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Effect of *Foeniculum vulgare* (fennel) vaginal cream on vaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled trial

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ABSTRACT

Objective: Vaginal atrophy is one of the main concerns of postmenopausal women. The aim of the present study was to investigate the effect of fennel vaginal cream on vaginal atrophy in postmenopausal women in Ahvaz, Iran.
Materials and methods: This double-blind randomized controlled trial was conducted on 60 postmenopausal women (45–65 years of age) in Ahvaz, Iran. The study participants were randomly divided into one of two groups, receiving either a placebo ($n = 30$) or fennel 5% vaginal cream ($n = 30$) administered as one application per day (5 g/day) for 8 weeks.
Main outcome: The vaginal pH and maturation vaginal index (MVI) were measured at baseline and 8 weeks after the intervention, while the vaginal atrophy symptoms was measured at baseline and at 2, 4, and 8 weeks after the intervention. The data were analyzed using the independent *t*-test, chi-square test, paired sample *t*-test, and the generalized estimating equation.
Results: The number of superficial cells increased significantly in the fennel group after 8 weeks compared to the control group (76.1 ± 15.3 vs. 11.8 ± 8, $p < 0.001$). The number of intermediate and parabasal cells decreased significantly in the fennel group compared to the control group ($p < 0.001$). The vaginal pH decreased significantly at the 8-week follow-up in the fennel group compared to the control group (100% vs. 7.4%, $p < 0.001$). All women in the fennel group had an MVI of 65–100 at the 8-week follow-up, whereas almost half (40.7%) of the women in the control group had an MVI of 50–64 ($p < 0.001$).
Conclusion: According to results of this study, fennel is an effective means to manage the symptoms of vaginal atrophy in postmenopausal women and is devoid of side effects. Larger studies are necessary to confirm the positive impact of fennel for vaginal conditions occurring among postmenopausal women.

1. Introduction

Vaginal atrophy is a common condition that occurs among postmenopausal women due to reductions in the estrogen levels [1]. Vaginal atrophy affects approximately 40% of the postmenopausal women globally [2]. In a large cohort study, the prevalence of vaginal atrophy ranged from 27% to 55% [3]. The signs and symptoms of atrophic vaginitis include pale epithelium, dryness of the labia and vagina, inflammation, petechiae, and increased friability [4]. Vaginal atrophy is usually diagnosed by laboratory tests such as the Papanicolaou smear, measuring the level of endogenous hormones, and determining vaginal pH, because the vaginal pH levels may increase by >5 units [4]. Vaginal atrophy may negatively influence the quality of life for postmenopausal women. In an international study involving 4246 middle-aged women, the results showed that 39% of postmenopausal women had moderate to severe symptoms of vaginal atrophy and 42% did not have any information about the treatments for vaginal atrophy. More than 50% of women with vaginal atrophy stated that the condition negatively affects their quality of life [5].

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According to the North American Menopause Society, vaginal moisturizing, continued sexual activity, and vaginal lubricants are first-line treatment for vaginal atrophy [6]. Some women need local hormone replacement therapy with estrogen to alleviate the symptoms of vaginal atrophy [7]. However, the effects of local estrogen on the endometrium after a year of use has not been studied in randomized controlled trials. The safety of local estrogen use by survivors of breast cancer is also not clear [8].

Many women seek relief from vaginal atrophy by using alternative medicine because they fear the risks associated with hormone replacement therapy. The use of herbal and other complementary medical treatments has increased in many countries over the past decade. Multiple surveys have shown that women, particularly middle-aged women, and women with high levels of education and income, are more likely to be use alternative medicine [9].

Phytoestrogens can reduce the severity of menopausal symptoms, such as vasomotor issues, vaginal atrophy, sleep quality, and bone tissue metabolism [10]. One source of phytoestrogens is *Foeniculum vulgare* (fennel), which is an annual plant that belongs to the Umbelliferae (Apiaceae) family [11].

Foeniculum vulgare is a popular medicinal plant possessing various pharmacological actions that have been mentioned in traditional Iranian medicine and modern phytotherapy. This herb has shown antioxidant, cytotoxicity, anti-inflammatory, antimicrobial, bronchodilation, estrogenic, diuretic, lithontriptic, galactagogic, emmenagogic, antithrombotic, hypotensive, gastroprotective, hepatoprotective, memory enhancement, and ant-mutagenic activities [12].

Iranian women tend to reach menopause at a younger age than women in other countries. A study on 804 women in Northern Iran found that the mean age of menopause was 47.6 ± 4.45 years [13], while the age of menopause is 50.8 years in European countries [14].

There is no data regarding the effects of fennel on vaginal atrophy among postmenopausal women. Therefore, in this study, we aimed to determine the effects of fennel vaginal cream on vaginal atrophy in a sample of postmenopausal women from Ahvaz, Iran.

2. Materials and methods

This double-blind placebo-controlled randomized trial containing two groups was conducted on 60 postmenopausal women in Ahvaz, Iran. The Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences approved the design of the study (ethical code: ajums.REC.1393.249). The protocol of the study was registered in the Iranian Registry for Randomized Controlled Trials (reference number: IRCT2014102919743N1). This study started in January 2015 and ended in June 2015. The inclusion criteria required that the participants age be between 45 and 65 years; had natural menopause confirmed by amenorrhea for at least 12 months or by the elevation of FSH and LH in laboratory tests; had symptoms of vaginal atrophy; engaged in sexual activity; and were monogamous. The exclusion criteria included vaginal infection, hormonal use during the 8 weeks prior to the study, smoking, alcohol use, uterine bleeding from unknown causes, and phytoestrogen use in the past month.

An informed written consent was obtained from each participant prior to data collection. Eligible women were randomly assigned into two groups receiving either fennel 5% vaginal cream (5 g/day) ($n = 30$) or placebo ($n = 30$) for 8 weeks. All women in the study received the same basic information about the research.

The following equation was used to calculate sample size [15]:

$$n = \frac{\left(s_1^2 + s_2^2\right)}{\left(\bar{x}_1 - \bar{x}_2\right)^2}\left(z_{1-\frac{\alpha}{2}} + z_{\beta}\right)^2$$

In this equation, $\alpha = 0.05$, $\beta = 0.1$, $1 - \beta = 90\%$, $P = 3.3\%$, $p = 36\%$, and $n = 26$. The power of the study was set to 90%. We added 20% for attrition, and the total number of individuals in each sample group was calculated to be 30.

2.1. Production of fennel vaginal cream

Both the fennel and placebo creams were manufactured in the laboratory of the Pharmacy School of Ahvaz Jundishapur University of Medical Sciences. In order to make an extract of fennel, fennel seeds were mixed with ethanol 80% and stored for 72 h. The extract was then dried using a rotary and freeze dryer. The extract was kept in the refrigerator, away from light, until the time of formulation. Dried fennel extract was mixed with 5% final concentration with oil in water (O/W) emulsion cream base. Stearic acid, spermaceti, glycerin and water were selected for base formulation. In the oil phase stearic acid and spermaceti were mixed and heated to be melted in 70 °C. Glycerin and water were mixed and heated to the same temperature, as the aqueous phase. The aqueous phase was added to oily phase and mixed with continuous stirring until cooling. As preservative, propyl paraben and methyl paraben were added to oil and aqueous phases, respectively. During this period, the required amounts of the herbal extracts (5%) were added with constantly stirring.

The fennel extract was mixed with an appropriate carrier and made with a concentration of 5%. The fennel and placebo creams were tested for acidity, uniformity, and liquidity. The placebo cream was manufactured using the appropriate carrier with a similar color and appearance to the fennel cream.

2.2. Randomization

Women who met the inclusion criteria were randomly assigned into one of the two groups: fennel ($n = 30$) and placebo ($n = 30$). The vaginal creams were provided two codes by the pharmacologist, one (A) for fennel and one (B) for placebo. The researcher who distributed the vaginal creams was unaware of these codes.

2.3. Intervention

Participants were randomly allocated into one of the two groups, receiving either placebo or fennel 5% vaginal cream, one application per day (5 g/day) for 8 weeks. Each participant received a checklist to record their daily usage of cream and to note if they had any side-effects. The participants were also requested to bring in their empty tubes to ensure correct usage. Each participant received at least 8 tubes of fennel or placebo during the study period (each for 1 week).

2.4. Outcome measures

A questionnaire was designed to measure the socio-demographic characteristics of the participants. The symptoms of vaginal atrophy were evaluated using a checklist. In order to evaluate vaginal atrophy, each participant was asked whether they had symptoms such as vaginal dryness, vaginal itching, burning, and dyspareunia. Vulvar or vaginal paleness during the physical examination also was recorded. These signs and symptoms were subsequently classified as follows: none = 0, mild = 1, moderate = 2, and severe = 3. Each participant was assessed for atrophy symptoms at baseline, and during weeks 2, 4, and 8 of the study. These assessments were performed by a midwife who was not aware of the intervention conditions of the participants.

In order to assess the vaginal cytology, a vaginal smear was taken, and the numbers of cells in each category were counted at baseline and at 8 weeks after the intervention. The samples were

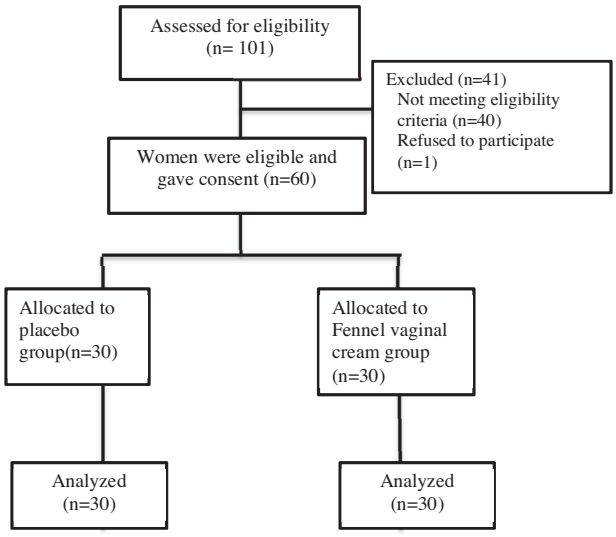

Fig. 1. Flow diagram of recruitment and retention of participants in the study.

obtained from the vaginal mucosa by rotating a special brush (Viba Brush; Rovers BV, Oss, Netherlands) near the posterior fornix of the vagina. Smears were then put on a glass slide and fixed with Spray-Cyte immediately. All vaginal smears were stained using the Papanicolaou procedure and analyzed at the reference laboratory (Noor) in Ahvaz, Iran.

The vaginal samples were used to determine the maturation index, which describes the proportion of parabasal, intermediate, and superficial cells. The vaginal maturation index has a range of 0–100. The maturation value (MV) was calculated according to the following equation:

$MV = (0 \times \%\,\text{parabasal cells}) + (0.5 \times \%\,\text{intermediate cells}) + (1.0 \times \%\,\text{superficial cells})$ [16].

Vaginal pH was measured at baseline and at 8 weeks after the intervention using pH meter strips (Macherey Nagel, Germany). In order to measure the vaginal pH, a speculum was inserted in the vagina. The indicator strip was inserted in the lateral vaginal fornix and placed there for at least 60 s by an investigator. The color changes were recorded according to the indicators on the strips.

2.5. Statistics

All data were entered using the SPSS version 22. The Kolmogorov–Smirnov test was used for testing the normal distribution. The independent *t*-test and chi-square test were used to compare differences between the two groups for continuous and categorical data. The paired sample *t*-test was used to evaluate the differences in the means within each group. The generalized estimating equation was implemented to assess the treatment effects on the symptoms of vaginal atrophy.

3. Results

In this randomized controlled trial, 60 postmenopausal women were recruited and assigned randomly to receive either fennel 5% or placebo cream for vaginal atrophy. No participants withdrew during the study or prior to the 8-week follow-up (Fig. 1). The mean ages of the participants in the fennel and placebo groups were 53.73 ± 3.6 and 52.90 ± 3.4 years, respectively. The mean ages of menopause onset were 49.5 ± 1.99 and 49 ± 1.9 years in the fennel and placebo groups, respectively. The two groups did not show any significant differences with regard to the socio-demographic characteristics (Table 1).

Table 1
Socio-demographic characteristics of participants in the fennel and control groups.

Variables	Fennel ($n=30$) Mean ± SD or *N* (%)	Control ($n=30$)	*p* value
Age (year)	53.73 ± 3.6	52.90 ± 3.4	0.366
Age of menopause (year)	49.53 ± 1.99	49.03 ± 1.90	0.325
Body mass index (kg/m^2)	24.65 ± 3.9	23.46 ± 3.29	0.209
Education			
High school	20(66.7%)	16(53.3%)	0.509
Diploma	7(23.3.%)	8(26.7%)	
University education	3(10%)	6(20%)	
Job			
Employee	5(16.7%)	4(13.3%)	0.59
Housewife	23(76.7%)	21(70%)	
Retired	2(6.7%)	5(16.7%)	
Economic situation			
Low	9(30%)	11(36.7%)	0.83
Moderate	14(46.7%)	12(40%)	
High	7(23.3%)	7(23.3%)	
Number of intercourses per week			
0	2(6.7)	3(10)	0.94
1	13(43.3)	12(40)	
2	6(20)	7(23.3)	
3	7(23.3)	5(16.7)	
4	2(6.7)	3(10)	

The number of superficial cells increased in the fennel group after 8 weeks as compared to the control group (76.1 ± 15.3 vs. 11.8 ± 8, $p < 0.001$; Table 2). The number of intermediate and parabasal cells decreased significantly in the fennel group as compared to the control group ($p < 0.001$).

Table 3 demonstrates that after the 8-week intervention, participants in the fennel group showed significant improvements in symptoms, including itching (100% without itching in the fennel group compared to 43.3% in the control group, $p = 0.017$), dryness (100% without dryness in the fennel group vs. 3.3% in the control group, $p < 0.001$), pallor (100% vs. 0% without pallor in the fennel and control groups respectively, $p < 0.001$), and dyspareunia (93.3% without dyspareunia in the fennel group compared to 0% in the control group, $p < 0.001$). Despite the improvement in the burning symptoms of the fennel group, this difference was not significant ($p = 0.14$). The vaginal pH decreased significantly at the 8-week follow-up in the fennel group compared to the control group (100% vs. 7.4%, $p < 0.001$). All women in the fennel group had maturation vaginal index (MVI) values of 65–100 at the follow-up, but only 40.7% in the control group had MVI levels of 50–64 ($p < 0.001$) (Table 4). No adverse effects were reported during the study period in either group.

4. Discussion

This study was conducted in order to investigate the effects of fennel vaginal cream on vaginal atrophy among postmenopausal women. Based on the results of this study, fennel vaginal cream could improve vaginal cytology, decrease vaginal pH, and reduce the symptoms of vaginal atrophy such as itching, pallor, dryness, and dyspareunia. We could not find any previous study that assessed the effects of fennel on vaginal atrophy. However, because an active biological compound in fennel is phytoestrogen [17], we referred to studies that assessed the phytoestrogen effects on vaginal atrophy. Phytoestrogens are plant compounds with estrogen-like properties. The two major classes of phytoestrogens are isoflavones and lignans; soybeans are rich in isoflavones, and lignans are found in flaxseed, whole grains, legumes, fruits, and vegetables. The chemical structures of isoflavones and lignans are similar to those of estradiol [18]. Although, the effect of phytoestrogen on menopausal complications such as hot flashes are

Table 2
Comparison of vaginal cytology at baseline and 8 weeks after intervention in the fennel and control groups.

Variables	Fennel ($n=30$)		Control ($n=30$)		p value between group
	Mean ± SD				
	Before	After	Before	After	
Superficial p value within group	6.3 ± 6.8 <0.001	76.1 ± 15.3	6.2 ± 4.4 <0.001	11.8 ± 8	<0.001
Intermediate p value within group	67.8 ± 16.8 <0.001	21.2 ± 15.2	75.2 ± 8.7 0.57	75.2 ± 8.9	<0.001
Parabasal p value within group	25.9 ± 11.2 <0.001	2.3 ± 2.5	20 ± 6.9 <0.001	12.7 ± 6.6	<0.001

Table 3
The symptoms of vaginal atrophy at baseline, 2, 4 and 8 weeks after intervention in fennel and placebo groups.

Variables	Fennel (n= 30)				Control ($n=30$)				B (SE)
	N (%)								
	Weeks								
	Base	2nd	4th	8th	Base	2nd	4th	8th	
Burning									
None	5(16.7)	10(33.3)	15(50)	29(96.7)	7(23.3)	7(23.3)	7(23.3)	8(26.7)	0.55(0.37)[a]
Mild	6(20)	6(20)	15(50)	1(3.3)	15(50)	15(50)	14(46.7)	14(46.7)	
Moderate	6(20)	14(46.7)	0	0	7(23.3)	7(23.3)	8(26.7)	7(23.3)	
Severe	13(43.3)	0	0	0	1(3.3)	1(3.3)	1(3.3)	1(3.3)	
Itching									
None	6(20)	11(36.7)	28(93.3)	30(100)	9(30)	9(30)	13(43.3)	15(50)	0.84(0.35)[*]
Mild	13(43.3)	16(53.3)	2(6.7)	0	16(53.3)	17(56.7)	12(40)	11(36.7)	
Moderate	5(16.7)	3(10)	0	0	3(10)	2(6.7)	3(10)	2(6.7)	
Severe	6(20)	0	0	0	2(6.7)	2(6.7)	2(6.7)	2(6.7)	
Dryness									
None	1(3.3)	2(6.7)	7(23.3)	30(100)	0	0	0	1(3.3)	1.79(0.25)[**]
Mild	0	6(20)	22(73.3)	0	2(6.7)	3(10)	03(10)	4(13.3)	
Moderate	4(13.3)	21(70)	0	0	5(16.7)	15(50)	15(50)	17(56.7)	
Severe	25(83.3)	1(3.3)	0	0	23(76.7)	12(40)	12(40)	8(26.7)	
Pallor									
None	0	1(3.3)	5(16.7)	30(100)	0	0	0	0	1.92(0.38)[**]
Mild	1(3.3)	4(13.3)	24(80)	0	3(10)	3(10)	3(10)	3(10)	
Moderate	7(23.3)	9(30)	1(3.3)	0	6(20)	6(20)	6(20)	6(20)	
Severe	22(73.3)	16(53.3)		0	21(70)	21(70)	21(70)	21(70)	
Dyspareunia									
None	0	2(6.7)	20(66.7)	28(93.3)	0	0	0	0	1.79(0.25)[**]
Mild	1(3.3)	6(20)	9(30)	2(6.7)	2(6.7)	2(6.7)	3(10)	3(10)	
Moderate	3(10)	21(70)	1(3.3)	0	4(13.3)	18(60)	18(60)	22(73.3)	
Severe	26(86.7)	1(3.3)	0	0	24(80)	10(33.3)	9(30)	5(16.7)	

[a] Not significant.
[*] $p<0.05$.
[**] $p<0.001$.

studies in some studies, but their effects have been not confirmed. A meta-analysis was conducted by Chen et al., on the efficacy of phytoestrogen on menopausal symptoms. Results showed that the in the seven studies about Kupperman index (KI), data showed no significant effect in compare to the placebo. However the results of 10 studies about hot flashes showed the significant reduction in frequency of hot flashes compared to the control [19]. The positive effect of phytoestrogens on vaginal atrophy in compared with premarin or conjugated equine estrogen (CEE) in postmenopausal women have been examined and confirmed in some studies [18,20].

In a study on the effects of fennel on the cervix and vagina in ovariectomized mice, 18 rats with estimated weights of 200 g were randomized into three groups: one control group and two ovariectomized groups. One ovariectomized sample group ($n=6$) received 5 mg/kg subcutaneous estradiol daily and the other ($n=6$) received 700 mg/kg/day fennel via an intraperitoneal injection for 30 days. Microscopy results revealed that the thickness of the epithelium in the vagina and cervix increased in both of the groups that received estradiol and fennel, and significant congestion was observed in both groups as well. However, the changes in the estradiol group were more evident [21]. These results support the findings of the present study; however, because we used fennel for 8 weeks, the effects on the vagina were more evident.

A study conducted by Rasul et al., with the aim of evaluating the anti-aging effect of fennel on the skin, was conducted with 11 volunteers. In that study, a topical cream containing fennel extract was prepared and compared with a base cream. The topical fennel cream showed significant improvements on skin moisture and trans-epidermal water loss. The texture of the skin also increased significantly after 4, 8, and 12 weeks of fennel cream use [22]. The moisturizing factor of fennel is due to the linoleic acid that consists of 54.9% of fennel extracts [23]. These results also support our findings that fennel has effects that include moisturizing and keeping water in the mucus and skin.

Table 4
Results of pH and MVI of participants in two groups of fennel and placebo at baseline and 8 weeks after intervention.

Variables	Fennel ($n = 30$)		Control ($n = 30$)		p value between group
	Before	After	Before	After	
pH					
<5	0	33(100)	0	2(7.4)	<0.001
5–5.49	3(9.1)	0	3(11.1)	5(18.5)	
5.5–6.49	21(63.6)	0	11(40.7)	14(51.9)	
>6.5	9(27.3)	0	13(48.1)	6(22.2)	
MVI					
0–49	30(100)	0	30(100)	16(59.3)	<0.001
50–64	0	0	0	11(40.7)	
65–100	0	30(100)	0	0	

Lima et al. conducted a study with 60 postmenopausal women, who were treated with either isoflavone 4% vaginal gel (1 g/day) or a placebo. They found that the isoflavone gel could decrease vaginal atrophy and dyspareunia and also increased the amounts of intermediate and superficial cells [24]. These results provide further support for our findings.

4.1. Strengths and limitations of study

To the best of our knowledge, this is the first time that a study has assessed the effects of fennel on vaginal atrophy in postmenopausal women. Although in recent years, policy makers in Iran have shown increased attention to the health needs of postmenopausal women, there is no public health center for the screening and treatment of menopause-related symptoms for postmenopausal women in Iran. Many postmenopausal women believe these symptoms are normal, and therefore, do not seek treatment. The results of this study can be useful for many postmenopausal women who suffer from menopause symptoms but are not willing to use hormone therapy.

We only followed the postmenopausal women in our study for 8 weeks. Further studies with longer durations and larger sample sizes that would compare fennel to local estrogen therapy could potentially reveal more beneficial effects associated with this herb. Furthermore, this study did not measure the serum levels of estrogen, which is another possibility for future investigations. Finally, the administration of non-commercial preparations, such as fennel vaginal cream, is associated with additional risks. Non-standardized synthesis of hormonal preparations may lead to variable bioavailability and bioactivity attributed to the use of different pharmaceutical excipients, on the grounds of lacking efficacy and safety data. This subject should also be addressed in future studies.

5. Conclusion

According to results of this study, fennel is an effective therapy for vaginal atrophy in postmenopausal women, which is also devoid of the side effects. Larger studies are necessary to confirm the positive impacts of fennel on the vaginal symptoms occurring in postmenopausal women.

Ethical approval

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ethical Code: ajums.REC.1393.249). This study was registered in the Iranian Randomized Controlled Trial (IRCT2014102919743N1). All participants signed an informed consent prior to data collection.

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Authors' contributions

Masoumeh Yaralizadeh was responsible for design, data collection and writing manuscript in Persian. Parvin Abedi was responsible for design, data interpretation and writing manuscript in English. Shahnaz Najar was involved in design and interpretation of data. Foroogh Namjooyan was responsible in the production of fennel and placebo and also interpretation of data. Amal Saki was responsible for design, data analyzing and interpretation.

Conflict of interest

None.

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References

[1] D.J. Portman, M.L. Gass, Vulvovaginal Atrophy Terminology Consensus Conference Panel, Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society, Menopause 21 (2014) 1063.
[2] G.A. Bachmann, N.S. Nevadunsky, R. Wood Johnson, Diagnosis and treatment of atrophic vaginitis, Am. Fam. Physician 61 (May (10)) (2000) 3090–3096.
[3] A. Stenberg, G. Heimer, U. Ulmsten, S. Cnattingus, Prevalence of genitourinary and other climacteric symptoms in 61-year-old women, Maturitas 24 (1996) 31–36.
[4] L. Pandit, J.G. Ouslander, Postmenopausal vaginal atrophy and atrophic vaginitis, Am J. Med. Sci. 314 (1997) 228–231.
[5] R.E. Nappi, M. Kokot-Kierepa, Women's voices in the menopause: results from an international survey on vaginal atrophy, Maturitas 67 (3) (2010) 233–238.
[6] North American Menopause Society, The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 14 (3 pt. 1) (2007) 355–369.
[7] L. Cardozo, G. Bachmann, D. McClish, D. Fonda, L. Birgerson, Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the hormone and urogenital therapy committee, Obstet. Gynecol. 92 (1998) 722–727.
[8] The North American Menopause Society, Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society, Menopause 20 (9) (2013) 888–902, http://dx.doi.org/10.1097/gme.0b013e3182a122c2.
[9] M.J. Minkin, R. Maamari, S. Reiter, Postmenopausal vaginal atrophy: evaluation of treatment with local estrogen therapy, Int. J. Womens Health 6 (2014) 281–288, http://dx.doi.org/10.2147/ijwh.s57900.
[10] S. Bedell, M. Nachtigall, F. Naftolin, The pros and cons of plant estrogens for menopause, J. Steroid Biochem. Mol. Biol. 139 (2014) 225–236, http://dx.doi.org/10.1016/j.jsbmb.2012.12.004.
[11] L.M. Pastore, R.A. Carter, B.S. Hulka, E. Wells, Self-reported urogenital symptoms in postmenopausal women: women's health initiative, Maturitas 49 (4) (2004) 292–303.
[12] R. Rahimi, M.R.S. Ardekani, Medicinal properties of *Foeniculum vulgare* Mill. in traditional Iranian medicine and modern phytotherapy, Chin. J. Integr. Med. 19 (1) (2013) 73–79, http://dx.doi.org/10.1007/s11655-013-1327-0.
[13] A.A. Abdollahi, M. Qorbani, H. Asayesh, A. Rezapour, M. Noroozi, M. Mansourian, M.A. Soleimani, H. Ansari, The menopausal age and associated factors in Gorgan, Iran, Med. J. Islam Repub. Iran 27 (May (2)) (2013) 50–56.
[14] J. Dratva, F. Gómez Real, C. Schindler, U. Ackermann-Liebrich, M.W. Gerbase, N.M. Probst-Hensch, et al., Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies, Menopause 16 (March–April (2)) (2009) 385–394, http://dx.doi.org/10.1097/gme.0b013e31818aefef.

[15] S. Rosa Lima, S. yamada, B. Reis, S. Postigo, L. Antonieta, G. Silva, et al., Effective treatment of vaginal atrophy with isoflavone vaginal gel, Maturitas 74 (2013) 252–258.
[16] J.A. Van der Laak, C.P. Schijf, H.M. Kerstens, T.H. Heijnen-Wijnen, P.C. de Wilde, G.J. Hanselaar, Development and validation of a computerized cytomorphometric method to assess the maturation of vaginal epithelial cells, Cytometry 35 (March (3)) (1999) 196–202.
[17] F. Jaffary, A. Ghannadi, H. Najafzadeh, Evaluation of the prophylactic effect of fennel essential oil on experimental osteoporosis model in rats, Int. J. Pharmacol. 2 (2006) 588–592.
[18] S. Bedell, M. Nachtigall, F. Naftolin, The pros and cons of plant estrogens for menopausa, J. Steroid Biochem. Mol. Biol. 139 (January) (2014) 225–236, http://dx.doi.org/10.1016/j.jsbmb.2012.12.004.
[19] M.N. Chen, C.C. Lin, C.F. Liu, Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review, Climacteric 18 (March (2)) (2015) 260–269, http://dx.doi.org/10.3109/13697137.2014.966241.
[20] S. Jaroenporn, N. Urasopon, G. Watanabe, S. Malaivijitnond, Improvements of vaginal atrophy without systemic side effects after topical application of *Pueraria mirifica*, a phytoestrogen-rich herb, in postmenopausal cynomolgus macaques, J. Reprod. Dev. 60 (June (3)) (2014) 238–245, http://dx.doi.org/10.1262/jrd.2013-144.
[21] L. Nourman, N. Alboghobaish, H. Najafzadeh, Comparison the effect of fennel extract and estradiaol valerat on the cervix and vagina after ovarectomy in rat, The 11th Weterinary Congress (2009) http://www.civilica.com/Paper-THVC15-THVC15_764 html (in Persian).
[22] A. Rasul, N. Akhtar, B.A. Khan, T. Mahmood, S.U.Z. Zaman, H.M. Shoaid Khan, Formulation development of a cream containing fennel extract: in vivo evaluation for anti-aging effects evaluation for anti-aging effects, Pharmazie 67 (2012) 54–58, http://dx.doi.org/10.1691/ph.2012.1083.
[23] G. Singh, S. Maurya, M.P. de Lampasona, C. Catalan, Chemical constituents, antifungal and antioxidative potential of *Foeniculum vulgare* volatile oil and its acetone extract, Food Control 17 (9) (2006) 745–752.
[24] S.M. Lima, B.F. Bernardo, S.S. Yamada, B.F. Reis, G.M. da Silva, M.A. Galvão, Effects of *Glycine max* (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial, Maturitas 78 (July (3)) (2014) 205–211, http://dx.doi.org/10.1016/j.maturitas.2014.04.007.