



Comparison of effects of pomegranate peel and Mefenamic acid consumption on the treatment of Menorrhagia: A Triple-Blind Randomized Controlled Trial

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General Note

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ABSTRACT

Background: Menorrhagia is a type of menstrual disorder and a major health problem for many women. The consumption of pomegranate peel is a way to treat menorrhagia in the Traditional Persian Medicine (TPM). **Objective:** The present study aimed to compare the impact of two oral capsules of pomegranate peel extract and mefenamic acid on the treatment of Menorrhagia. **Method:** In the present triple-blind randomized controlled trial on 56 women aged 20-50 years with menorrhagia (intervention group: n=28, control group: n=28), the intervention group received 250 mg capsules of pomegranate peel extract; and the control group received 250 mg capsules of mefenamic acid in 7 days of menstruation three times a day for 3 months. Pictorial Blood Loss Assessment Chart (PBAC) scores and amount of Blood hemoglobin (Hb) and scores of Menorrhea Questionnaire (MQ) were utilized to evaluate the amount and duration of bleeding. **Results:** PBAC scores significantly decreased from 352.07 (33.26) to 166.85 (27.42) ($p < 0.001$) in the pomegranate group and from 303.18 (24.84) to 171.03 (27.3) in the mefenamic acid group, but the difference was not significant between two groups. Furthermore, a significant increase was seen in scores of MQ and amount of Hb in both groups after the treatment ($p < 0.05$). However, no significant difference was found between both groups. **Conclusion:** The pomegranate peel extract reduces bleeding, improves quality of life and increases the blood Hb in women with menorrhagia. Accordingly, it can be used in menorrhagia.

Keywords: Menorrhagia; Mefenamic acid; Pomegranate peel; Traditional Persian medicine.

1. INTRODUCTION

Menstrual disorder is a major health problem for many women (Duckitt, 2010 and Protheroe, 2004). Menorrhagia is the medical term for menstrual periods with abnormally heavy or prolonged bleeding (Fritz, 2011). This problem increases with age and reaches its peak before menopause (Duckitt, 2010).

Normal menstrual period is from 3 to 6 days with bleeding an average amount of 35 to 80 cc per period. If bleeding is more than 80 cc or more than 7 days in each period, it is called the menorrhagia (Marret et al., 2010). Menorrhagia is highly prevalent; and one third of all women experience high menstrual bleeding during their life (Hurskainen et al., 2007). The incidence of abnormal uterine bleeding is 11 to 13 percent of the general population increasing by age to 24 percent until the age of 36 to 40. (Marret et al., 2010) Various studies have reported the prevalence of this disease to be 3.5% to 22.9% in Iran (Etiologies of hyper menorrhea, 2013). Menorrhagia may be caused by systemic diseases or uterine structural disorders or iatrogenic causes. Systemic factors include endocrine disorders such as thyroid disorders and anovulation or coagulation diseases such as thrombocytopenia and Von-will brand disease (Protheroe, 2004). Topical factors include endometrial hyperplasia, adenomyosis, endometriosis, pelvic inflammatory diseases, benign and malignant tumors, uterine fibroids and pregnancy disorders. However, no pathological cause is found in many women with menorrhagia (Hurskainen et al., 2007). Abnormal uterine bleeding is an account for about two thirds of hysterectomy cases in women. Surgical complications increase the risk of morbidity and mortality and impose a high cost on treatment systems (Protheroe, 2004 and Marret et al., 2010).

Due to the high prevalence of Menorrhagia and its complications, including the women's sense of excessive weakness and fatigue and limitation of social and professional activities, anemia and a decrease in the quality of life, its timely treatment is significantly important (Karlsson et al., 2014). The applied treatments for menorrhagia include three categories of oral medications, intrauterine devices and surgical procedures. Oral medications are divided into hormonal and non-hormonal groups. Non-hormonal drugs include NSAIDs like Mefenamic acid and anti-fibrinolytic drugs like Tranexamic acid that have common gastrointestinal complications (Tansaz et al., 2016). Hormonal drugs cause many complications such as weight gain, painful breasts, headaches, thrombotic events, skin problems such as acne, increased speed of bone demineralization, diabetes and side effects of menopause such as vaginal dryness and menopausal flushing; hence, these drugs can be prescribed for short term (Tansaz et al., 2016). In different countries and cultures, complementary and traditional therapies are used to treat menorrhagia and menstrual bleeding. The Traditional Persian Medicine (TMP), which is an old rich complementary and alternative medicine school, has many therapeutic methods for controlling high uterine bleeding. In the TMP, much menstrual bleeding is defined as "Effrat-e-Tams" or "Kesrat-e-Tams" (Tansaz et al., 2016).

The pomegranate peel is one of the materia medica a method of treating menorrhagia in the traditional Iranian medicine (Goshtasebi et al., 2015). Pomegranate peel with the scientific name of pomegranatum (*Punica granatum L.*) peel has many therapeutic effects, including the treatment of menorrhagia (Ricci et al., 2006). Pomegranate is a valuable fruit, and its dried peel and

fruit juice is a strong antioxidant that is used in many diseases (Ricci et al., 2006). In books of the Iranian medicine, the pomegranate is known with the Arabic name "Roman", which its peel and the French word "Grenade" has energizing and astringent effects (Shafiei and Nojavan, 2018).

Pomegranate and its products, which had specified effects and were investigated in previous studies, were selected according to the recommendation of the World Health Organization (WHO) for the use of medicinal plants, which grow in the regional nature of each country (WHO, 2005), as well as parameters such as availability, reasonable price, low complications and long storage capability (Goshtasebi et al., 2015). The present study aimed to compare the effect of oral capsule of pomegranate peel extract and mefenamic acid on the treatment of Menorrhagia.

2. MATERIAL AND METHOD

Study design and participants

The present study was a triple-blind randomized controlled trial that was conducted with the aim to evaluate the effect of two oral capsules of pomegranate peel extract and mefenamic acid on the treatment of menorrhagia in Tehran (Iran) during September 2017 to October 2018. Participants of study included menorrhagia women referred to two centers, Mostafa Khomeini Hospital and traditional medicine center of Shahed University. In the study, participants were visited in person if they have the inclusion criteria. After providing necessary explanations by the presenter, informed written consent forms were obtained from patients. In the first visit, the volume of bleeding and bleeding duration were evaluated using the obtained score from the PBAC (Pictorial Blood Loss Assessment Chart) in four times, before entering the study, and after the first, second and third menstrual periods.

In the study, the PBAC and Hb scores were considered as the primary outcome and scores of menorrhagia quality (MQ) and bleeding duration were as the secondary outcome of study.

The participants' inclusion criteria of study were as follows: the willingness to participate in the study, aged 20 to 50 years, confirmation of menorrhagia (scores above 100 for the PBAC questionnaire), Hemoglobin higher than 10, non-pregnancy, non-lactation, normal endometrial thickness, and uterine size of less than 10 cm (using the ultrasound), normal CBC test, absence of adnexal or ovarian mass (rather than simple cysts of less than 2 cm), lack of sub- mucosal or intramural fibroids, lack of subserosal fibroids of larger than 4 cm, lack of systemic diseases, organic diseases, bleeding diseases, normal examination of gynecology and pap smear, lack of concurrent use of herbal medicines, hormonal and anticoagulant drugs and other specific diseases.

In the present study, the exclusion criteria included patient's unwillingness to continue to participate in the project, pregnancy during the study, the occurrence of any intolerance to the herbal product, the incidence of anemia (Hb of less than 10), the patient's need for other interventions, as well as surgery.

Sample size

The sample size was equal to 20 by consideration of $\alpha = 0.05$, $\beta = 0.1$ and $d = 1$ using $n = \frac{2 \left(\frac{Z_{\alpha} + Z_{\beta}}{2} \right)^2}{d^2}$ formula. According to the 50% sample loss, 10 samples were added to this number. Finally, 30 samples were considered in each group in the present study.

Data collection instruments

The Pictorial Blood Loss Assessment Chart (PBAC) is a visual questionnaire to measure the volume of bleeding. In this questionnaire, horizontal rows indicate number of menstrual days and vertical rows represent blood-stained pads in mild, moderate and severe grades. In this questionnaire with 98% sensitivity and 97% specificity, when PBAC score is equivalent to 100 or more, the menstrual bleeding volume is considered to be 80 cc or more (El-Nashar et al., 2015).

Hb level of blood was measured at the beginning and end of study for each patient. The questionnaire for assessing menorrhagia quality of life (Menorrhagia Questionnaire =MQ) included 13 specific questions in the field of women's menstrual bleeding at the beginning and end of study (Ruta et al., 1995). The bleeding duration was also measured due to the horizontal row of the PBAC questionnaire at the beginning and end of study.

Ethics requirements

The present study was approved by the Medical Ethics Committee of Shahed University on 30/10/2017 with a code of IR.Shahed.REC.1396.60, and also registered and confirmed with a code of IRCT2017090936103N1 at the Iranian Registry of Clinical Trials (IRCT) on 18/11/2017.

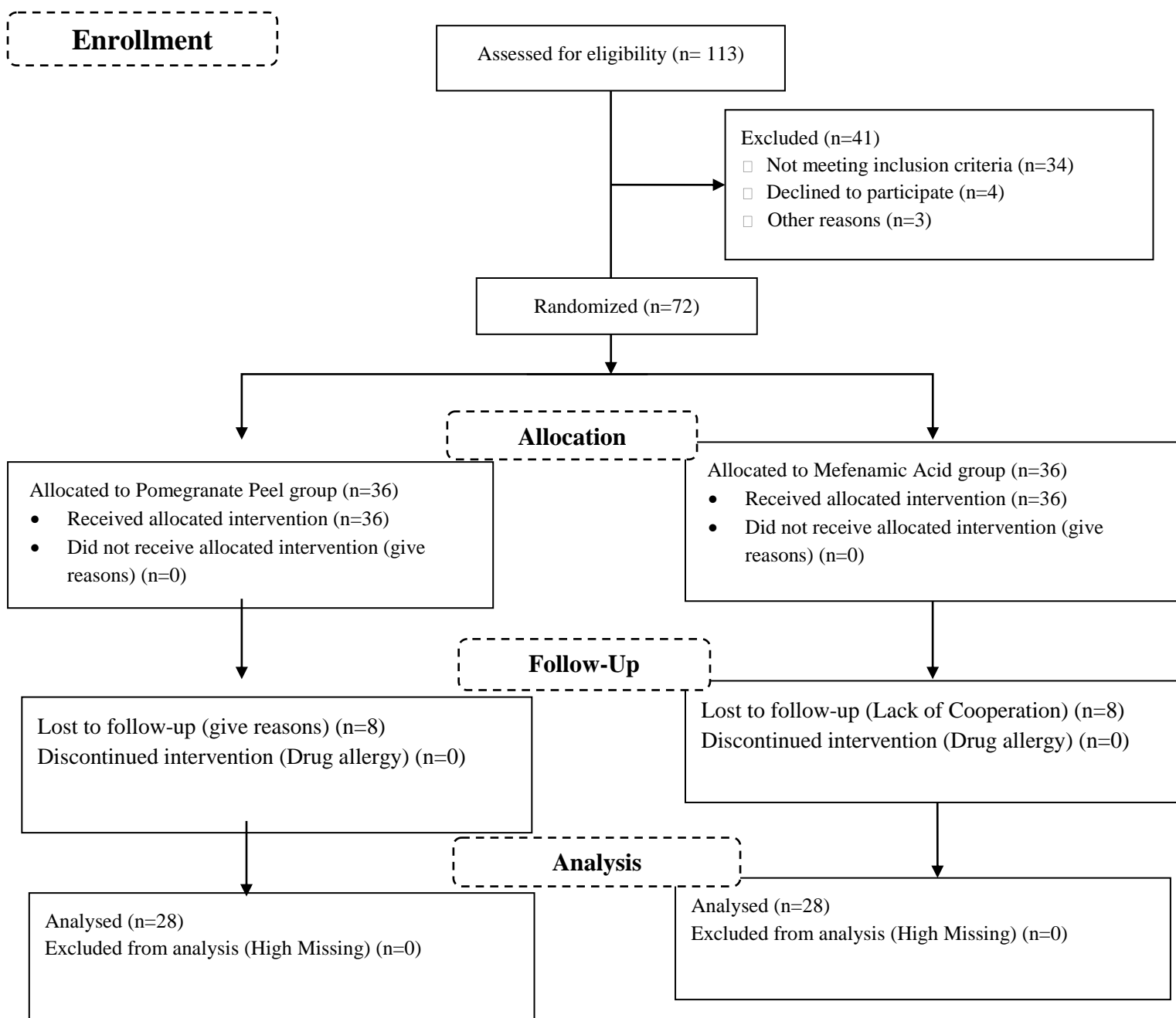


Figure 1: Follow diagram of study

Preparation of pomegranate and mefenamic acid capsules

For the medicine preparation, as the sour pomegranate peel has a more astringent feature than other types, 30 kilograms of red sour pomegranate were prepared from the Iranian gardens (Ramsar city) and extracted from in pharmaceutical laboratory of Shahed University. The seeds were separated from peel and washed; and 5.2 kg of fresh peel was dried far from light and dust at 30 °C. For the preparation of aqueous extract, 1 liter of boiled water was poured over 500 g of dry peel, and then boiled at 50-60 °C for an hour, and filtered. The resulting extract was placed in the Bain-marie for condensation at 40 °C, and then the dry extract was grinded. The dry pomegranate peel extract was poured into 250 mg capsules similar to mefenamic acid after standardization based on phenol and Gallic acid (according to the standard of Gallic acid, the total phenol content per gram of extract is 358.83 ± 29 mg of Gallic acid). In this product, there is 250 mg of dry pomegranate peel extract. In the present study, drugs were prepared and coded in 21 mefenamic acid capsules and 21-capsule packs of pomegranate peel with the same design, so that the researchers did not know about type of consumed drug and gave them to researchers

Intervention study

After selecting patients, they were randomly assigned (random block assignment) to two 28-participant groups including the intervention group (pomegranate peel capsule), and control group (Mefenamic acid capsule). The target drugs were produced and encoded without mentioning name of drug and in same shapes by the company and participants were asked to use them by the same instructions. In the study, two groups were asked to take one capsule three times a day after meal for a week after the menstruation start. This process was repeated for 3 menstrual periods (7 days per month). Patients were also asked to note any side effects of drug and say them to investigators.

Statistical analysis

The present study implemented descriptive statistics (mean, standard deviation, correlation, frequency and proportion) and inferential statistics (Chi-square test, Independent T test, Mann-Whitney test, Repeated ANOVA, and Friedman test) proportional to normal or abnormal response variable using the Kolomogrov-Smirnov (K-S) test. In the study, SPSS21 was used and a level of 5% was considered as the significant level.

3. RESULTS

In the present study, 113 participants were included in the study. Among them, 41 were excluded due to lack of inclusion criteria and 72 ones were assigned to two 36-participant groups. In the study, 8 participants from the pomegranate peel group, and 8 participants from the Mefenamic acid group gave up to continue the project for various reasons, and eventually, 28 participants in each group continued the project until the end, and finally 56 participants were analyzed (Fig. 1). There was no significant difference between two groups in terms of age, education, occupation and marriage. In other words, both groups were homogeneous in terms of demographic characteristics. (Table 1) The mean of menstrual bleeding (PBAC) significantly decreased after the study compared to before the study ($p < 0.001$) in both groups (Table 2). There was also a significant improvement in MQ and Hb variables as well as duration of bleeding in the pre and post cycles of study (Table 3); however, there was no significant difference in results of both groups (Tables 2 and 3).

Table 1 The frequency distribution of age, education, occupation and marriage according to the two groups

		Pomegranate Peel (n=28)		Mefenamic Acid (n=28)		P-value
		N	%	N	%	
		Age	Lower year 25	6	21.4%	
	26 to 35 year	11	39.3%	10	35.7%	
	36 to 40 year	6	21.4%	7	25.0%	
	Upper year 40	5	17.9%	6	21.4%	
Education	Lower Diploma	7	25.0%	6	21.4%	0.198
	Diploma	8	28.6%	13	46.4%	
	Associate Degree	4	14.3%	6	21.4%	
	License or upper	9	32.1%	3	10.7%	
Occupation	Housewife	26	92.9%	27	96.4%	0.999
	Other	2	7.1%	1	3.6%	
Marriage	Married	22	78.6%	23	82.1%	0.999
	Single	6	21.4%	5	17.9%	

The p-value calculated using chi square test.

4. DISCUSSION

In the present study, which was the first to compare the effects of pomegranate peel and mefenamic acid on the treatment of Menorrhagia, the results indicated a significant reduction in women bleeding in each group during three menstrual cycles compared to before the study, but the difference was not significant in the comparison of mefenamic acid and pomegranate peel groups before and after the study, meaning that both drugs were equally effective in the treatment and control of abnormal uterine bleeding. In this regard, results of the present study were consistent with a research by Memarzadeh et al. on the use of

pomegranate flower extract for women's abnormal uterine bleeding (Memarzadeh et al.,). Gashtasebi et al. (2015) also compared the effect of anti-hemorrhagic pomegranate flower with Tranexamic acid capsule on abnormal menstrual bleeding with endometrial origin. Both pomegranate flower and Tranexamic acid products reduced amount of bleeding based on the PBAC score and improved the quality of life (Goshtasebi et al., 2015).

Table 2 The mean of PBAC score during time according to the two groups

	Group				P-value
	Pomegranate Peel (n=28)		Mefenamic Acid (n=28)		
	Mean	SD	Mean	SD	
Before intervention	352.071	33.2552	303.179	24.8406	0.239
First menstruation	204.464	23.1539	197.346	22.6318	0.826
Second menstruation	195.954	29.4970	182.318	25.2487	0.609
Third menstruation	166.848	27.4166	171.033	27.3051	0.474
	P-value	<0.001	P-value	<0.001	

SE: Standard Error, the p-value calculated based on repeated measurement ANOVA or Friedman test.

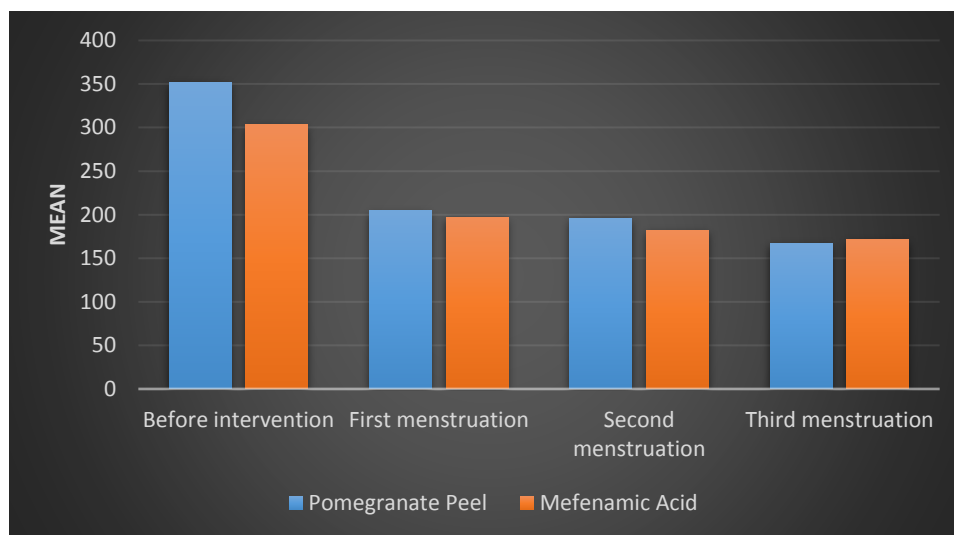


Figure 2 The Mean Pictorial Blood Loss Assessment Chart

Table 3 The mean of MQ, HB and duration before and after treatment according to the two groups

		Before		After		Diff	P-value	P-value
		Mean	SD	Mean	SD			
MQ	Pomegranate Peel	54.02	16.31	41.50	12.64	-12.52	0.002	0.835
	Mefenamic Acid	52.67	12.67	42.14	18.80	-10.53	0.014	
		P-value	0.730	P-value	0.903			
HB	Pomegranate Peel	12.15	1.48	12.70	1.25	0.55	<0.001	0.359
	Mefenamic Acid	11.92	1.13	12.37	1.12	0.45	0.016	
		P-value	0.515	P-value	0.339			
Duration	Pomegranate Peel	8.00	1.54	7.68	2.08	-0.32	0.475	0.860
	Mefenamic Acid	7.67	1.57	6.79	1.64	-0.88	0.020	
		P-value	0.435	P-value	0.124			

SD: standard division

The p-value calculated based on independent t-test, paired sample t-test, Mann-Whitney U or Wilcoxon rank test.

Furthermore, some studies reported effects of extracts of herbs such as *Portulaca* (Shobeiri et al., 2009), *Achillea Wilhelmsi*, Myrtel fruit (Qaraaty et al., 2014) on Menorrhagia. A systematic review study investigated effects of three plants, Pomegranate flower, Myrtel fruit and Ginger, on abnormal uterine bleeding (HMB, IHMB) (Javan et al., 2016). In a study by Ricci et al. on the antioxidant effect of pomegranate peel, they found that pomegranate and its components had a high therapeutic value. Furthermore, the pomegranate peel as an astringent was used to treat menorrhagia and diarrhea (Ricci et al., 2006). It is also noted that the pomegranate peel, which is not usually used and is considered as a useless material, has the best antioxidant activity and fully active aqueous extracts in all experiments; hence, this extract can be used as a rich source of antioxidants in the human diet (Ricci et al., 2006).

Previous studies found that the most health benefits of pomegranate peel belonged to tannins like ellagitannins, ellagic acid, punicalagins, flavonoids and phenolic compounds (Barathikannan et al., 2016 and Emami et al., 2010). The components in pomegranate fruit and peel are potentially capable of preventing or treating cancer and diseases such as bleeding of different human body tracts (Ricci et al., 2006 and N Syed et al., 2013).

In TPM literature, sure pomegranate has the cold and dry temperament, so is astringent (Emami et al., 2010) and astringent drugs can strengthen organs and treat bleeding, including menorrhagia, gastrointestinal bleeding and oral hemorrhage (Avicenna, 1999). According to studies, the astringent feature is due to the presence of tannin compounds and it is from 25 to 28 percent in the pomegranate peel (Healthcare, 2007). No serious side effects were observed during the study except for a person (4%) with mild gastric irritation, and it was 4 individuals (14%) in the mefenamic acid group.

Side effects were less common in the intervention group; and the major side effects were seen in two groups of gastrointestinal complications, thereby confirming the higher safety of pomegranate peel. However, studies on pomegranate peel indicated that it had pharmacological compounds similar to pomegranate flower, *Portulaca* and Myrtel fruit, but it was more available and affordable in different regions and was usually considered as a useless material (Ricci et al., 2006 and Barathikannan et al., 2016 and Healthcare, 2007).

On the other hand, due to the absence of serious complications of pomegranate peel in the present research and other studies (Emami et al., 2010 and Bassiri Jahromi et al., 2015) and the presence of multiple complications in the use of hormonal drugs and according to studies such as weight gain, painful breasts, headache, thrombotic events, skin problems like acne, increased bone demineralization speed, diabetes, and menopausal complications such as vaginal dryness and flushing, and common gastrointestinal complications with the consumption of non-hormonal drugs such as mefenamic acid (Karlsson et al., 2014), Pomegranate peel seems to be a safe and effective drug for the treatment of menorrhagia with its phenolic and tannin compounds and its astringent properties (Emami et al., 2010 and Bassiri Jahromi et al., 2015).

Limitation

Conflicting variables such as psychological state, diet, and the rate of exercise of patients may affect uterus functions and the results of the study. Small sample sizes, a short period of follow-up were the limitations of the study.

Suggestion

It is suggested to perform further studies with larger sample sizes in longer periods. It is also possible to study the effect of pomegranate peel extract on Structural Causes of menorrhagia. It is also possible to study the different doses of pomegranate peel extract to find appropriate doses.

5. CONCLUSION

Since no complication has been reported for different therapeutic doses of pomegranate peel extract, and its use is simple and effective in reducing bleeding in women with menorrhagia. As a result, "pomegranate peels extract" can be introduced as a good first-line choice for the treatment of menorrhagia.

Authors

All research has been done by the authors.

Conflict of interest

The authors declared no conflict of interest.

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