TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 7, Issue 2, Spring 2022

Original Research

The Efficacy of Vaginal Suppository Based on *Alcea angulata* Freyn & Sint. (A Persian Medicine Product) in Patients with Vaginal Atrophy: A Randomized, Double-Blind, Placebo-Controlled Trial

Alieh Kianitalaei[1,2], Zohre Feyzabadi[3], Nasser Behnampour[4], Shokuhsadat Hamedi[5], Faride Akhlaghi[6], Marzieh Qaraaty[1,2]*

[1]Clinical Research Development Unit, Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran
[2]Department of Persian Medicine, School of Medicine, Golestan University of Medical Science, Gorgan, Iran
[3]Department of Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Biostatistics Department, Faculty of Health, Golestan University of Medical Sciences, Gorgan, Iran
[5]Department of Persian Pharmacy, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[6]Department of Obstetrics and Gynecology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Received: 22 Jul 2021 **Revised:** 9 Feb 2022 **Accepted:** 12 Feb 2022

Abstract

Vaginal atrophy is one of the most common complaints in postmenopausal women. Symptoms of vaginal atrophy include dryness, itching, bleeding, and dyspareunia. According to Traditional Persian Medicine (TPM), the using of moisturizing plants can treat dry mucous membranes. TPM suggests the use of marshmallow (*Alcea angulata*) to moisturize dry mucus with its mucilage. The aim of this study was to evaluate the effect of *Alcea* on the treatment of vaginal atrophy. This double-blind, clinical trial was conducted on 60 postmenopausal women with vaginal atrophy (40 – 65 years of age). The patients were randomly assigned into two groups of treatment and control (n = 30). The treatment group received *Alcea* vaginal suppository 5% (125 mg), and the control group received placebo. Both groups used suppositories every night for two weeks and every other night for six weeks. Vaginal Maturation Value (VMV), symptoms of vaginal atrophy, and pH were compared before and after the intervention. Data were analyzed using SPSS 16. VMV was increased in the treatment group, from 40.30 ±13.27 to 46.40 ± 11.27, ($p < 0.0001$) compared to the control group, in which the change of VMV was not significant ($p < 0.122$). The vaginal pH was significantly decreased in the treatment group, from 6.45 ± 0.92 to 5.52 ± 0.62, ($p < 0.0001$) compared to the control group, in which the change of pH was not significant ($p < 0.257$). The symptoms were significantly reduced in the treatment group. It seems that *Alcea* vaginal suppository can be useful as a natural product to relieve the symptoms of vaginal atrophy.

Keywords: Menopause; Vaginal atrophy; Traditional persian medicine; Herbal medicine; *Alcea angulata*; Phenolic compounds

Introduction

Vaginal atrophy is the second most common complaint of women referring to menopause clinic after hot flashes [1,2]. Genitourinary atrophy causes vaginal dryness, vaginal itching, dyspareunia, dysuria, and urgency in urinary excretion [2,3]. Reducing estrogen level increases tissue fragility of urogenital tissue [1,4-6]. Some of the subjective symptoms of vaginal

Citation: Kianitalaei A, Feyzabadi Z, Behnampour N, Hamedi S, Akhlaghi F, Qaraaty M. **The Efficacy of Vaginal Suppository Based on *Alcea angulata* Freyn & Sint. (A Persian Medicine Product) in Patients with Vaginal Atrophy: A Randomized, Double-Blind, Placebo-Controlled Trial**. Trad Integr Med 2022;7(2):171-179.

*Corresponding Author: Marzieh Qaraaty
Department of Persian Medicine, School of Medicine, Golestan University of Medical Science, Gorgan, Iran
Tel: +98-9128027050
Email: dr.qaraati@goums.ac.ir

atrophy include non-elastic, smooth, thin, and hypopigmented epithelium, decrease of acidity, erythema or petechiae, and micro-fissures [2,4,7,8]. Vaginal atrophy can be diagnosed by obtaining a history, clinical examination and assessment of Vaginal Maturation Value (VMV), Vaginal Cell Maturation Index (VMI), and vaginal acidity [9,10].

It is estimated that 10-40% of women after menopause experience vaginal atrophy that needs treatment [11]. Systemic and local estrogen therapy is very effective in removing symptoms of vaginal atrophy [1-3]. Due to serious side effects, estrogen therapy has been limited and other treatments have been considered [3,11]. The North American Menopause Society (NAMS) statement on vaginal atrophy claims that nonhormonal moisturizers and lubricants should be first-line treatments [1]. The use of vitamin D [12], vitamin E [13-15], hyaluronic acid [16], moisturizers [17], lubricants [1], phytoestrogen (such as fennel, red clover, and fenugreek) [18-20] and laser [4,21] are suggested as estrogen substitutes to improve vaginal atrophy [22-24]. The vaginal moisturizer (such as Replens) binds to the epithelium, and releases purified water and hydrates the underlying cells. Replens have significant effect on the vaginal cells in patients with atrophic symptoms [17].

Traditional Persian Medicine (TPM) with a comprehensive view on etiology, and considering several variables, has been effective in the treatment of diseases. These variables include part of human nature (mizaj), sex, age, racial/ethnic, season, region, profession [25]. TPM provides valuable preparations (phytopharmaceuticals) which are proposed as putative therapeutic medications in numerous health complications [26].

According to TPM (particularly The Canon of Medicine), plants containing glaze or mucilage can be used to treat mucosal dryness. One of the plants with hydrating properties is marshmallow (*Alcea*); Which is used to moisturize dry and inflamed mucosa, and was used in this trial to relieve the symptoms of vaginal atrophy [27,28]. *Alcea angulata* Freyn & Sint. (syn: *Althaea angulata*) is one of the medicinal plants that has been consumed in Iran since ancient times. The genus of *Alcea* was formerly *Althaea*, and later, according to the botanical definition, flowers of more than 3 cm in diameter were called *Alcea*. It has been used to treat cough, fever, eczema, and inflammation [27]. *Althaea* and *Alcea*, commonly known as "*khatmi*" in manuscripts of TPM, belong to the Malvaceae family [29]. The aim of the present study was to evaluate the effect of *Alcea* on vaginal atrophy.

Materials and Methods

Study design

This study is a double-blind, randomized, placebo-controlled study to determine *Alcea* vaginal suppository effect on postmenopausal women with vaginal atrophy, between April 2019 to September 2019. This study was conducted at the Women's Clinic of *Umm al-Banin* Hospital, Mashhad, Iran,

This study was approved by Golestan University of Medical Sciences (ethical approval code: IR.GOUMS.REC.1397.230), and was registered in the Iranian Registry of Clinical Trial (IRCT) with the number: IRCT20180923041099N1. This project information was initially explained to the patients, and the information about the study was given to them in the written form. They were asked to sign a consent form before participating in the study.

The inclusion criteria included the participant's age between 40-65 years, had complained of vaginal atrophy and, had amenorrhea for at least 12 months, or laboratory confirmation of menopause (FSH>40), or after surgery (bilateral oophorectomy). The exclusion criteria were allergy to *Alcea*, the existence of side effects, and the application of less than 80% of suppositories. No entry criteria included vaginal infection, hormonal use during the eight weeks before the study, and vaginal bleeding with unknown causes.

Blinding description: This study is conducted randomly, double-blind, and controlled by placebo. Both types of vaginal suppositories were quite similar in color, shape, and size, so the participants were unaware of the type of treatment. The researcher provided *Alcea* suppository and placebo to clinical care providers, and she distributes them according to the patient's condition. Therefore, only clinical care providers were aware of the type of treatment, and the researchers and patients were blinded during the intervention.

Randomization: Eligible women were randomly divided into treatment group (*Alcea* vaginal suppository) (n = 30) and control group (placebo) (n = 30). Randomization was done by the block sampling method.

Sample size: Considering the variable VMV in two groups, the sample size was determined using the two means formula with a 95% confidence level and 80% power test [12,30].

Statistical analysis

The data were analyzed using SPSS software (version16). Participants who did not complete the trial were not included in the statistical analysis. Data were checked for normality by the Shapiro-Wilk test. Demographic and clinical characteristics were analyzed using Chi-square, Fisher's exact, Mann-Whitney, Independent t-student, Paired t-test and Wilcoxon tests. ANCOVA test (adjusted baseline values) was used to compare the mean between the two groups. Value of P less than 0.05 was considered statistically significant.

Preparation of suppositories

Alcea angulata flower (*khatmi*) was prepared with a Voucher number (FUMH-E 1009) from the Faculty of

Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran.

The flowers were dried in the shade and extraction was done by the maceration method using aqueous solvent. The extraction process was performed in the laboratory of Mashhad Medical School.

To prepare the suppository, first 5% of the aqueous extract was mixed with the suppository base. The suppository base contained 30% polyethylene glycol (PEG) 600 and 70% PEG 4000 (Merck & Co, Germany). Thus, 95 g of PEG with the above ratio was mixed with 5 g of aqueous extract. It was then inserted into the suppository shells, so each suppository contained 125 mg of *Alcea* extract.

The placebo vaginal suppository was the same in shape, size, and color as the *Alcea* vaginal suppository. The base of the placebo suppository contains polyethylene glycol (4000 and 600) without any plant extract, but to make the placebo suppositories precisely the same as *Alcea* suppositories, the brown color (Magnolia Color and Flavor, number B3) was added [31]. *Alcea* vaginal suppository was standardized with the Folin-Ciocalteu method based on its total phenol [32]. The total phenol content of the aqueous extract is standardized by evaluating gallic acid [33]. Total phenolics were measured spectrophotometrically using a calibration curve obtained from measuring the absorbance of a known gallic acid standard concentration with the Folin-Ciocalteu method [34]. The total phenol content was calculated as 0.633 mg per *Alcea* suppository according to the standard curve formula.

Microbial restriction tests were performed on *Alcea* suppositories and placebo in the Microbiology Laboratory of Ghaem Hospital in Mashhad. The presence of *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, total mold and yeast counts, and total aerobic mesophilic bacterial counts were evaluated. The standard operating procedure was based on USP32-NF27-test 62 United States Pharmacopeia and National Formulary [35]. The results of microbial culture test from suppository were reported negative, or within an acceptable range.

Intervention: Patients used vaginal suppositories (*Alcea* and placebo) every night for two weeks, followed by every other night for a further six weeks (at bedtime). Due to the anti-inflammatory, moisturizing and emollient properties of *Alcea*, this study was designed to evaluate the effect of herbal suppository based on *Alcea* in vaginal atrophy treatment. A researcher and gynecologist made medical history and physical examination for all patients. Demographic characters such as age, education, exercise, occupation, and Body Mass Index (BMI) were assessed.

The symptoms of vaginal atrophy (dryness, irritation, itching, dyspareunia, and intercourse bleeding) were compared based on the Visual Analog Scale (VAS) before and after the intervention. A pH meter was used to measure vaginal acidity. A vaginal pH test over 5.0, may indicate estrogen deprivation [1]. Vaginal smear was performed at the beginning and end of the intervention to examine the maturation of superficial, intermediate, and basal cells. The samples were sent to the pathology laboratory. If VMI shows high intermediate and parabasal cell ratios compared to superficial cells, it can confirm physical examination findings in vaginal atrophy [1,36]. The amount of VMV was calculated using the pathologist report and the following formula [14].

Equation 1.

$$VMV = (0.5 \times \text{intermediate cells}) + (\text{superficial cells})$$

The primary outcome was the possible changes in VMV score after the intervention. The secondary outcome was the possible changes in pH, and the severity of patient complaints of vaginal atrophy symptoms.

Results

Out of 96 patients assessed for eligibility to participate in the study, 60 patients were included in the study and were randomly divided into two groups. In the treatment group, two patients dropped out due to frequent urination and irritation of the vaginal mucosa. In the control group, two patients were excluded due to travel and absence at the end of the intervention. Therefore, in each group, 28 patients were assessed. The consort flow chart is presented in figure 1.

Demographic analysis

As shown in table 1, the mean age of patients was 56.60 ± 5.48 years in the treatment group, and 54.56 ± 5.89 years in the placebo group. There was no difference between the two groups in terms of mean age, cause of menopause, educational level, BMI, and employment status.

Primary outcome

Vaginal maturation value

After 8 weeks of treatment, the mean score of VMV was increased to 6.09 in treatment group (p-value < 0.0001), and in placebo group was added to 1.1 (p-value < 0.122) (Table 2 and Figures 2).

Vaginal pH

The mean score of pH in the treatment group showed a 0.93 decrease (P value < 0.0001); also in the placebo group, a decrease of 0.05 was seen (P value < 0.257) figure 3 and table 3.

Vaginal atrophy symptoms

Vaginal atrophy symptoms were compared with Wilcoxon and Mann-Whitney tests in the intervention and

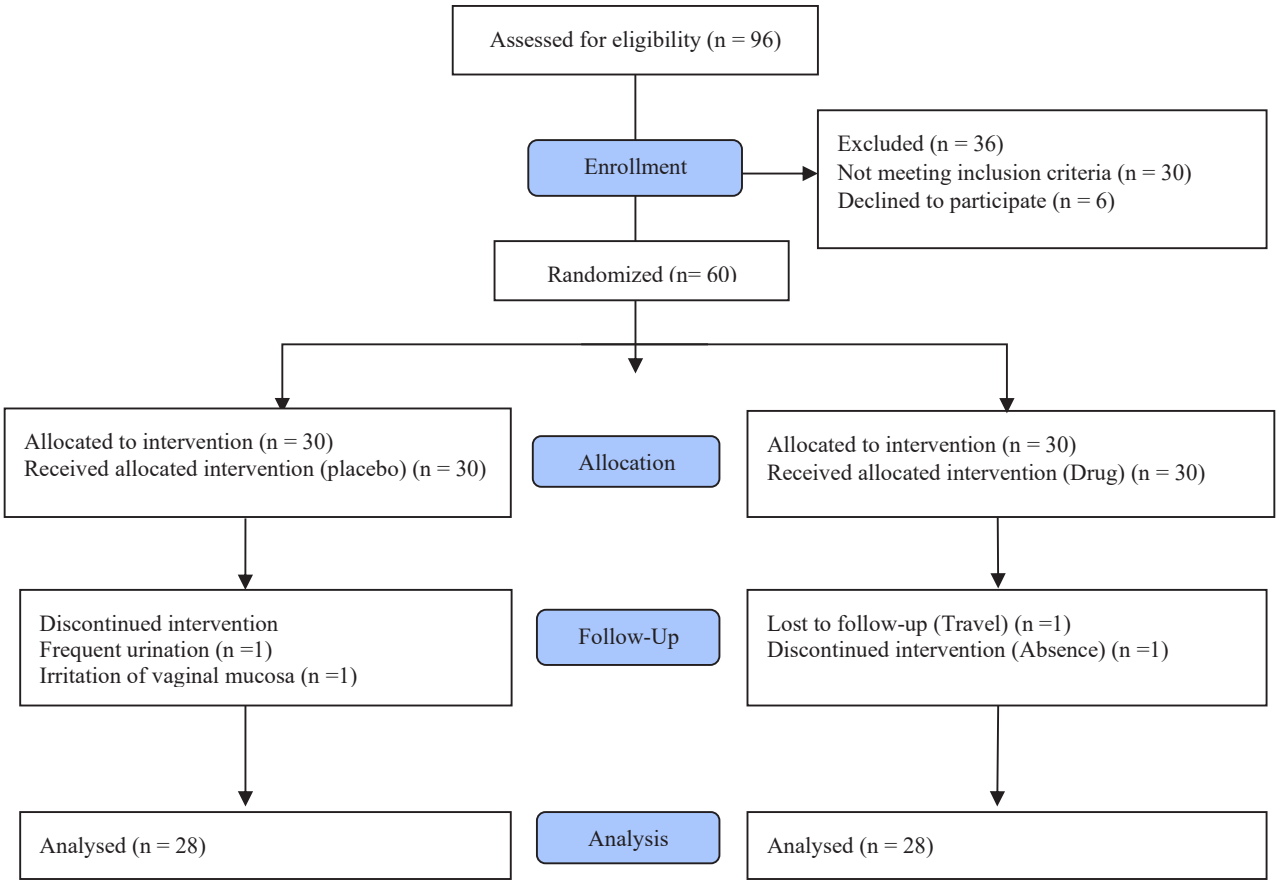

Figure 1. CONSORT flow diagram of study

Table 1. Baseline characteristic of patients

Variable		Treatment N (%)	Placebo N (%)	P value
Education level	Elementary	2(25%)	6(75%)	0.082[a]
	Secondary	6(50%)	6(50%)	
	High school	12(75%)	4(25%)	
	University	8(40%)	12(60%)	
Occupat--ion	Housewife	19(59.4%)	13(40.6%)	0.105[b]
	Employed	9(37.5%)	15(62.5%)	
Exercise	Athlete	20(61.8%)	12(38.2%)	0.001[a]
	Sedentary	8(34.6%)	16(65.4%)	
The cause of menopause	Normal	19(42.9%)	26(57.1%)	0.019[b]
	Hysterectomy	9(81.8%)	2(18.2%)	
Age (Year)		56.60±5.48	54.56±5.89	0.172[C]
BMI[e]		27.39±3.87	26.58±3.95	0.520[d]
Number of intercourse (per month)		3.30±1.80	4.23±2.03	0.112[d]
Duration of menopause (Year)		10.63±5.65	7.27±5.88	0.044[d]

a: Fisher's exact test

b: Chi-square test

c: Independent t-test

d: Mann-Whitney

e: Body Mass Index test

Table 2. Comparison of vaginal maturation value (VMV) before and after intervention

Variable		Group	Before	After	P-value	Mean Difference	P value
VMI[a]	Superficial	Treatment	9.46±6.16	15.46±6.39	0.0001[d]	6.00±4.81	0.002 [c]
		placebo	17.50±14.37	17.57±14.54	0.864[d]	0.07±1.71	
	Intermediate	Treatment	61.86±21.99	61.50±19.10	0.71[d]	-0.35±6.84	0.854 [c]
		placebo	46.07±18.58	47.61±19.36	0.109[d]	1.43±5.44	
	Basal	Treatment	28.86±23.33	23.21±19.92	0.001[d]	-5.64±7.28	0.003 [c]
		placebo	36.43±25.42	35.18±25.60	0.291[d]	-1.25±5.39	
VMV[b]		Treatment	40.30±13.27	46.39±11.27	0.0001[d]	6.08±5.62	0.012 [c]
placebo			40.21±18.36	41.11±18.61	0.122[d]	0.89±3.47	

a: Vaginal Maturation Index
b: Vaginal Maturation value
c: ANCOVA
d: Wilcoxon

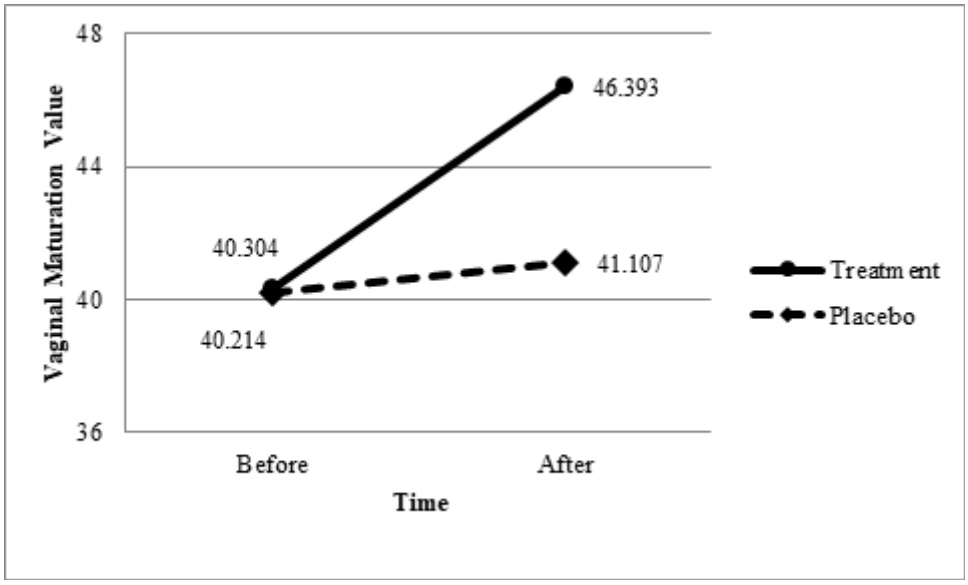

Figure 2. Comparison of vaginal maturation value before and after intervention

placebo groups at the beginning and end of the study. The results indicated a significant difference between the mean score of irritation, itching, dyspareunia, and bleeding in the treatment and placebo groups at baseline, so comparing the mean scores between the two groups after the intervention was not appropriate. Rather, the difference between the mean before and after the intervention in the groups should be the decision criterion. In the treatment group, the mean dryness score decreased to 49.18 (P value < 0.0001), also in the placebo group it decreased to 12.32 (P value < 0.001). Irritation, itching, dyspareunia, and bleeding were significantly reduced in the treatment group compared to the placebo group (Table 3).

Discussion

Medicinal plants are widely regarded as a viable alternative to chemical drugs. The use of herbs in the treatment of dry mucous membranes has been common since ancient times due to their minor side effects, naturalness, and low cost [37]. To the best of our knowledge, this study is the first randomized placebo-controlled trial on the effect of aqueous extract of *Alcea* flowers in postmenopausal women with vaginal atrophy. The results of this study showed that *Alcea* vaginal suppository had notable advantages over placebo in treatment of vaginal atrophy. As explained, during menopause, vaginal moisture is reduced due to decreased estrogen hormone secretion [7]. Blood

supply to the genitourinary tract is decreased, causing symptoms such as vaginal dryness and dyspareunia [8]. Due to the contraindications of hormone therapy, many postmenopausal women use alternative therapies to treat menopausal symptoms.

A. angulata is one of the medicinal plants that has been consumed in Iran [38,39]. It has been used to treat cough, fever, eczema, and inflammation [27]. *Althaea* and *Alcea*, commonly known as "*khatmi*" in manuscripts of TPM, belong to the Malvaceae family [29]. The extract of *Althaea* and *Alcea* has been approved by Commission E to treat bronchitis, cough, gastritis, and oral or pharyngeal irritation [28,40]. The other *Alcea* activities include: anti-tussive [41], anti-bacterial [42], anti-fungal [43], anti-viral [44], and repair of DNA damage caused by UV-A [45].

The *Alcea* has been known since ancient times, and "Pedanius Dioscorides" the author of "Materia Medica" or "Hashayesh", (40-90 AD) has described it [46].

Table 3. Comparison of vaginal atrophy symptoms before and after intervention

Variable	Group	Before	After	P Value	Mean Difference	P Value
Dryness	Treatment	73.75±18.44	24.57±17.86	0.0001 [a]	49.17±17.56	0.0001 [c]
	Placebo	66.25±21.56	53.92±19.12	0.001 [b]	12.32±10.49	
Irritation	Treatment	52.32±36.06	19.64±20.08	0.0001 [a]	32.67±25.65	0.0001 [c]
	Placebo	33.4±31.65	26.9±25.83	0.001 [b]	6.51±8.43	
Itching	Treatment	13.04±22.17	3.92±8.75	0.007 [a]	9.11±15.75	0.037 [c]
	Placebo	5.04±14.13	3.2±8.52	0.142 [b]	1.83±5.95	
Dyspareunia	Treatment	65±30.49	20.18±18.48	0.0001 [a]	44.82±23.23	0.0001 [c]
	Placebo	33.75±27.75	24.82±25.91	0.001 [a]	8.93±6.71	
Bleeding	Treatment	5.71±10.6	0.71±2.62	0.007 [a]	5.00±9.13	0.120 [c]
	Placebo	1.43±5.86	0.54±2.08	0.180 [b]	0.89±3.86	

a: Wilcoxon
b: paried t-test
c: ANCOVA

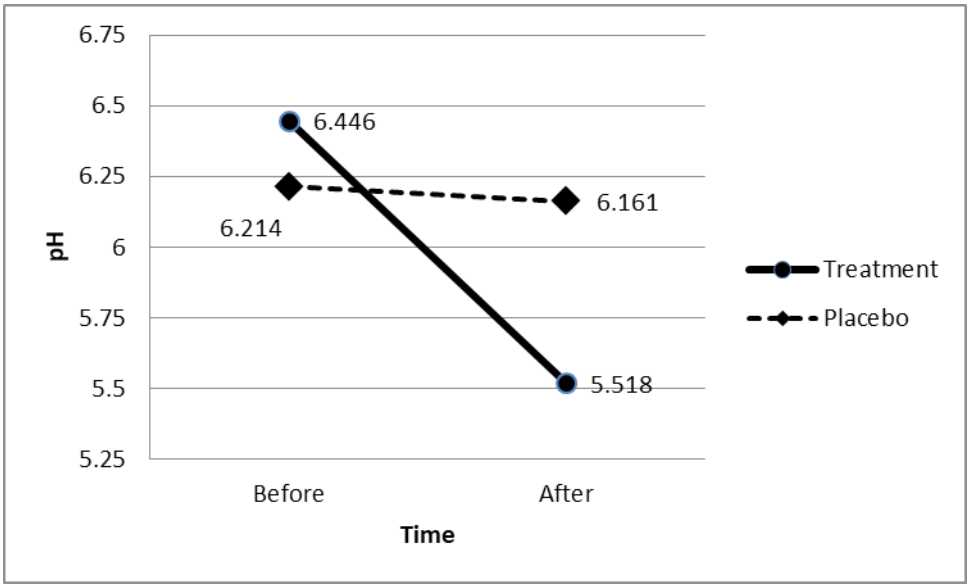

Figure 3. Comparison of vaginal pH before and after intervention

Phytochemical investigations revealed that the whole part of *Alcea* contains a mucilage, scopoletin, phenolic acid, and flavonoids [47]. Therefore, the presence of the anti-inflammatory components and mucilage in the *Alcea* extract can render the *Alcea* suppository a potential source to reduce dryness.

This study was performed as a non-hormonal treatment method in postmenopausal women with complaints of vaginal atrophy. Data on the effects of vaginal suppository are described separately in our study. All of the symptoms were significantly reduced in the *Alcea* group.

Emamverdikhan et al. [48] showed that the symptoms of vaginal atrophy, were decreased with vitamin E suppository and estrogen vaginal cream. But, due to the difference in the shape of the drug, it could not be blinded. The mean of VMV in the vitamin E group increased from 43.78 ± 13.75 to 80.59 ± 19.23, and in the estrogen cream group increased from 42.86 ± 14.40 to 91.57 ± 14.10 ($p < 0.001$). But, in this study the mean of VMV increased in the *Alcea* group from 40.30 ± 13.27 to 46.40 ± 11.27, ($p < 0.0001$) compared to the placebo group, which increased from 40.21 ± 18.36 to 41.11 ± 18.61, ($p < 0.122$).

Vaginal pH in the vitamin E group decreased from 8.38 ± 1.02 to 6.61 ± 1.83 ($p < 0.001$), compared to the estrogen group decreased from 8.07 ± 0.97 to 5.26 ± 1.21 ($p < 0.001$). But in the present study the vaginal pH significantly decreased in the *Alcea* group, from 6.45 ± 0.92 to 5.52 ± 0.62, ($p < 0.0001$) compared to the placebo group, which decreased from 6.21 ± 0.92 to 6.16 ± 0.85, ($p < 0.257$).

Although vitamin E suppository and estrogen cream have been shown to improve vaginal maturation, vaginal acidity, and clinical symptom better than *Alcea* suppository, the hydrating property of aqueous extract of *Alcea* has been able to reduce both clinical symptoms and alter vaginal acidity and vaginal maturity for improvement compared with placebo, although the ability of *Alcea* suppository less than vitamin E suppository, and estrogen cream, have been reported.

No serious adverse events were recorded during the intervention. In the *Alcea* group, brief side effects were reported: irritation of the vaginal mucosa (probably due to suppository allergies) and frequent urination (possibly due to the moisturizing properties of *Alcea* extract).

Alcea vaginal suppository, with its moisture mechanism and by hydration of the vaginal epithelium, could reduce menopausal symptoms in women with low estrogen levels and in patients who had hysterectomy and oophorectomy. Further clinical trials with larger populations, and longer duration and comparison with estrogen as the control group are recommended for more definitive results.

The limitation of this study was the lack of follow-up of patients after the end of treatment. Hence, we cannot report recurrence. Also, the age group participating in the study was less willing to participate in such studies due to shame and shyness.

It is recommended that the effect of *Alcea* extract to be investigated in premenopausal ages. Also, vaginal products in the form of gel should be examined in future studies.

Conclusions

Although *Alcea* vaginal suppository was unsuccessful in the definitive treatment of vaginal atrophy, it had a beneficial effect to reduce the symptoms of vaginal atrophy on postmenopausal women, so it can be suggested as an alternative treatment for this condition.

Conflict of Interests

There is no conflict of interest.

Acknowledgments

This study was conducted as a postgraduate thesis supported by the Clinical Research Development Unit (CRDU), Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran. This paper is a part of a Ph.D. student dissertation. We want to thank Leila Vaezzadeh, Dr. Lida Jarahi, Dr. Jalal Mirmousavi, and Mashhad University of Medical Sciences and Gynecology Clinic Umm al-Banin hospital in Mashhad.

References

[1] Kingsberg S, Kellogg S, Krychman. Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy. Int J Womens Health 2009;1:105-111.

[2] Novak E. Berek & Novak's Gynecology. Lippincott Williams & Wilkins 2007.

[3] Castelo-Branco C, Biglia N, Nappi RE, Schwenkhagen A, Palacios S. Characteristics of post-menopausal women with genitourinary syndrome of menopause: Implications for vulvovaginal atrophy diagnosis and treatment selection. Maturitas 2015;81:462-469.

[4] Cagnacci A, Gallo M, Gambacciani M, Lello S. Correction to: joint recommendations for the diagnosis and treatment of vulvo-vaginal atrophy in women in the peri- and post-menopausal phases from the Societa Italiana per la Menopausa (SIM) and the Societa Italiana della Terza Eta (SIGiTE). Minerva Ginecol 2019;71:345-352.

[5] Palma F, Xholli A, Cagnacci A. The most bothersome symptom of vaginal atrophy: evidence from the observational AGATA study. Maturitas 2018;108:18-23.

[6] Nappi RE, Palacios S, Particco M, Panay N. The REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey in Europe: country-specific comparisons of postmenopausal women's perceptions, experiences and needs. Maturitas 2016;91:81-90.

[7] Rahn DD, Carberry C, Sanses TV, Mamik MM, Ward RM et al. Vaginal estrogen for genitourinary syndrome of menopause.

Obstet Gynecol 2014;124:1147-1156.
[8] Kelley C. Estrogen and its effect on vaginal atrophy in post-menopausal women. Urol Nurs 2007;27:40-45.
[9] Palacios S. Managing urogenital atrophy. Maturitas 2009;63:315-318.
[10] Yörük P, Uygur M, Erenus M, Eren F. The role of vaginal maturation value assessment in prediction of vaginal pH, serum FSH and E2 levels. Marmara Med J 2006;19:52-57.
[11] Menopause NAMSJ. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007;14:355-369.
[12] Rad P, Tadayon M, Abbaspour M, Latifi SM, Rashidi I, et al. The effect of vitamin D on vaginal atrophy in postmenopausal women. Iran J Nurs Midwifery Res 2015;20:211-215.
[13] Golmakani N, Parnan Emamverdikhan A, Zarifian A, Sajadi Tabassi SA, Hassanzadeh M. Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial. Int Urogynecol J 2019;30:831-837.
[14] Parnan Emamverdikhan A, Golmakani N, Sharifi Sistani N, Shakeri MT, Hasanzade Mofrad M, et al. Comparing two treatment methods of vitamin E suppository and conjugated estrogen vaginal cream on the quality of life in menopausal women with vaginal atrophy. 2014;2:253-61.
[15] Parnan Emamverdikhan A, Golmakani N, Tabassi SA, Hassanzadeh M, Sharifi N, et al. A survey of the therapeutic effects of Vitamin E suppositories on vaginal atrophy in postmenopausal women. Iran J Nurs Midwifery Res 2016;21:475-481.
[16] Ziagham Z, Abbaspoor Z, Abbaspour M. The comparison between the effects of hyaluronic acid vaginal suppository and vitamin E on the treatment of atrophic vaginitis menopausal women. J Arak Uni Med Sci 2012;15:57-64.
[17] Van der Laak JA, de Bie LM, de Leeuw H, de Wilde PC, Hanselaar A. The effect of Replens® on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. J Clin Pathol 2002;55:446-451.
[18] Beck V, Rohr U, Jungbauer A. Phytoestrogens derived from red clover: an alternative to estrogen replacement therapy? J Steroid Biochem Mol Biol 2005;94:499-518.
[19] Yaralizadeh M, Abedi P, Najar S, Namjoyan F, Saki A. Effect of foeniculum vulgare (fennel) vaginal cream on vaginal atrophy in postmenopausal women: a double-blind randomized placebo-controlled trial. Maturitas 2016;84:75-80.
[20] Saffari M. Comparison effects of fenugreek extract vaginal cream and ultra low dose vaginal estrogen on atrophic vaginitis [PhD thesis]. School of Nursing and Midwifery, Tabriz University of Medical Sciences, Iran; 2019.
[21] Di Donato V, D'Oria O, Scudo M, Prata G, Fischetti M, et al. Safety evaluation of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy: a prospective observational study. Maturitas 2020;135:34-39.
[22] Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010;26:404-412.
[23] Lima SMRR, Yamada SS, Reis BF, Postigo S, da Silva MALG, et al. Effective treatment of vaginal atrophy with isoflavone vaginal gel. Maturitas 2013;74:252-258.
[24] Parsons A, Merritt D, Rosen A, Heath III H, Siddhanti S, et al. Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstet Gynecol 2003;101:346-352.
[25] Qaraaty M, Kamali SH, Dabaghian FH, Zafarghandi N, Mokaberinejad R, et al. Effect of myrtle fruit syrup on abnormal uterine bleeding: a randomized double-blind, placebo-controlled pilot study. DARU J Pharm Sci 2014;22:45.
[26] Talebi M, Zarshenas M, Yazdani E, Moein M. Preparation and evaluation of possible antioxidant activities of Rose traditional tablet "[Qurs-e-Vard]" a selected Traditional Persian Medicine [TPM] formulation via various procedures. Curr Drug Discov Technol 2021;18:8.
[27] Avicenna. The Canon of Medicine: Great Books of the Islamic World 1999.
[28] Jean B. Pharmacognosie, phytochimie, plantes médicinales. 4th ed. Lavoisier 2009.
[29] Mozaffarian V. Identification of Medicinal and Aromatic Plants of Iran 2013.
[30] Ziagham S, Abbaspour Z, Abbaspour MR. The comparison betweenthe effects of hyaluronic acid vaginal suppository and vitamin E on the treatment of atrophic vaginitis in menopausal women. J Arak Uni Med Sci 2012;15:57-64.
[31] Nikakhtar Z, Hasanzadeh M, Hamedi SS, Najafi MN, Feyzabadi Z, et al. The efficacy of vaginal suppository based on myrtle in patients with cervicovaginal human papillomavirus infection: a randomized, double-blind, placebo trial. Phytother Res 2018;32:2002-2008.
[32] Abass H, Kamel R, Abdelbary A. Metronidazole bioadhesive vaginal suppositories: formulation, in vitro and in vivo evaluation. Int J Pharm Pharm Sci 2012;4:344-355.
[33] Yazdani E, Talebi M, Zarshenas M, Moein M. Evaluation of possible antioxidant activities of barberry solid formulation, a selected formulation from Traditional Persian Medicine (TPM) via various procedures. Biointerface Res Appl Chem 2019;9:4517-4521.
[34] Hamedi S, Shams-Ardakani MR, Sadeghpour O, Amin G, Hajighasemali D, et al. Designing mucoadhesive discs containing stem bark extract of Ziziphus jujuba based on Iranian traditional documents. Iranian J Basic Med Sci 2016;19:330-336.
[35] Pharmacopeia U. US Pharmacopeial Convention United States Pharmacopeial Convention. Rockville 2014.
[36] Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric 2010;13:132-140.
[37] Goudarzi M, Mehrabadi ME, Salemi Z, Amri J, Noori M, et al. Effect of hydroalcoholic extract of allium noeanum Reut. ex Regel on ethylene glycol-induced kidney stone in male wistar rats. Trad Integr Med 2021;6:184-192.
[38] Pakravan M. Fora of Iran. Research Institute of Forests and Rangelands. Tehran 2008.
[39] Pakravan M, Ghahraman A. New species and new records of *Alcea* for the flora of Iran. 2002.
[40] Deters A, Zippel J, Hellenbrand N, Pappai D, Possemeyer C, et al. Aqueous extracts and polysaccharides from Marshmallow roots (Althea officinalis L.): cellular internalisation and stimulation of cell physiology of human epithelial cells in vitro. J Ethnopharmacol 2010;127:62-69.
[41] Nosal'ova G, Strapkova A, Kardosova A, Capek P, Zathurecký L, et al. Antitussive action of extracts and polysaccharides of

marsh mallow (Althea officinalis L., var. robusta). Die Pharmazie 1992;47:224-226.
[42] Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with anticancer activity (part 1). Int J Pharm 2015;5:104-124.
[43] Al-Snafi AE. The pharmaceutical importance of *althaea* officinalis and *althaea* rosea: a review. Int J Pharmtech Res 2013;5:1378-1385.
[44] Kumar SS, Sudhakar S, Kapil S, Snigdha T. Ethno-pharmacological review on *Althaea* officinalis. World J Pharm Pharm Sci 2016;5:425-432.
[45] Curnow A, Owen SJ. An evaluation of root phytochemicals derived from althea officinalis (Marshmallow) and astragalus membranaceus as potential natural components of UV protecting dermatological formulations. Oxid Med Cell Longev 2016;2016:7053897.
[46] Osbaldeston TA, Wood RP. Dioscorides: De materia medica. A new indexed translation in modern EnglishIbidis Press. Johannesburg 2000.
[47] Kianitalaei A, Feyzabadi Z, Hamedi S, Qaraaty M. *Althaea* officinalis in traditional medicine and modern phytotherapy. J Adv Pharm Educ Res 2019;9:154-161.
[48] Emamverdikhan AP, Golmakani N, Tabassi SA, Hassanzadeh M, Sharifi N, et al. A survey of the therapeutic effects of Vitamin E suppositories on vaginal atrophy in postmenopausal women. Iran J Nurs Midwifery Res 2016;21:475-481.