Original Article

Preparation and Standardization of Vaginal Suppository from *Punica granatum* Flower Extract Known as "Golnar" in Persian Medicine

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ABSTRACT

Background: *Punica granatum* L. flower, known as "Persian Golnar", is used in Persian medicine to treat excessive menstrual bleeding. Most therapeutic activities of pomegranate are due to the presence of phenolic compounds such as ellagitannins and gallotannins. **Aim:** This study served the purpose of developing and standardizing *P. granatum* vaginal suppository. **Materials and Methods:** Total phenolic and tannin content were assessed for both the extract and the final formula. Moreover, physicochemical properties of vaginal suppository such as appearance, weight variation, melting point, and dissolution test were evaluated. **Results and Discussion:** It was indicated by the findings of this study that the odorless suppositories have a brownish-red color and uniform appearance with an average weight of 2.06 ± 0.04 and a melting time of 28.93 ± 0.40. 100% of the plant extract was released for up to 90 min after administration. The results also indicated that the average phenolic percentages of the extract and suppositories were 17.03 % and 15.73% within three days respectively. **Conclusion:** *P. granatum* flower extract as a vaginal suppository can be applied as an anti-hemorrhagic agent due to the presence of polyphenols, particularly tannins, in the extract.

Key words: Menorrhagia, *Punica granatum* Flower, Vaginal Suppository, Total Phenolic Compounds, Total Tannins.

INTRODUCTION

Menorrhagia, as one the most common abnormalities of women's health, has multiple etiologies such as inflammation and structural uterine pathology.[1] The management of menorrhagia is a necessity because of the upcoming serious problems such as anemia.[2] Non-steroidal anti-inflammatory drugs (NSAIDs) are applied in menorrhagia but they have caused some serious side effects such as gastrointestinal disorders.[3]

There have been many studies revealing that medicinal plants such as *Annona senegalensis, Cissampelo smucronat*, *Cassytha filiformis*, *Newboulda laevis* are applied for menorrhagia due to their astringent activity.[4] Many plants with high proportion of tannins show astringent properties and can commonly cause vasoconstriction activity as hemostatic agents.[5] Moreover, in traditional manuscripts of Persian medicine several plants have been used to treat heavy menstrual bleeding. In Persian medicine, pomegranate flower known as "Persian Golnar" has been used for treating excessive menstrual bleeding.[6-8] *Punica granatum* L. known as pomegranate is commercially planted for its edible fruit. It is usually cultivated in South East Asia,

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Mediterranean region and the United States.[9] Some biological activities of *P. granatum* have been reported. Quite a lot of studies have been published on antioxidant,[10] anti-carcinogenic[11] and anti-inflammatory[12] effects of pomegranate components. Pomegranate possesses lots of medical applications, e.g. cardiovascular diseases, diabetes, alzheimer, dental conditions, erectile dysfunction, male infertility, arthritis, obesity and protection from ultraviolet (UV) radiation.[13] Most therapeutic activities of pomegranate result from the presence of phenolic compounds such as ellagitannins and gallotannins.[14]

According to the traditional background of *P. granatum* and its pharmacologic properties such as anti-hemorrhagic, anti-oxidant and anti-inflammatory activities, the present study investigated the preparation and standardization of vaginal suppository formula of *P. granatum* flower extract.

MATERIALS AND METHODS

Ethical Considerations

The present study was approved by the Ethics Committee of Pharmaceutical Science Research Center of TUMS with the code of IR.TUMS.PSRC.REC.1394, 22 on 2015/10/25.

Preparation and Authentication of the Plant

Punica granatum flowers were purchased from a local herbal drug market (Tehran, Iran). The sample was identified by Professor *G. Amin* and deposited at the Herbarium of Faculty of Pharmacy, Tehran University of Medical Sciences (PMP-530). The flowers were powdered using a grinder.

All chemicals and reagents were of analytical grade from Merck (Munich, Germany) and Sigma Aldrich (Milan, Italy) companies.

Extract Preparation

One hundred g of powdered flowers were extracted with hydro-alcoholic solvent (ethanol 70%) using maceration method at room temperature for three days. The extract was condensed by rotary evaporator under 40°C and then lyophilized. The brownish-red extract (extractionyield= 45%) was obtained and kept in fridge for further experiments.[15]

Total Phenolic Content

According to the Folin-Ciocalteu method with some changes, total phenolic compounds were performed. Two hundred µL of the ethanol extract were mixed with 1.5 ml of tenfold diluted Folin-Ciocalteu reagent. The mixture was kept at room temperature for 5 min and then 1.5 ml Na_2CO_3 7.5 % solution was added. The mixture was also kept at room temperature. After 90 min, the absorbance level was evaluated at 725 nm using a UV-Visible spectrophotometer (GBC, Cintra 40). Total phenolic content was quantified by calibration curve obtained by evaluating the absorbance of the known concentrations of gallic acid standard solutions [10 - 150 µg mL–1 in 80% methanol]. The results were determined as gallic acid equivalent (GAE) per one-gram dry powder and reported as mean value ± standard deviation (SD).[16]

Tannin Assay

Determination of total tannin content of the sample was performed according to Hajimahmoodi *et al*. 2013. Three g of the flower powder were mixed with 250 mL of deionized double distilled water. Then the mixture was filtered through sample filter (Control Biogen-Spain). Twenty-five mL of the infusion were poured into 1 L conical flask and then equal volume of indigo solution [0.6%] and 750 mL deionized distilled water were added. The final solution was titrated with KMNO4 (0.1 N aqueous solution) until the blue colored solution turned into a golden yellow color. The blank test was performed by titration of the mixture of 25 mL indigo carmine and 775 mL double distilled water. All samples were done in triplicates. The tannin percentage [%] in the samples was estimated as follows:

$$T\ (\%) = [V - V0]\ 0.004157 \times 250 \times 100/g \times 25$$

Where V is the volume of $KMNO_4$ (0.1 N aqueous solution) applied in the sample titration; V0 is the volume of $KMNO_4$ used in the titration of the blank as mL; g as gram is the mass of the sample taken for the analysis.[17]

Formulation of Vaginal Suppositories

Final plant extraction was formed as vaginal inserts with water base. The weight of each suppository was 2 g. Formulation of suppository was prepared by total extract of *P. granatum* flowers (10%), tween 80, PEG 4000, PEG 400 and distilled water. The inserts were made with 3 different proportions from PEG 4000 to PEG 400 (95%, 90%, 85%).

Physicochemical Properties

The following experiments were conducted on suppositories. The prepared suppositories were evaluated for physicochemical parameters via organoleptic properties, weight variation, melting time and *in-vitro* drug release. The tests were carried out several times and the results were tabulated.

Organoleptic Properties

The suppositories have a uniform appearance. The color of them is brownish-red because of the *P. granatum* flower extract. Also, the suppositories were odorless.

Weight Variation

According to BP pharmacopeia, twenty suppositories were randomly selected and weighted. Then, their average weight and percentage deviation value was determined. There must be no more than two suppositories differing from the average weight by more than 5% and no suppositories differing from the average weight by more than 10%.[18]

Melting Time

Melting Time is the measuring time for all suppositories to melt or disperse when immersed in water bath kept at 37±1°C.[19-22]

Tannin and Phenolic Content Assay in Suppository

Based on the method described previously, the amount of tannin and phenolic contents in suppositories was determined.

Dissolution Test of Suppositories

One of the most important quality control tools for evaluation *in vitro* is Dissolution Test.[19] The rate of drug release was measured in the 500 ml of water dissolution medium at a temperature of 37 ± 0.5°C for 90 min at a speed of 50 rpm/min with USP pharmacopoeia No.1 dissolution apparatus (basket method) and a sampling time interval of 15 min. Finally, the amount of plant extract released from the suppository was calculated at certain times. The samples were then centrifuged and diluted and the amount of total phenol content was determined by spectrophotometric measurement at 725 nm by UV-Visible spectrophotometer. The mean and standard deviation of the released extract were calculated and the percentage of releasing was plotted against time.

This test was performed on all three different percentages of suppositories (85%, 90% and 95%) and a comparison was made between the release rates of the extract from suppositories at certain times.

RESULTS AND DISCUSSION

Total Tannin Content

As shown in Table 1, total tannin contents of the extract and the formulation were assessed. Total tannin contents of extract and suppository were 5.04 ± 0.053 and 4.73 ± 0.23 respectively.

Table 1: Total tannin content of *Punicagranatum* flower extract and suppository.

Sample	Total tannin percentage (%)	
	P. granatum extract	Suppository
1	5.1	4.53
2	5.05	4.99
3	4.97	4.67
SD	0.053	0.23
Mean	5.04	4.73

Table 2: Total phenolic content of *Punicagranatum* flower extract in three different days.

	First day	Second day	Third day
Total phenolic content of the extract (mg/l)	0.1706	0.1715	0.1689
	0.1697	0.1724	0.1695
	0.1702	0.1706	0.1694
Mean	0.1702	0.1715	0.1693
SD	0.343	0.706	0.245
Mean percentage of phenolic content (%)	17.02	17.15	16.93

Determination of total phenolic content

As seen in Tables 2 and 3, the total phenolic content of pomegranate flower extract and the formulation were declared in terms of gallic acid equivalent. The average phenolic percentage of the extract and suppository within three days were 17.03 % and 15.73% respectively.

Determination of Weight Variation

According to Table 4, there were no more than 2 suppositories differing from the average weight by more than 5% and no suppository differing from the average weight by more than10%. Their average weight was 2.06 ± 0.046.

Determination of Melting Point

As shown in Table 5, melting point was assessed in triplicate and the obtained mean was 28.93 ± 0.404.

In vitro Release of Extract from Suppository

According to Figure 1, the amount of released extract from samples was measured based on the percentage of released total phenolic. The samples were then centrifuged and diluted and the amount of total phenol content was determined by spectrophotometric measurement at 725 nm by UV-Visible spectrophotometer.

This test was performed on all three different percentages of suppositories (85%, 90% and 95%) and a comparison

Table 3: Total phenolic content of *Punica granatum* suppositories in three different days.

	First day	Second day	Third day
Total phenolic content of the *P. granatum* suppository (mg/l)	0.1589	0.1548	0.1579
	0.1593	0.1553	0.1581
	0.1586	0.1549	0.1583
Mean	0.1589	0.1550	0.1581
SD	0.238	0.216	0.208
Mean percentage of phenolic content of the suppository (%)	15.89	15.50	15.81

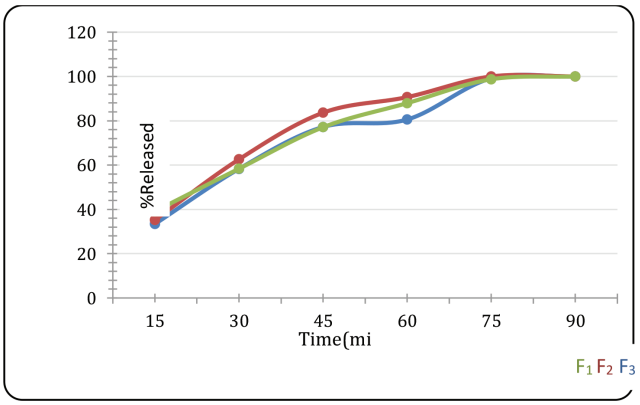

Figure 1: Comparison of average release of extract (total phenol content) from all three formulations. F1) suppository 85% F2) suppository 90% F3) suppository 95%

Table 4: Weight variation (g) for 20 suppositories.

2.00	1.99	2.01	2.04	2.03	1.97	2.00	2.01	2.05	1.98
2.10	2.15	1.98	2.04	1.99	2.00	2.12	2.12	2.00	2.04

Table 5: Melting point of *Punica granatum* suppository at temperature 37±1°C.

P. granatum suppository	Melting Time (minute)
1	28.5
2	29.3
3	29
SD	0.404
Mean	28.93

was made between the release rates of the extract from suppositories at certain times. Based on the statistical studies, it can be concluded that the amount of final release of the plant extract, 75 min after suppository administration in the bases of 85%, 90% and 95%, was not statistically significant and in all the bases 100% of the plant extract was released up to 90 min after administration (Figure 1).

P. granatum flowers contain many polyphenols such as tannins including ellagitannins and gallotannins. Pomegranate ellagitannins such as punicalagin exerted significant anti-oxidant and anti-inflammatory activities.[20,21] Punicalin, another ellagitannin isolated from pomegranate, showed inhibitory effect on carrageenan-induced inflammation in the rat.[22] The extracts of pomegranate possess potent anti-inflammatory effect.[23] Furthermore, because of their astringent effect, tannins are used as vasoconstrictors.[24] Previous studies have shown that tannin-rich plants possess anti-hemorrhagic effect. Some reports exhibited that the presence of tannins could be responsible for the anti-hemorrhagic effect of plants.[4,25] Gopalakrishnan *et al.* introduced ellagic acid as an effective anti-hemorrhagic agent.[26] Moreover, presence of phytosterols is proven in pomegranate. A clinical trial on the herbal formula containing pomegranate revealed that the formula regulated hormone in follicular phase due to the presence of phytoestrogen compounds.[27] Similar to our study, another clinical study showed that oral administration of *P. granatum* flowers has shown significant anti-hemorrhagic activity against heavy menstrual bleeding of endometrial origin compared to tranexamic acid.[28]

Elfalleh *et al.* (2012) depicted that the total phenolic and tannin contents of pomegranate flower extract were 66.29 (GAE mg/g dry weight) and 148.24(TAE mg/g dry weight) respectively which is more than the result of this study.[29]

Similar to our study, Mahboubi *et al.* (2015) exhibited that methanol fraction of pomegranate flower contained 18.1 mg GEA/g total phenolic content.[30]

According to our findings, the total phenolic content of the extract is slightly higher than the total phenolic content of the suppository; however, the difference is not statistically significant. It could be due to the presence of suppositories' excipients that have prevented the release of the total phenolic compounds. It seems that the prepared suppositories show a suitable formulation due to the short release time of phenolic compounds (90 min). Also, reducing the release time could improve patient compliance and formulation effectiveness.

Limitations of the study include the provision of plant raw materials as well as maintaining the stability of active ingredients in the finish product.

CONCLUSION

According to our results and traditional background, *Punica granatum* flower extract as vaginal suppository can be applied as an anti-hemorrhagic agent due to the presence of polyphenols in the extract, particularly tannins. Further stability studies and clinical trials of the formulation can be considered in the future.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

GAE: Gallic acid equivalent; **PEG:** Polyethylene glycol.

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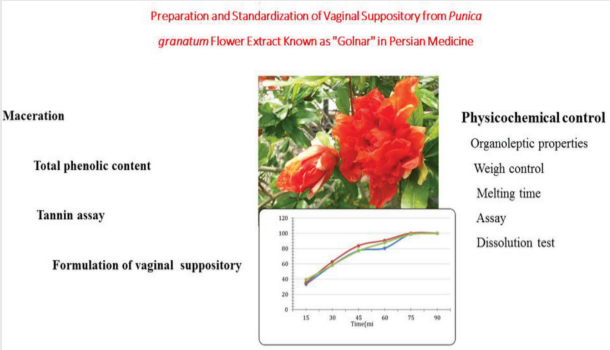
PICTORIAL ABSTRACT



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SUMMARY

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