

## Anti-hemorrhagic activity of *Punica granatum* L. flower (Persian Golnar) against heavy menstrual bleeding of endometrial origin: a double-blind, randomized controlled trial

Azita Goshtasebi<sup>1</sup>, Ziba Mazari<sup>2</sup>, Samira Behboudi Gandevani<sup>3</sup>, Mohsen Naseri<sup>4</sup>

Received: 21 April 2014

Accepted: 31 December 2014

Published: 18 April 2015

### Abstract

**Background:** Heavy menstrual bleeding of endometrial origin (HMB) is a major healthcare problem in premenopausal women and affects several aspects of women's health and quality of life (QoL). The aim of this study was to compare the efficacy of Persian Golnar (PG) and tranexamic acid (TA) on heavy menstrual bleeding of endometrial origin (HMB) and patients' QoL.

**Methods:** A double-blind randomized controlled trial with parallel design and block randomization technique was conducted. A total of 94 women with HMB were randomly assigned to take either PG or TA for 5 days from day 1 of menses for three consecutive menstrual cycles. Blood loss was measured by the pictorial blood loss assessment chart (PBAC). Hematological assessments were made before the intervention and after treatment. QoL as a secondary outcome was evaluated using SF-36 and the menorrhagia questionnaire (MQ). Statistical analysis was performed using t-test, paired t-test,  $\chi^2$  test, Mann-Whitney test, and Wilcoxon signed-rank test.

**Results:** In each group, 38 women (80.8%) completed the 3-month follow-up. Both PG and TA reduced blood loss. PBAC mean (SD) score was reduced from 304.92 (176.17) and 304.44 (192.72) to 164.60 (100.24) and 143.13 (96.07) after the third treatment cycle, respectively ( $p < 0.001$ ). Furthermore, mean hemoglobin, Hb (SD) concentrations in the PG and TA groups increased significantly from 12.06 (0.86) and 11.53 (0.86) mg/dl to 13.02 (0.82) and 12.72 (0.88) mg/dl ( $p < 0.001$ ). QoL was significantly improved in both groups ( $p < 0.001$ ). However, there were no significant differences between the groups after the intervention.

**Conclusion:** The results of the present study demonstrate the efficacy of PG in treating HMB in terms of clinical and QoL indicators.

**Keywords:** Menstrual disturbance, Bleeding, Iran, *Punica granatum*, Tranexamic acid.

**Cite this article as:** Goshtasebi A, Mazari Z, Behboudi Gandevani S, Naseri M. Anti-hemorrhagic activity of *Punica granatum* L. flower (Persian Golnar) against heavy menstrual bleeding of endometrial origin: a double-blind, randomized controlled trial. *Med J Islam Repub Iran* 2015 (18 April). Vol. 29:199.

### Introduction

Heavy menstrual bleeding of endometrial origin (HMB) is a common clinical problem among premenopausal women and is clinically defined as regular menstrual cycles lasting more than 7 days and/or blood loss greater than or equal to 80 ml in the absence of recognizable pelvic pathology

or general bleeding disorders (1, 2). Several drug classes are recommended for the treatment of HMB; however, most of them are not accepted by patients because of either failure in controlling the bleeding or side-effects (3).

*Punica granatum* Linn. (PG), commonly known as pomegranate, is a small tree from

<sup>1</sup>. (Corresponding author) MD, MCH specialist, Family Health Research Group, Health metrics Research center, Iranian Institute for Health Sciences Research, ACECR, Tehran, Iran. [agoshtasebi@ihsr.ac.ir](mailto:agoshtasebi@ihsr.ac.ir) & [azita\\_goshtasbi@yahoo.com](mailto:azita_goshtasbi@yahoo.com)

<sup>2</sup>. Msc, Family Health Research Group, Health metrics Research center, Iranian Institute for Health Sciences Research, ACECR, Tehran, Iran. [zibamazarij@yahoo.com](mailto:zibamazarij@yahoo.com)

<sup>3</sup>. PhD Candidate in Reproductive Health, Reproductive Endocrinology Research centre, Research Institute for Endocrine Science, Shaheed Beheshti University of Medical Science, Tehran, Iran. [s.behboudi@hotmail.com](mailto:s.behboudi@hotmail.com)

<sup>4</sup>. MD, PhD, Shahed Traditional Iranian Medicine Research Center, Tehran, Iran. [naseri@shahed.ac.ir](mailto:naseri@shahed.ac.ir)

the Punicaceae family. *P. granatum* is a medicinal herb and plenty of information about its usefulness has been published in the traditional medicine literature (4, 5). However, scientific evidence on its effectiveness is limited. During recent years, an increasing number of researchers have reported therapeutic properties of *P. granatum*, such as antioxidant, anti-inflammatory, anti-carcinogenic, and antimicrobial effects of the flower, seeds, or peel (6-11). *P. granatum* flower (Persian Golnar; PG) is a medicinal herb of the pomegranate flower. Pomegranate is a native plant in southern Iran (12). PG has been used extensively for treating many diseases, particularly bleeding disorders such as excessive menstrual bleeding, gingivitis and diarrheal diseases in traditional Iranian medicine (13, 14).

The present study investigated the efficacy of PG in comparison with TA for treating HMB of endometrial origin concerning blood loss, quality of life and hematologic indices.

## Methods

### *Trial Design*

A randomized, double-blind clinical trial, using a parallel technique and equal allocation ratio was conducted to determine the efficacy, acceptability, and safety of PG in comparison with oral tranexamic acid as the recommended standard drug (3) for HMB.

### *Participants*

In this study 123 eligible patients (aged 20–49 years) complained of heavy menstrual bleeding interfering with their daily activities that had a BMI of 19–29 kg/m<sup>2</sup>) were examined by a gynecologist. Using appropriate tests such as pelvic ultrasound and endometrial biopsy pathologic causes of endometrial bleeding were ruled out. Ninety-four patients were enrolled in the study from July 2010 to Dec 2011 subsequently randomly assigned to groups. Seventy-six women completed the study. Recruited women were non-anemic (hemo-

globin (Hb) of  $\geq 10.5$  g/dl), had no history of previous thromboembolic disorders, chronic illnesses, or other diseases known to interfere with menstrual bleeding, such as leiomyomas greater than 3 cm, and had no history of iron supplementation, anticoagulant agents, oral contraceptive, or other hormonal drug use. Women who had an IUD in situ were excluded.

### *Study setting*

The study took place at gynecology clinic, west Tehran health center (Shahid Beheshti University of Medical Sciences), Tehran, Iran during July 2010 to Dec 2011.

### *Interventions*

After a control cycle, the patients were randomly allocated to one of the two treatment regimens: 500 mg of tranexamic acid (250 mg capsules, Amin pharmaceutical company, Isfahan, Iran) or 500 mg PG every 6 h for 5 consecutive days from the first day of menses for 3 cycles. Dried PG flowers were prepared by the Iranian traditional research center in 250 mg capsules, identical to the TA dosing regimen. The drugs were supplied to each subject in blinded containers.

### *Outcomes*

Baseline data on clinical and quality of life (QoL) outcomes were obtained at the control menstrual cycle and after the third intervention cycle. The pictorial blood loss assessment chart (PBAC) is a simple visual assessment technique (15). It was used as a semi-objective tool to determine the changes in menstrual blood loss (Fig. 1). In this study, patients were provided with medium-sized Panberes sanitary towels. An Iranian version of the (16) Menorrhagia Questionnaire (MQ) as a menorrhagia-specific QoL measure was applied to estimate the effect of menorrhagia on the perceived health status of the patient. It consists of 13 questions and produces a final transformed score that ranges from zero to 100, where zero is the best possible and 100 the worst possible score. An Iranian version of the

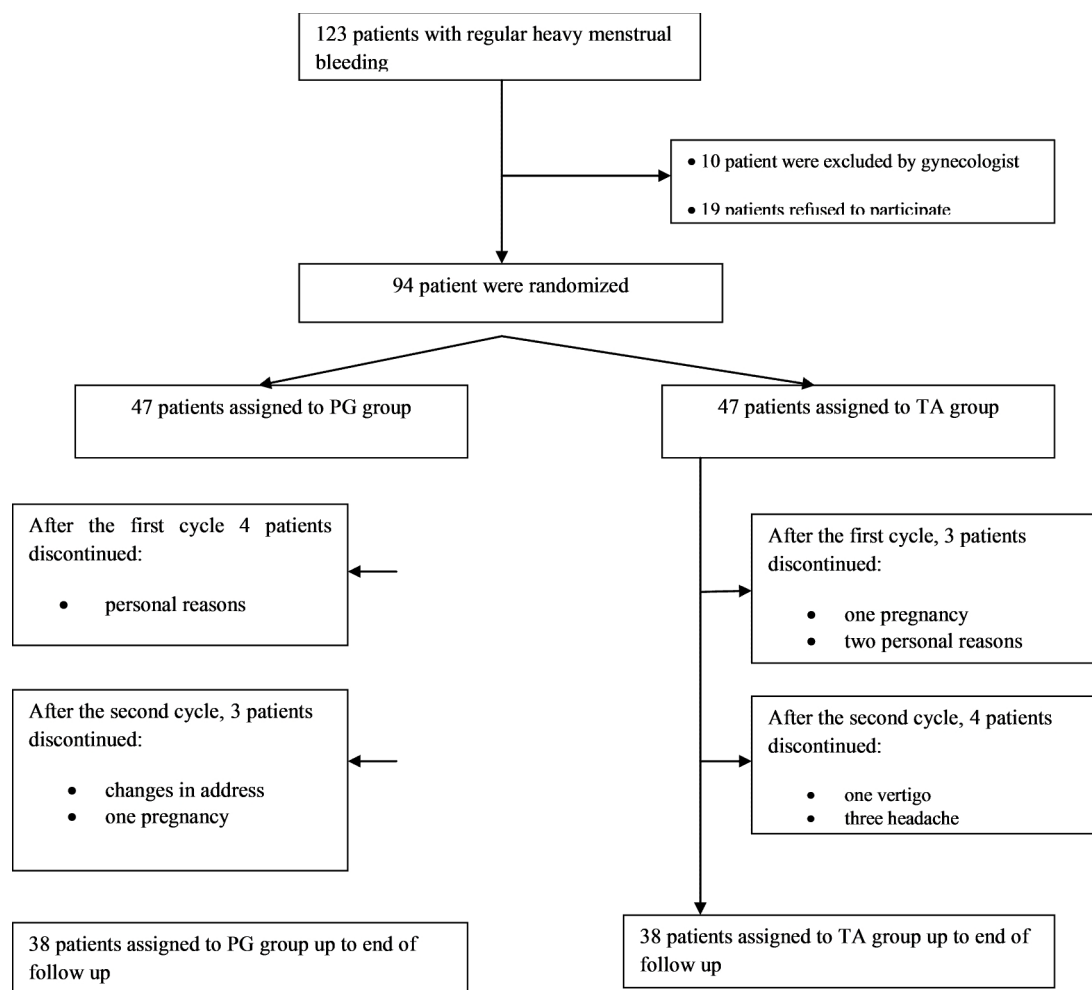


Fig. 1. Summary of patients randomized to TA or PG

36-Item Short Form Health Survey (SF-36) Questionnaire (17) was used to measure physical and mental components of health related QoL (HRQoL) from baseline to after completion of the treatment course. In addition, hematological indices were measured before and after the intervention. Hb and serum ferritin values were determined by the cyanmethohemoglobin method and radioimmunoassay, respectively. All patients were given a chart to report side effects of the treatment on a daily basis.

#### Sample size

For a significance level of 0.05 and power of 90%, in order to find a 40 cc difference in blood loss between the two groups, the number of subjects required in each set was calculated to be 37. Assuming a 25% drop out rate after randomization, we recruited

47 patients in each treatment branch.

#### Randomization

Randomization was performed using blocked randomization; sequentially numbered and sealed opaque envelopes containing one of the two assignments created in blocks of 6 (with an equal opportunity for receiving each intervention) were used for assigning participants to treatment groups. Patients and the midwives assessing outcomes were blinded about the treatment.

#### Follow-up

Women were followed-up at 1, 2, and 3 months after treatment. During these periods, women were interviewed about their bleeding patterns or any side effects or adverse reactions of the drugs.

### Statistical analysis

All statistical analyses were performed using SPSS version 11.5. The results were presented as mean  $\pm$  SD. Comparisons between groups were performed using t-test, Paired t-test,  $\chi^2$ , Mann–Whitney test, Wilcoxon signed ranks test. The statistical significance level was set at 0.05.

### Ethics

Approval for this trial was obtained from the ethics committee of the Tarbiat Mo-dares University, Tehran, Iran and the trial was registered in the Iranian Registry of Clinical Trials at [www.irct.ir](http://www.irct.ir) (IRCT 138802091641N2). The study design and method were explained to participants and then a signed informed consent for participation in a randomized-controlled study was obtained from each subject.

### Results

In both groups, 38 women (80.8%) completed the 3-month follow-up (Fig. 2). Characteristics of these women were not statistically different from others ( $p > 0.05$ ). After the first cycle of treatment, in the TA group, three patients dropped out of the study (one case of pregnancy and two of in-compliance) and in the PG group four patients were excluded (non-compliance). After the second cycle, in the TA group, four patients discontinued the treatment (one case of vertigo and three of head-

Fig. 2. The pictorial blood loss chart.

The numbers 1-8 represent the consecutive days of a bleeding episode, the columns could be added to the chart if needed.

aches), and in the PG group three patients did not continue the treatment (two cases of change in address, one of pregnancy).

The socio-demographic and obstetric characteristics of women studied are shown in Table 1. There were no significant differences between the two groups with regard to age, parity, education, occupation or BMI. The mean ages (SD) of women in the TA and PG groups were 31.50 (8.83) and 31.89 (6.96) years, respectively.

Duration of bleeding and menstrual blood loss decreased significantly in both groups over the follow-up period (Table 2).

Table 1. The socio-demographic and obstetric characteristics of the studied women

|                  | TA<br>group (n = 38) | PG<br>group (n =38) | p    |
|------------------|----------------------|---------------------|------|
| Age, n (%)       |                      |                     |      |
| 20-30 (years)    | 15 (39.5)            | 17 (44.7)           | 0.89 |
| 31-40 (years)    | 19 (50)              | 13 (34.2)           |      |
| 41-45 (years)    | 4 (10.5)             | 8 (21.1)            |      |
| Education n (%)  |                      |                     |      |
| 0-9(years)       | 10 (26.3)            | 6 (15.8)            | 0.98 |
| 10-12 (years)    | 13 (34.2)            | 19 (50)             |      |
| ≥13(years)       | 15 (39.4)            | 13 (34.2)           |      |
| Occupation n (%) |                      |                     |      |
| student          | 8 (21.05)            | 9 (23.7)            | 0.26 |
| employment       | 8 (21.05)            | 3 (7.9)             |      |
| housewife        | 22 (57.9)            | 26 (68.4)           |      |
| Parity, n (%)    |                      |                     |      |
| ≤2               | 29 (76.2)            | 30 (72.5)           | 0.99 |
| ≥3               | 9 (23.8)             | 8 (27.5)            |      |

Table 2. Comparison the characteristics between and within study participants

| Variable                    | TA group (n= 38)           |                           |                 | PG group (n=38)            |                           |                 | ***<br>p |
|-----------------------------|----------------------------|---------------------------|-----------------|----------------------------|---------------------------|-----------------|----------|
|                             | Before treatment mean (SD) | After treatment mean (SD) | Mean difference | Before treatment mean (SD) | After treatment mean (SD) | Mean difference |          |
| Duration of bleeding (days) | 8.0 (1.82)                 | 6.65 (1.37)*              | 1.31            | 8.0 (1.39)                 | 6.5(1.35)**               | 1.5             | 0.99     |
| (PBAC) score                | 304.4 (192.71)             | 143.13(96.00)*#           | 161.31          | 304.9(176.11)              | 164.0(100.21)**#          | 140.31          | 0.30     |
| Hemoglobin g/dL             | 11.5 (0.86)                | 12.7 (0.88)*©             | 1.19            | 12.6 (0.86)                | 13.0 (0.83)**©            | 0.96            | 0.09     |
| Hematocrite (%)             | 36.7(4.86)                 | 40.9 (4.19)*©             | 4.27            | 37.8(4.45)                 | 42.9(5.1)**©              | 5.01            | 0.60     |
| Ferritin ng/dL              | 9.4 (5.84)                 | 16.4 (6.79)*#             | 7.01            | 12.1 (10.79)               | 23.5 (13.5)**#            | 11.37           | 0.26     |

# Wilcoxon signed ranks test, © Paired t-test

\* p&lt; 0.001 compared with TA before treatment.

\*\* p&lt; 0.001 compared with PG group before treatment

\*\*\*p after treatment comparison of TA and PG groups (t-test, Mann-Whitney test)

### Hemorrhage

PBAC mean (SD) score was reduced in the TA and PG groups, respectively from 304.4 (192.7) and 304.9 (176.1) before treatment, to 143.1 (96) and 164 (100.2) in the third treatment cycle ( $p < 0.001$ ), with no statistically significant difference between the groups after treatment. The mean PBAC score, plotted over time by sequence of treatment is shown in Fig. 3.

In addition, hematological assessments showed that Hb, Hct (hematocrit), and ferritin values increased significantly in both groups over the follow-up period (Table 2). However, no statistically significant differences were observed between the TA and PG groups.

### Quality of Life

Regarding HRQoL, the Menorrhagia Questionnaire (MQ) and SF-36 question-

naire mean scores (in most physical and mental components) improved drastically after treatment in both randomized groups, but there were no difference between post-treatment scores in two groups (Table 3).

### Side effects

Of the 94 patients who used the medications for at least one cycle, 13 (13.8%) patients experienced adverse effects across both groups. Nine (19.1%) women in the TA group reported gastrointestinal symptoms such as nausea, vomiting, diarrhea, headache, and vertigo. In the PG group, four (8.5%) of the women experienced vomiting and breast tenderness. Although women in the TA group reported more side effects and less satisfaction, compared with those of the PG group, these differences were not statistically significant ( $p = 0.17$  and  $p = 1.00$ , respectively).

### Discussion

Heavy menstrual bleeding of endometrial origin (HMB) is one of the major healthcare problems in premenopausal women and several aspects of women's health and QoL are adversely affected by it. In the present study, we compared the efficacy and acceptability of PG, a herbal drug made from pomegranate flowers, with TA as the first choice treatment for treating HMB of endometrial origin.

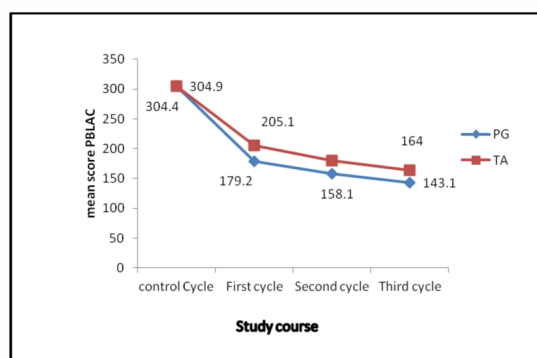


Fig. 3. Pictorial Blood Loss assessment chart mean scores (PBAC) over time by sequence of treatment

Table 3. Quality of life (QOL) assessment with MQ and SF-36 measures

|                                   |                      | TA group (n= 38)                 |                                 |                 | PG group (n=38)                  |                                 |                 | ***p |
|-----------------------------------|----------------------|----------------------------------|---------------------------------|-----------------|----------------------------------|---------------------------------|-----------------|------|
|                                   |                      | Before treatment<br>Mean<br>(SD) | After treatment<br>Mean<br>(SD) | Mean difference | Before treatment<br>Mean<br>(SD) | After treatment<br>Mean<br>(SD) | Mean difference |      |
| Menorrhagia Questionnaire (score) |                      | 47.6<br>(16.72)                  | 23.95<br>(13.78)*               | 23.61           | 42.05<br>(13.77)                 | 19.84<br>(10.18)**              | 22.2            | 0.14 |
| SF-36 Questionnaire (score)       |                      |                                  |                                 |                 |                                  |                                 |                 |      |
| Physical Health                   | Physical functioning | 79.1<br>(14.65)                  | 83.7<br>(11.83)*                | 4.60            | 79.2<br>(13.00)                  | 80.1<br>(11.88)                 | 0.92            | 0.19 |
|                                   | Role-physical        | 50.6<br>(28.76)                  | 62.5<br>(21.55)*                | 11.84           | 56.6<br>(27.63)                  | 61.2<br>(27.69)**               | 4.6             | 0.87 |
|                                   | Bodily pain          | 58.4<br>(24.33)                  | 60.3<br>(21.87)                 | 1.84            | 60.0<br>(20.53)                  | 66.3<br>(19.64)**               | 6.31            | 0.20 |
|                                   | General health       | 54.5<br>(19.98)                  | 67.3<br>(14.84)*                | 12.78           | 50.6<br>(20.19)                  | 57.0<br>(19.93)**               | 6.36            | 0.01 |
| Mental Health                     | Vitality             | 47.63<br>(23.29)                 | 63.5<br>(15.72)*                | 15.92           | 46.6<br>(20.66)                  | 61.0<br>(17.05)**               | 14.47           | 0.50 |
|                                   | Social functioning   | 67.4<br>(20.66)                  | 75.3<br>(13.78)*                | 7.89            | 64.1<br>(15.42)                  | 78.0<br>(12.13)**               | 13.81           | 0.40 |
|                                   | Role-emotional       | 51.7<br>(33.51)                  | 59.6<br>(23.45)*                | 7.89            | 57.9<br>(29.69)                  | 63.1<br>(27.71)**               | 5.2             | 0.48 |
|                                   | Mental health        | 61.0<br>(25.00)                  | 74.1<br>(15.69)*                | 13.05           | 63.0<br>(23.66)                  | 70.4<br>(17.51)**               | 7.36            | 0.33 |

\* p&lt; 0.001 compared with TA before treatment (Paired t test)

\*\* p&lt; 0.001 compared with golnar group before treatment (Paired t test)

\*\*\*p after treatment comparison of TA and PG groups (t test)

Furthermore, we compared the improvement of QoL after the intervention between and within the groups. Although SF-36 is still a valuable measure in the clinical setting, its limitations in assessing some problems that patients with menorrhagia may experience indicate that it is of limited use in this situation. Many scholars have suggested that disease-specific measures can assess treatment success more concisely (18). Therefore, we used both MQ (disease specific) and SF-36 (generic HRQoL) tools to evaluate the impact of treatment regimens on both aspects of QoL. Present findings showed that PG, in comparison with TA, is a safe and effective drug for the treatment of HMB. Women in both groups experienced significant reductions in duration and amount of bleeding, an improved QoL, and increased Hb and ferritin levels. Reductions in HMB were apparent during the first treatment cycle and were maintained over three cycles. Although no severe side effects were reported and there were no significant differences between the TA and PG groups, patients tolerated PG better and were more satisfied. This may be due to the smaller number of side effects observed in the PG group.

We did not use chemical extracts of PG and it is impossible to relate the therapeutic

effects to a specific component of PG, but these preliminary results may lay the foundations for future studies. Considering the concerns about the potential for thromboembolic events in patients undergoing anti-fibrinolytic therapy, it seems that PG could be a new safe alternative for anti-fibrinolytic agents in menorrhagia patients.

Although hysterectomy and other less-invasive surgical treatments are recommended as highly effective methods for treating menorrhagia (3), particularly in refractory cases, cost and risk of anesthesia along with short and long term morbidities make them the last treatment modality to be offered. Therefore, forthcoming investigations into PG properties may establish it as an efficient and inexpensive alternative for invasive hysterectomy, particularly in women who are in their late reproductive stage and have a normal uterus with no significant pathology.

Several studies have investigated the efficacy of TA in the reduction of HMB symptoms (19, 20). In 2006, Kriplani et al (21) compared TA and medroxy progesterone acetate for treating HMB. Similar to our findings, their results demonstrated that TA significantly decreased menstrual blood loss; but they did not record ferritin levels and subjective outcomes such as HRQoL.

### Limitations

A placebo-controlled arm to demonstrate the efficacy of our regimens could confirm the observed effects. However, the consistency of QoL scores with the studied drug (bodily pain in TA group showed no difference before and after treatment, which was to be expected) may validate the success of the treatments.

Small sample size and short follow-up period may limit the comparability of the results. Furthermore, the efficacy of PG in treating HMB in patients suffering from anemia or women with abnormal BMI was not assessed. Moreover, patients with uterine fibroids greater than 3 cm were excluded. Concerning the risk of thromboembolic events, patients who were on OCPs were not enrolled in the trial and drug interactions between PG and OCPs was not evaluated.

### Conclusion

Both products were very effective in reducing menorrhagia as measured by PBAC scores, hematologic indices and improving QOL, with no statistically significant differences. In addition to antioxidant capacity, PG has been reported to have a wide range of biological actions including anti-inflammatory, antibacterial, antifungal, and anti-diabetic qualities (7-9, 12). Although previous studies reported pomegranate to be useful in controlling bleeding disorders caused by gingivitis (22, 23), this is the first study on the effect of PG on HMB; this has shown it to be as effective as TA, the recommended treatment choice for HMB.

### Acknowledgments

This study was funded by Tarbiat Mo-dares University research office as part of a Midwifery Master of Science dissertation.

### Conflict of interests

The authors have no conflicts to disclose.

### References

1. James AH, Kouides PA, Abdul-Kadir R, Dietrich JE,

Edlund M, Federici AB, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2011;158(2):124-34.

2. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, et al. Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2010 152(2):133-7.

3. CG44 NICE. Heavy Menstrual Bleeding. Clinical Guideline No. 44. National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence. 2007.

4. Rhazes MZ (Razi) Alhavi (The first Encyclopedia of Traditional Medicine), Electronic Version, Computerized by: Hatami H. Ministry of Health and Medical Education, Deputy of Research: 2009: 1979, p: 632. Available from: <http://www.elib.hbi.ir/persian/TRADITIONAL-MEDICINE/RAZI/ALHAVI-J06.pdf>.

5. Sina H, (Avicenna) Canon of Medicine, [K1FA3F-1], Ministry of Health and Medical Education, Deputy of Research: 2009. Available from: <http://www.elib.hbi.ir/persian/TRADITIONAL-MEDICINE/CANON-WEB/CANON-01/CANON-FAR-01%20245.pdf>.

6. Fawole OA, Makunga NP, Opara UL. Antibacterial, antioxidant and tyrosinase-inhibition activities of pomegranate fruit peel methanolic extract. *BMC Complement Altern Med* 2012;12:200.

7. Ismail T, Sestili P, Akhtar S. Pomegranate peel and fruit extracts: A review of potential anti-inflammatory and anti-infective effects. *Journal of Ethnopharmacology* 2012;143(2):397-405.

8. Jurenka JS. Therapeutic applications of pomegranate (*Punica granatum* L.): a review. *Altern Med Rev*. 2008 Jun;13(2):128-44.

9. Miguel MG, Neves MA, Antunes MD. Pomegranate (*Punica granatum* L.): A medicinal plant with myriad biological properties-A short review. *J Med Plants Res* 2010;4:2836-47.

10. Zhang L, Yang X, Zhang Y, Wang L, Zhang R. In vitro antioxidant properties of different parts of pomegranate flowers. *Food and Bioproducts Processing* 2011; 89(3):234-40.

11. Colombo E, Sangiovanni E, Dell'agli M. A review on the anti-inflammatory activity of pomegranate in the gastrointestinal tract. *Evid Based Complement Alternat Med*. 2013;2013:247145.

12. Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. *Inflamm Allergy Drug Targets* 2009 Mar;8(1):2-10.

13. Hajimahmoodi M, Shams-Ardakani M, Saniee P, Siavoshi F, Mehrabani M, Hosseinzadeh H, et al. In vitro antibacterial activity of some Iranian medicinal plant extracts against *Helicobacter pylori*. *Nat Prod Res* 2011 Jul; 25(11):1059-66.

14. Sadeghi N, Jannat B, Oveisi MR, Hajimahmoodi M, Photovat M. Antioxidant activity of Iranian pomegranate (*Punica granatum* L.) seed extracts. *Journal of Agricultural Science and Technology* 2009;11(5):633-8.

15. Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menor-

rhagia and normal menstrual blood loss. *Obstet Gynecol* 1995 Jun;85(6):977-82.

16. Mazari Z, Goshtasebi A, Moukhah S, Saki F. The menorrhagia questionnaire (MQ): translation and validation study of the Iranian version. *Payesh* 2012;11(1):83-8.

17. Montazeri A, Goshtasebi A, Vahdaninia M, Gandek B. The Short Form Health Survey (SF-36): translation and validation study of the Iranian version. *Qual Life Res* 2005 Apr;14(3):875-82.

18. Ruta DA, Garratt AM, Chadha YC, Flett GM, Hall MH, Russell IT. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? *Qual Life Res* 1995 Feb;4(1):33-40.

19. Lukes AS, Moore KA, Muse KN, Gersten JK, Hecht BR, Edlund M, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. *Obstet Gynecol* 2010 Oct;116(4):865-75.

20. Naoulou B, Tsai MC. Efficacy of tranexamic acid

in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review. *Acta Obstet Gynecol Scand* 2012 May;91(5):529-37.

21. Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. *J Obstet Gynaecol* 2006 Oct;26(7):673-8.

22. Sastravaha G, Gassmann G, Sangtherapitikul P, Grimm WD. Adjunctive periodontal treatment with *Centella asiatica* and *Punica granatum* extracts in supportive periodontal therapy. *J Int Acad Periodontol* 2005 Jul;7(3):70-9.

23. Abdollahzadeh S, Mashouf R, Mortazavi H, Moghaddam M, Roozbahani N, Vahedi M. Antibacterial and antifungal activities of *punica granatum* peel extracts against oral pathogens. *J Dent (Tehran)* 2011 Winter;8(1):1-6.