A Double-blind, Randomized Clinical Trial study of *Plantago major* L. Syrup on Menorrhagia

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Abstract

Objective: Menorrhagia is a common and costly complaint of patients in gynecology. *Plantago major* L. (*P.major*) is one of the herbal remedies recommended by Persian medicine for menorrhagia. **Materials and methods:** In this study, women with menorrhagia who did not have abnormal findings in para-clinical evaluation, were divided into two groups: herbal drug (*P.major* syrup) and placebo (simple syrup). After one cycle, menstrual blood loss based on Pictorial Blood Loss Assessment Chart (PBAC), menstrual duration, hemoglobin and hematocrit were assessed in both groups. **Results:** 65 patients completed the study. In the herbal drug group, menstrual blood loss and menstrual duration decreased from 205.5 ± 8.38 to 185.03 ± 12.30 (P< 0.001) and from 8.30 ± 0.85 to 7.68 ± 1.62 (P= 0.003), respectively. Although the difference between groups in terms of blood loss in the baseline was not significant, it became significant after intervention (P< 0.001). Also, after intervention hemoglobin and hematocrit were significantly increased from 11.82 ± 0.39 to 11.99 ± 0.20 and from 35.47 ± 1.18 to 35.69 ± 1.32 resp. (P< 0.001) in herbal drug group, however they were decreased significantly in placebo group. No adverse effects were reported after using the herbal drug. **Conclusions:** *P.major* may be a good candidate for further study to be considered as a safe and effective remedy for menorrhagia.

Keywords: Abnormal uterine bleeding, Menorrhagia, Hyper Menorrhea, Persian medicine, *Plantago major* L.

Significance | The study highlights *Plantago major*'s potential to reduce menorrhagia severity and duration, offering a promising complementary treatment with minimal side effects.

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1. Introduction

Among the clinical complaints of women in the field of gynecology, abnormal uterine bleeding (AUB) is of particular importance because one in three people who refer to health care centers complains about this problem (ACOG, 2012). AUB is one of the problems that causes high costs for countries as it directly and indirectly imposes an economic burden of about $ 13 billion per year(Fathima & Sultana, 2012; Henry et al., 2020). One form of AUB is menorrhagia or hypermenorrhea. Bleeding more than 80 cc during menstruation or menstruation for more than 7 days objectively defines menorrhagia(Fathima & Sultana, 2012). But in several studies based on subjective diagnosis or complaint of abnormal increase in menstrual bleeding, the prevalence of menorrhagia has been reported above 35% (Marsh et al., 2014; Zhao et al., 2014). In addition to the occupational and social aspects of life, menorrhagia also affects daily activities and thus reduces the quality of life of the women involved (Cihangir et al.,

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(2013). The results of a research showed that on average, the annual health system costs for women with menorrhagia are $ 2,604 more than healthy women, and these women are 2.7 times more likely to require hospitalization(Fraser et al., 2015). Treatment of menorrhagia is currently divided into two categories: invasive and non-invasive. Invasive treatment includes methods such as endometrial ablation and hysterectomy. In addition, hormonal drugs, NSAIDs and anti-fibrinolytics are also widely used for the non-invasive treatment of menorrhagia (Levy-Zauberman et al., 2017). Despite various treatment methods, only one-third of women with menorrhagia are satisfied with improving their problems within a year of treatment(RCOG, 2014). In addition, decreased bone mineral density, coagulopathy, obesity and gastrointestinal complications, regarded as some side effects of pharmacological treatment, are especially caused by hormonal drugs(Bahman et al., 2018; Davies & Kadir, 2017).

In recent years, people in both developed and developing countries have turned to herbal medicine, and even this tendency is increasing(Ekor, 2014; Yehya et al., 2022). Moreover, the results of a new study showed that about 70% of German gynecologists use complementary and integrative medicine (IM) for their patients, of which phytotherapy is one of the most common(Grimm et al., 2021). Meanwhile, as one of the branches of complementary and traditional medicine, Persian medicine (PM) can be helpful in the treatment of today's problematic diseases due to the availability of 10,000 years of experience of Iranian physicians and the priority of safe and low-risk therapeutic methods (Araj-Khodaei et al., 2020). PM pays special attention to the prevention of diseases. It also considers lifestyle modification as the first priority of treatment. More importantly, herbal medicines are used for treatments of various diseases, which leads to a significant reduction in treatment costs(Hadavand et al., 2019). Accordingly, the efficacy and safety of these methods have been demonstrated in several clinical studies(Naseri et al., 2021; Olounabadi et al., 2021; Safari et al., 2020). Based on Avicenna's opinion, normal menstruation not only indicates a woman's health but also is necessary in preventing diseases in the long run (Avicenna, 2005). Therefore, special attention has been paid to the treatment of menstrual disorders such as menorrhagia, which is mentioned in PM resources as "Kasrat-e-Tams" (Jorjani, 2012; Qaraaty et al., 2014).

Avicenna considers *Plantago major* L. (*P.major*) with the name of "Lesan-ol-hamal" to be one of the best treatment options to control the bleeding of various organs(Avicenna, 2005). This plant, which has a cold and dry temperament in Persian pharmacy books, has also been shown to be very useful for bleeding diseases such as increased uterine bleeding, hemorrhoid bleeding, hemoptysis and gastrointestinal bleeding. In addition to these therapeutic effects, reducing uterine pain is another property of this plant that has been mentioned (Tonekaboni, 2011).

One of the benefits of *P.major* is its perfect safety and this feature minimizes the possibility of serious complications (Najafian et al., 2018). In a clinical trial, the effect of *P.major* vaginal suppository was evaluated, which significantly reduced menstrual bleeding in women with Uterine Leiomyoma(Navaei et al., 2020). The current study aims to evaluate the effect of a syrup prepared from *P.major* on women with menorrhagia.

2. Materials and methods

2.1. Participants

The participants were women aged 35 to 50 years who had referred to the gynecology clinic of Mostafa Khomeini Hospital with the chief complaint of prolonged or severe vaginal bleeding. Eligible volunteers who filled out written consent participated in the study.

Inclusion criteria: Uterine bleeding for more than 7 days or/and Pictorial Blood Loss Assessment Chart (PBAC) score over 100, dilation and curettage (D&C), gynecological examination and Pap smear test, agreement to receive PM treatment and no response to hormone therapy or refusal to use hormone therapy due to its complications and normal endometrial biopsy.

Exclusion criteria: Use of hormonal drugs, mefenamic acid and other herbs during the study, adverse drug reaction, need for other interventions and surgery, severe bleeding that hormonal therapy or emergency treatment is needed, history of coagulopathy, comorbidity of chronic diseases such as diabetes, lupus and thyroid problems, comorbidity of uterine or ovarian or other malignancies, submucosal or intramural fibroids larger than 2 cm, uterus larger than 12 cm, pregnancy or lactation, unwillingness to continue the trial.

At the beginning of the study, through a complete medical history and gynecological examination, the initial evaluation of patients was performed. In addition, TSH was measured to exclude patients with thyroid disorders, and ultrasound was performed to assess ovarian and uterine abnormalities.

Sample size:

Based on the results of a previous study (25) with 90% confidence and 80% test power, the number of required samples in each group based on changes in the mean days of menstrual bleeding, which was 6.48 with standard deviation of 0.82 in the control group and was 5.87 with a standard deviation of 0.72 in the drug group and also according to the significance level with a p-value < 0.001 in the two groups is equal to 26 patients in each group and with 50% drop it was determined to be equal to 40 people in each group and a total of 80 people. These individuals were entered into the study groups (intervention and control) by blocked

randomization method with block size of 4.The age and weight of all patients were assessed to evaluate the true effect of *P.major* on menorrhagia by matching the groups.

Ethical approval: This study is a double-blind clinical trial with control group that was conducted in Mostafa Khomeini Hospital, in Tehran, Iran, from April to October 2020. The steps of this study were based on the Helsinki Statement and the objectives of the study were explained to all participants before entering the trial and their written consent was obtained. The study protocol was approved by the Ethics Committee of Shahed University on December 31, 2020 (No: IR.SHAHED.REC.1398.107).

2.2. Preparation of P. major extract

All steps of the herbal drug (*P. major* syrup) and placebo (simple syrup) preparation were performed in "Sanabel" pharmaceutical company. *P. major* syrup is registered as BARSHAN® in the Food and Drug Administration of Iran with a license number 665/21740.

In order to prepare the herbal drug, *P. major* seeds were prepared from a reliable seller in the market of medicinal plants and its scientific name was approved in the Herbarium, School of Pharmacy, Tehran University of Medical Sciences and a voucher number was assigned to it (No. 18547). To make the syrup, 100 g of the seeds were first washed with cold water and then boiled with 4 liters of water for ten minutes. After cooling slightly, the mixture was filtered to separate the extract from the seeds. Then the extract was gently heated with the addition of sugar (65% w/w). Finally, 400 ml of syrup was obtained. The preparation was standardized based on 1.25 mg of total flavonoids per 5 ml of syrup.

The placebo was prepared as a simple syrup with a color similar to the herbal syrup. They were packaged in bottles of the same color and shape having a label with a specific code.

2.3. Intervention

It was a double-blind clinical trial. Eligible patients were randomly assigned to receive a syrup bottle containing the drug or placebo. All bottles were coded, without mentioning the drug name and in the same form. In fact, the researchers, gynecologist, and patients were all blind until the end of the study and the mentioned codes were installed by an independent person on the glass containing medicine and placebo. These codes, which identified the drug or placebo, were kept in a confidential list by this person until the end of the study.

Both P. major and placebo syrups were given to patients with similar instructions. All patients had to consume one tablespoon (5 ml) of the syrup every 8 hours. Patients were required to start taking the medication or placebo from the first day of menstruation and continue for a menstrual cycle. Iron supplement (ferrous sulfate 50 mg daily) was also prescribed for all patients as a routine treatment.

2.4. Outcome measure

Menstrual bleeding and related blood markers were measured as the main outcomes in this study. Evaluation of the menstrual blood loss was performed according to Pictorial Blood Loss Assessment Chart (PBAC) at the beginning and end of the study. Furthermore, patients were instructed to compare the menstrual duration (number of bleeding days) in the cycle during treatment and the previous cycle in terms of decrease, increase or no change to mark in the relevant questionnaire. Hemoglobin (Hb) and hematocrit (Hct) were assessed before and at the end of the intervention.

2.5. Statistical analysis

The information obtained from the questionnaires was entered into IBM Corporation SPSS 24 software. The normality of the data was checked by Kolmogorov-Smirnov test.

To compare the means of variables with normal distribution in the two groups, t-test and Mann-Whitney test were used. To compare the means in each group before and after the intervention, paired t-test or Wilcoxon test were used and to compare categorical variables chi-square test was used. $P < 0.05$ was considered significant in all stages.

3. Results

In this study, 80 patients with menorrhagia were randomly divided into two groups of 40 patients. Six patients in the intervention group and 9 patients in the control group were excluded from the study due to lack of follow-up for the final measurement of hemoglobin and hematocrit. The reason for not following up was the onset of COVID-19 epidemic in Iran and patients' unwillingness to leave home quarantine. Finally, 65 patients completed the study as depicted in the CONSORT diagram in Figure 1.

As shown in Table 1, initial assessment indicated that there was no significant difference in age and weight between patients in the two groups.

As displayed in Table 2, both the menstrual blood loss and menstrual duration in the intervention group were significantly reduced compared to the beginning of the study. In addition, the increase in Hb and Hct in patients in this group was significant.

4. Discussion

The results of this study showed that *P.major* may be effective in reducing bleeding severity and duration as well as improving complications caused by menorrhagia such as anemia. As mentioned in PM, it is believed that *P. major* is also useful in many other bleeding diseases. Similar results were obtained in a study by Nejati et al., which showed that *P. major* syrup also reduced postpartum hemorrhage by 20%(Ebrahimi Varzaneh et al., 2020; Nejati et al., 2018). The main biochemical components of *plantago*

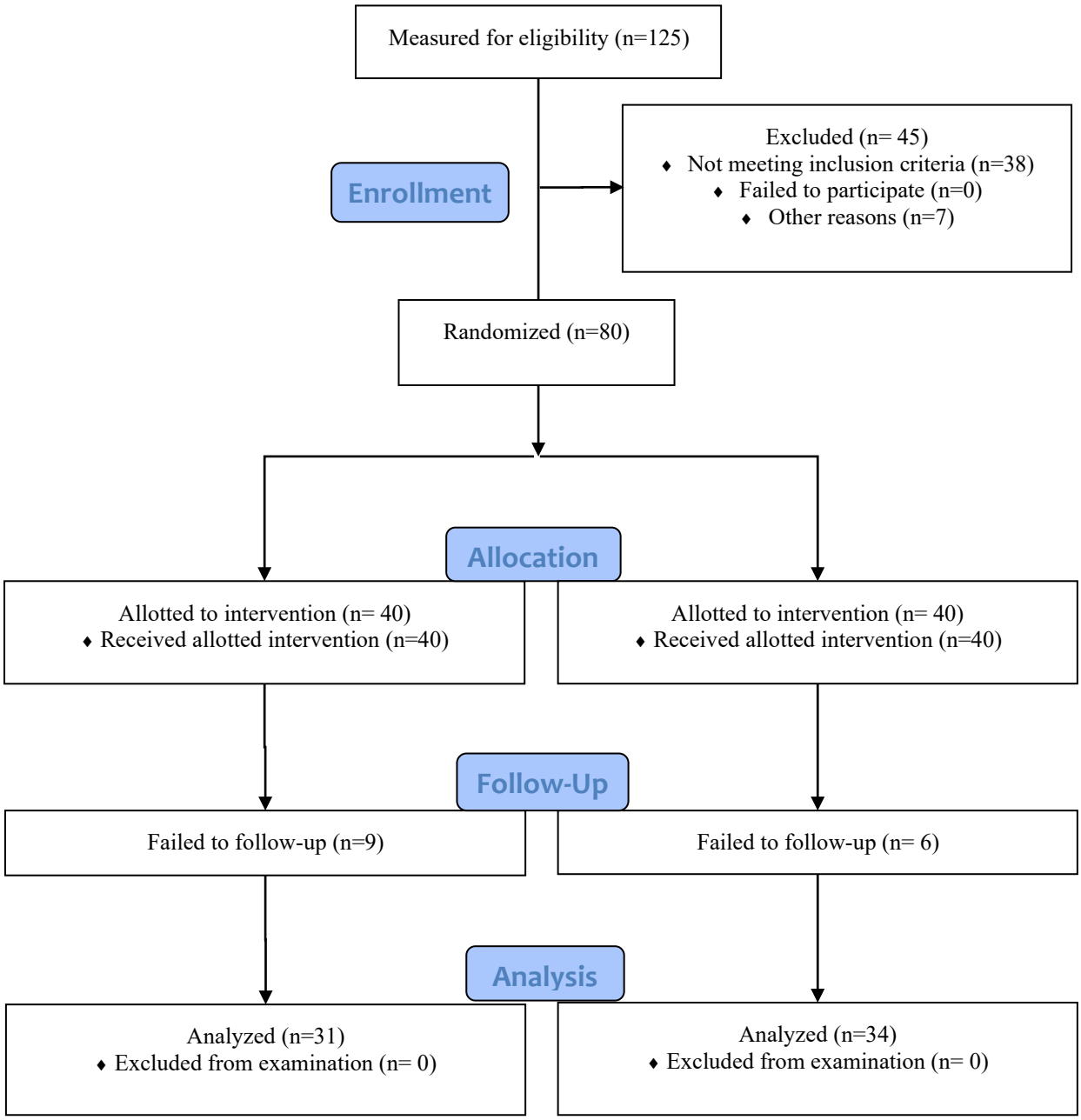

Figure 1. The CONSORT diagram

Table 1. Age and weight of study groups

Characteristic	Intervention (N=34)	Control (N=31)	*P value*
Age (year)	41.33 ± 3.97	41.35 ± 3.59	0.977
Weight (kg)	69.75 ± 5.14	70.33 ± 6.02	0.648

Table 2. Menstrual bleeding rate and blood parameters of study groups

Characteristic	Group	Before intervention	After intervention	*P value**
Menstrual blood loss (cc)	Herbal drug	205.5 ± 8.38	185.03 ± 12.30	P<0.001
	Placebo	203.75 ± 6.27	201.62 ± 10.27	P=0.107
	P-value**	P=0.294	P<0.001	
Menstrual duration (day)	Herbal drug	8.30 ± 0.85	7.68 ± 1.62	P=0.003
	Placebo	8.13 ± 0.757	8.17 ± 0.747	P=0.532
	P-value	P=0.363	P=0.187	
Hb (mg/dL)	Herbal drug	11.82 ± 0.39	11.99 ± 0.20	P<0.001
	Placebo	11.90 ± 0.43	11.89 ± 0.19	P<0.001
	P-value	P=0.094	P=0.940	
Hct (%)	Herbal drug	35.47 ± 1.18	35.69 ± 1.32	P<0.001
	Placebo	35.98 ± 0.60	35.86 ± 0.64	P=0.016
	P value	P=0.101	P=0.501	

* ***P value*** **paired t-test** ** ***P value*** **t-test**

major L. are ursolic acid, oleanolic acid and α-linolenic. Astringent and anti-hemorrhagic effects of this plant could be attributed to these components (Soltani et al., 2020; Zhakipbekov et al., 2023) These acids are believed to be responsible for the major properties of Plantago major. However, the exact mechanism of anti-hemorrhagic effects of these compounds is not yet fully understood. As pentacyclic triterpnoids, ursolic acid and oleanolic acid are probably able to activate vascular endothelial growth factor (VEGF) that stimulates endothelial cells to proliferate, migrate, and form tubes which is the main mechanism in angiogenesis and wound healing process (Jafari et al., 2020; Yusoff, 2017) . Another study has revealed that linoleic acid can increase the production of VEGF in various cell types such as macrophages, and cancer cells (Rodrigues et al., 2016). Furthermore, one of the possible mechanisms for the effect of *plantago major* L on such conditions is the contractile property of smooth muscles such as vasoconstriction, which is resulted from some of its active compounds(Bazafkan et al., 2014; Nejati et al., 2018). Another mechanism that might be involved is the generation of reactive oxygen species (ROS) that modulate the expression and activity of angiogenic factors and signaling pathways (Asif et al., 2016; Entezari Heravi et al., 2018). In the study of Khodabakhsh et al., the effect of *P. major* syrup on heavy menstrual bleeding was investigated and compared with mefenamic acid. The results suggested that this herbal drug may be as effective as mefenamic acid in reducing mensdural bleeding duration(Khodabakhsh et al., 2020). This observed effectiveness is in line with the findings of the current study that showed significant reduction of bleeding duration in herbal drug group. One of the differences between these two studies is the method of drug preparation. In our study, the aqueous extract of *P. major* seeds was used to prepare the syrup, but in the study of Khodabakhsh et al., the hydroalcoholic extract of the plant leaves was used.

Furthermore, the effect of several other PM based herbal medicine on AUB has been evaluated so far. The results of a study by Qaraaty et al. showed that syrup prepared from *Myrtus communis* L. was useful in reduceing the number of bleeding days in patients with abnormal uterine bleeding (Qaraaty et al., 2014). Similar to the current study, PBAC was used for evaluation of variables in the mentioned study.

Moreover, in Goshtasebi's study, which investigated the effect of *Punica granatum* L. flower (Persian Golnar) on heavy menstrual bleeding, PBAC was used and a significant decrease of its score as well as an increase in Hb were observed(Goshtasebi et al., 2015). However, it should be noted that intervention in the previously mentioned studies was performed for 3 menstrual cycles, while in the present study the effect of *P. major* syrup consumption was investigated in only one cycle which is one of the limitations of this study.

In spite of the limitations of the current study such as its short duration and loss of follow-up, the results were promising. *P. major* is known as a safe herbal remedy and due to its various beneficial effects, such as antioxidant, anti-inflammatory and anticancer properties, it may be a good supplement to common drugs in its reduced doses by diminishing side effects during its prolonged use for controlling bleeding in women.

Conclusion

In conclusion, the results of the current study showed that *P. major* is significantly effective in reducing the severity and duration of menstrual bleeding without any serious side effect. Therefore, this herbal medicine seems to be a good candidate for further studies to be considered as a complementary treatment of mild to moderate menorrhagia.

Author contribution

S.G. perfomed practical steps and collected data. Mohsen Naseri developed the main idea and designed the study. F.A. and S.F.J. assisted in writing the manuscript and editing. Y.K. drafted the manuscript. A.K. performed statistical analysis. S.H. supervised the clinical phase and assisted in designing the methodology. All authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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