Evaluation of efficacy of *Punica granatum L.* (Persian gulnar) on uterine leiomyoma related menorrhagia: a pilot study

Hajar Memarzadeh¹, Tahereh Eftekhar², Mojgan Tansaz¹, Fataneh Hashem Dabaghian³, Mohammad Kamalinejad¹, Tahereh Foroughifar³, Shamim Sahranavard⁴, Ghazaleh Heydarirad¹

¹Department of Traditional Medicine, School of Traditional Medicine, Traditional Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Traditional medicine, Tehran, Iran

²Department of Gynecology, School of medicine, Tehran University of Medical Sciences, Tehran, Iran

³Research Institute for Islamic and Complementary Medicine, Iran University of Medical Sciences

⁴Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁵Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

**Key words:** Menorrhagia, Leiomyoma, Iranian traditional medicine, *Punica granatum* L., Persian gulnar.

http://dx.doi.org/10.12692/ijb/6.9.18-25 Article published on May 08, 2015

**Abstract**

Uterine leiomyoma is a common problem for women and menorrhagia is its main symptom. In Iranian Traditional Medicine, *Gulnar* (abortive flower of *Punica granatum* Linn) has long been applied for its hemostatic effects. Many current medical treatments are associated with adverse health conditions and side effects so this study was done to assess the efficacy of Persian *Gulnar* on controlling symptoms of uterine leiomyoma related to menorrhagia. This was a before/after style pilot study conducted on 19 women aged 18-50 years and suffering from uterine leiomyoma related menorrhagia. The *Gulnar* syrup administration was repeated for 3 consecutive menstrual periods. Records were taken for menstrual duration and menstrual-blood loss and evaluations were made according to the Pictorial Blood loss Assessment Chart at the end of each menstrual period. Quality of life was assessed using the Menorrhagia Questionnaire. Also abdominal ultra-sonography, before intervention and after, at the end of the study, was done to evaluate leiomyoma size. Pictorial Blood Loss Assessment scores and means of numbers of bleeding days significantly declined after 3 months of treatment with the syrup. Results also showed significant changes of quality of life scores in the intervention group after 3 months compared to the baseline. The average uterine fibroid size decreased by 16.1% in the 3 months of the trial. In conclusion, pomegranate syrup seems to be effective in reduction of uterine size and leiomyoma bleeding and improving the quality of life.

*Corresponding Author: Mojgan Tansaz  tansaz_mojgan@yahoo.com*
Introduction

Half of all women aged 35–49 years have uterine leiomyomata (Fiscella et al., 2006) and the condition usually regresses after menopause (Fonseca-Moutinho et al., 2013).

The majority of women with uterine fibroids are asymptomatic but fibroids can cause problems such as abnormal uterine bleeding, urinary incontinence or retention, a sense of pelvic pressure or pain. The most common complaints are abnormal uterine bleeding, particularly heavy and prolonged bleeding (Khán et al., 2014). Menorrhagia associated with leiomyoma is an important medical problem for many women, and as such constitutes a public health concern (Stewart and Nowak, 1996). The problem may induce severe anemia (Appar et al., 2007) and in some cases menorrhagia can lead to a hysterectomy (Gorgen et al., 2009).

Leiomyoma management often involves surgical or radiologic intervention and there few medical therapies are practiced (Donnez, 2011). Medical treatment is only considered for temporary application because long-term treatment has substantial risks, however there are new medicinal treatments for which there is not yet enough evidence to determine the long term benefits and risks. Presently, GnRHa is the only FDA approved, short-term therapy administered to decrease fibroid size and improve symptoms. FDA has approved an intrauterine device (IUD), LNGIUS (Mirena), for additional use to treat heavy menstrual bleeding only in IUD users. Moreover, Gn-RHAs treatment has side effects such as hypoestrogenism; menopausal symptoms of hot flashes and vaginitis and a decrease in bone mineral density (Islam et al., 2013). Tranexamic acid, combined oral contraceptive (COC), and progestin are administered to reduce menstrual blood loss in women with uterine fibroids (Khan et al., 2014); but these treatments each have their own specific side effects as well as more general problems such as contributing to liver disease, obesity, thromboembolic diseases and other hormonal complications (Lo and Youde, 1996).


One report on evidence-based approaches published by the Agency for Healthcare Research and Quality noted ‘a notable lack of trial data indicating the effectiveness of medical remedies’ for treatment of uterine leiomyomata (Fiscella et al., 2006). Although Qaraaty et al., in a pilot study revealed that Myrtle (Myrtus communis L.) syrup was a potential treatment for abnormal uterine bleeding (Qaraaty et al., 2014). That study was based on more general uterine bleeding and was not specific to leiomyoma induced bleeding (Qaraaty et al., 2014). Another study reported that leiomyomata caused heavy menstrual bleeding and that even small leiomyomata were associated with an increased risk of heavy menstrual bleeding (Wegienka et al., 2003). Recently, there has been no effective, long-term medicinal therapy for this common and debilitating condition. So, research for a suitable treatment for leiomyoma is essential.

Use of herbal medicines is becoming progressively more popular worldwide (Steenkamp, 2003). In Iranian Traditional Medicine (ITM), most treatment is focused on medicinal herbs, although the use of medicinal herbs is not just the therapeutic method in traditional medicine, it can also be the basis of a medical remedy (Dabaghian et al., 2012; Ameri et al., 2014). Practitioners of ITM such as Ibn Sina (Avicenna, 980–1037 A.D) believed that normal menstruation was a sign of a well woman (Qaraaty et al., 2014); so, ancient Persian scholars advocated lifestyle modification and herbal medicines or other natural remedies to manage menstrual problems. According to the literature of ITM that describes menorrhagia as ‘Efrate-Tams’, there were various remedies applied for astringent and hemostatic activities, of which ‘Gulnar’ is mentioned (Ibn-e-sina, 2005). **Gulnar** is a Persian word that describes the
flower of *Punica granatum* Linn. (*Anar*) (Nazamuddin *et al*., 2013) that will not develop to form fruit. *Gulnar* is a bell-shaped flower, red in color and a native species of Iran. In ITM, *Gulnar* has long been administered to treat internal bleeding, dysentery, hematemesis, bleeding gum, epistaxis (Nazamuddin *et al*., 2013) and especially for menorrhagia (Ibn-e-sina, 2005). However, to our knowledge, no trial has yet examined the effect of *Gulnar* on menorrhagia associated with myoma. The main aim of this current study was to examine the effects of *Gulnar* syrup on reducing uterine leiomyoma related menorrhagia as a pilot, before/after clinical trial.

**Materials and methods**

**Preparation of syrup**

Dried *Gulnar* were collected from Darab city of Fars province of Iran and identified by Mohammad Kamalinejad, they were kept at herbarium of Shahid Beheshti University of Medical Sciences, under voucher number 8016.

Traditional preparation was based on Makhzan-ol-advieh (Storehouse of Medicaments, written by Aghili Khorasani in 1771 CE) ITM book about herbs, spices and medical vocabulary (Moddaberi, 2002). 100 gr of samples of *Gulnar* flower were macerated for 24 hours with 500cc of distilled water, filtered and boiled for 15 min. 100 g sorbitol was added to the extract. Syrup was prepared in bottles of 120 ml. *Gulnar* syrup was standardized based on total phenols (Folin-Ciocalteau method) and gallic acid content. Each 5 ml batch of syrup contained 519.231 mg total phenols as gallic acid equivalents.

The participants were each given 5 ml of prepared syrup three times a day for seven days starting from the onset of heavy bleeding. This treatment was repeated for three consecutive menstruation cycles.

**Study design**

This study was done as a before/after, phase 3 clinical trial to assess the efficacy and safety of *Gulnar* syrup, for treatment of leiomyoma related menorrhagia. All participants signed a written informed consent before inclusion in the study. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (approval number: 1-1-163-1173, 143). The trial was registered in the Persian Registry of Clinical Trials (IRCT) under the number IRCT2013120715703N1.

**Study Population**

Participants were premenopausal women between the ages of 18 and 50 years with a history of abnormal menstrual bleeding who came for visiting and treatments to clinic of School of Traditional Medicine, Shahid Beheshti University, and ultrasound evidence of uterine leiomyoma (sub mucosal leiomyoma, intramural leiomyoma, subserosal leiomyoma). Exclusion Criteria was 1) Ultrasound evidence of hyperplasia of the endometrium 2) Indication of uterine surgery (except Caesarean section or cervical conization). 3) Patients in receipt of progesterone, acetyl salicylic acid anticoagulant. 4) History of allergy to Persian *Gulnar*. 5) Known severe coagulation disorder. 6) Patients receiving Anti-fibrinolytic. 7) Hemoglobin below 9.5. 8) Patients with a positive pregnancy test. 9) Known hemoglobinopathies.

**Assessment of Uterine Bleeding**

Abdominal ultra-sonography, before intervention and after, at the end of the study, was done to evaluate leiomyoma size and to rule out any other pathologic disorder and to determine endometrial thickness.

Uterine bleeding was evaluated with the Pictorial Blood-loss Assessment Chart (PBAC) that objectively estimated menstrual-blood loss. The range of the PBAC scale is from 0 to over 500 (with no definite upper limit), and higher scores indicate greater severity of bleeding. Patients were requested to complete a PBAC questionnaire before the intervention and for each of the three menstrual cycles during the treatment. The number and degree of soiling of used sanitary pads was calculated each day. Also taken into account was the number and size of any passed clots (Cho *et al*., 2008).
A PBAC score of more than 100 (in the first 8 days of menstruation), is distinct for menorrhagia, which is the equivalent of more than 80 ml of blood loss (Donnez et al., 2012b). The PBAC chart had sensitivity of 80% and specificity of 88% in identifying menorrhagia (as distinct in the alkaline hematin method that is the most valid technique) (Wyatt et al., 2001). Quality of life was evaluated with the menorrhagia questionnaire (MQ-Iranian Version) (Qaraaty et al., 2014).

**Treatment**

Patients received 5 ml of Gulnar syrup, 3 times a day for seven days starting from the onset of heavy bleeding. Follow-up visits were organized, without additional treatment, for weeks 5, 9, and 13.

55 patients were interviewed from which, 24 patients were enrolled, 19 participants completed the study. 5 persons discontinued the study because of personal reasons. All participants were free to withdraw at any time during the progression of study (Figure 1).

Participants were not allowed to use any hormonal therapy, mefenamic acid, tranexamic acid, herbal medicine and medicinal herb during the study. Consumption of acetaminophen, oral iron therapy and analgesic opioids was allowed during the study.

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 17. Mean and standard deviation (SD) were presented for quantitative variables with normal distribution. Median and interquartile range (IQR) were presented for variables with non-normal distribution. Number and percent of frequency were presented for qualitative variables. Comparison of variables before and after treatment was done using Wilcoxon Signed Rank Test, repeated measures ANOVA and paired t-test.

**Results**

Baseline characteristics of the subjects are described on Table 1. The mean age of patients was 38.90 ± 6.82 years old, 19 patients were included in the analysis. The findings determined both before and after consumption of the syrup are shown in Table 2. Results showed that PBAC scores dropped significantly after consumption of the syrup (Table 2). The average MQ score showed an improvement of about 30% (P<0.001). The volume of menstrual blood loss accessed by PBAC scores also was reduced noticeably after taking the syrup. The average of the PBAC scores was decreased 36.9% in 3 months (p=0.001). The number of bleeding days in each menstrual cycle decreased from 9.84 to 7.42 in 3 months and the average of number of bleeding days decreased by 36.9% in 3 months (P<0.001). MQ scores decreased from 63.68±15.67 to 44.28±15.07 in 3 months. The average uterine fibroid size decreased by 16.1% in 3 months.

**Table 1.** Baseline characteristics of study subjects Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter</th>
<th>Duration of Abnormality (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>BMI</td>
<td>MQ score</td>
</tr>
<tr>
<td>38.90±6.82</td>
<td>26.41±3.97</td>
<td>63.68±15.67</td>
</tr>
</tbody>
</table>

The results of repeated measures ANOVA showed the statistically significant changes in PBAC score and menstrual duration after 3 months of intervention (p<0.001). Results of the pairwise comparison with Bonferroni adjustment for multiple comparisons are presented in table 2.

**Discussion**

In this study the effect of Gulnar on bleeding, uterine volume and the quality of life among women with severe uterine bleeding was evaluated. Findings from this current study show that treatment with Gulnar syrup for seven days starting from the onset of heavy bleeding substantially improved quality of life related to leiomyoma bleeding and reduced numbers of bleeding days among women with symptomatic
leiomyomata. The most marked improvement in symptoms and quality of life occurred during the first month of treatment. These results were similar to those reported in Fiscella et al that assessed quality of life and leiomyoma size in women with symptomatic uterine leiomyomata. In the Fiscella study, patients were given mifepristone (Fiscella et al., 2006). The results of a study by Gary et al demonstrated that infection and hemorrhage were mifepristone-related adverse events (Gary and Harrison, 2006). The study reported that these side effects appeared to be caused by long-term use of mifepristone. Our study identified a significant decline in blood loss at the beginning of the study compared to that recorded at the end of third month (a decrease from 265.78 to 162.36, p<0.001, Table 2), but there was no statistical difference between the monthly average menstrual blood loss during the study period.

Table 2. Changes of PBAC score, menstrual duration and MQ score during the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Title</th>
<th>Mean(±SD)</th>
<th>Mean difference (±SE) Compared with baseline</th>
<th>95% CI*</th>
<th>P values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBAC score</td>
<td>Baseline</td>
<td>265.78 ± 144.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 1st cycle</td>
<td>157.21 ± 84.76</td>
<td>108.57 ± 18.31</td>
<td>54.33-162.82</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After 2nd cycle</td>
<td>165.21 ± 107.28</td>
<td>100.57 ± 18.97</td>
<td>44.37-156.78</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After 3rd cycle</td>
<td>162.36 ± 99.98</td>
<td>103.42 ± 21.59</td>
<td>39.44-167.40</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Menstrual duration (day)</td>
<td>Baseline</td>
<td>9.84 ± 1.86</td>
<td></td>
<td>1.94 ± 0.37</td>
<td>0.85-3.04</td>
</tr>
<tr>
<td></td>
<td>After 1st cycle</td>
<td>7.89 ± 1.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2nd cycle</td>
<td>7.57 ± 1.70</td>
<td>2.26 ± 0.45</td>
<td>0.92-3.6</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After 3rd cycle</td>
<td>7.42 ± 1.77</td>
<td>2.42 ± 0.47</td>
<td>1.00-3.84</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>MQ score</td>
<td>Baseline</td>
<td>63.68 ± 15.67</td>
<td></td>
<td>19.40± 2.55</td>
<td>14.05-24.75</td>
</tr>
<tr>
<td></td>
<td>After 3rd cycle</td>
<td>44.28 ± 15.07</td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Uterine volume (mL)</td>
<td>Baseline</td>
<td>756933.7± 649377.2</td>
<td></td>
<td>213940.9 ± 32330.1</td>
<td>P=0.013</td>
</tr>
<tr>
<td></td>
<td>After 3rd cycle</td>
<td>542992.8 ± 363929.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One-way analysis of variance (ANOVA) was used to compare three rounds of treatment before and after each treatment. There was statistically significant difference between three rounds of treatment with Gulnar syrup

**P values <0.05 are significant.

These results are in accordance with those cited in other studies such as Rosshdy and Donnez (Donnez et al., 2012a; Rosshdy et al., 2013); also, the results of this study showed a significant reduction in the number of bleeding days (approximately ten days’ bleeding was reduced to seven days); however in the Rosshdy study there was no mention of reduced number of bleeding days; although results of the Rosshdy study demonstrated that treatment with green tea extract had a significant effect on increasing mean hemoglobin levels from 11.7 to 12.4 g/dL. In this study hemoglobin levels were not assessed at the end of the study period so this should be taken into account in future studies. Studies of Rosshdy and Donnez reported a significant reduction in total volume of uterine fibroids and significantly reduced the severity of fibroid-specific symptoms, however results of this study showed a significant reduction in uterine size but volume of uterine fibroids and severity of fibroid-specific symptoms were not determined; these subjects should therefore be evaluated in future studies. Results of this study also showed a significant improvement in quality of life (30.8%), similar to results of the Rosshdy and Fiscella studies (Fiscella et al., 2006; Rosshdy et al., 2013). Although a medline research revealed that no clinical trials have been done to date that evaluate the effect of pomegranate on leiomyoma bleeding, but according to previous studies, pomegranate juice is prepared by pressing the whole fruit and as such includes a high content of polyphenols, among that ellagitannins (ET) predominate in. pomegranate juice and its refined ETs inhibit cancer cell proliferation and inflammatory cell signaling (Adams et al., 2010). Tannins have an astringent property and can cause contraction of capillary endothelium that leads to decreased exudation and menorrhea loss (Fathima and Sultana, 2012).
Angiogenesis is a vital process for the development of new blood vessels, and is an important active chemical element but it also provides nutrition for tumor growth (Rahimi et al., 2012). It is also one of the causes of hemorrhage in patients with myoma (Livingstone and Fraser, 2002).

As studies have shown, control of inflammation by pomegranate involves inhibition of both COX and LOX enzymes and a decline in prostaglandin release from cells (Lansky and Newman, 2007) that acts similarly to the mechanism of non-steroidal, anti-inflammatory drugs (NSAIDs). Also prostaglandin synthetize inhibitors that can alleviate both heavy uterine bleeding and dysmenorrhea by decreasing production of endometrial prostaglandins (Grimes et al., 2006).

It seems Gulnar effects a reduction of bleeding possibly by the additive effect of the above-mentioned mechanisms. In this study, results showed that none of the participants reported any serious adverse events throughout the duration of the study. However, two cases of headache, two cases of increased appetite and one case of hives were reported. No incidence of endometrial hyperplasia or endometrial pathology was detected during the study and participants reported that they tolerated the medication well.

One limitation of this study was that the duration of assessment was restricted to 13 weeks. More data are needed to determine benefits and identify any risks of long-term treatment with Gulnar. In the present study the sample size was small; nonetheless, the study mentioned that treatment was associated with significant improvement in leiomyoma-specific quality of life, reduction in leiomyoma bleeding, number of bleeding days, and uterine size. Therefore, further study with a much larger sample is needed to determine whether pomegranate and its components have any effect on reduction in uterine volume or size. Also, hemoglobin levels should be evaluated before and after the study to determine the effect of pomegranate to improvement mean hemoglobin levels. Moreover, it is better to do some additional laboratory tests to assess liver and renal function over the treatment period to determine whether any adverse effects emerge.

**Conclusion**

Pomegranate syrup (at a dose of 5 ml, 3 times daily) seems to be effective in reduction of uterine size and leiomyoma bleeding in women who suffer of leiomyoma, and improving the quality of life in these patients.

**Acknowledgment**

This article is drawn from the PhD degree thesis titled “Evaluation of efficacy of *Punica granatum* L (Persian Gulnar) on uterine leiomyoma related menorrhagia” from the School of Traditional Medicine, Shahid Beheshti University of Medical Sciences. The authors gratefully acknowledge the help of the following individuals: Dr Seyedeh Atiyeh Naeimi, Dr Mohsen Rezaie Moghadam.

**References**

Adams LS, Zhang Y, Seeram NP, Heber D,
http://dx.doi.org/10.1158/1940-6207.CAPR-08-0225

http://dx.doi.org/10.3109/13880209.2014.928330

http://dx.doi.org/10.1097/01.AFP.0000243776.23317.bf

http://dx.doi.org/10.1016/j.ajog.2007.10.798

http://dx.doi.org/10.5897/JDE12.004


http://dx.doi.org/10.1016/j.eujim.2012.01.007

http://dx.doi.org/10.1097/01.AOG.0000243776.23391.7b

http://dx.doi.org/10.2147/IJWH.S50786


http://dx.doi.org/10.1007/s00404-008-0834-x

http://dx.doi.org/10.1002/14651858.CD006034.pub2

442-443.


