U Test, and Chi-Square (or Fisher's Exact) Test. Repeated measure analysis using linear mixed effect models was done to test the trend of changes in scores of each outcome variable over the study period while controlling for the baseline values (as covariates). All analyses were performed based on the intention-to-