



A Review of Pharmacological Treatments for Vaginal Atrophy in Postmenopausal Women in Iran

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Vaginal atrophy is one of the most common menopausal complications and is often overlooked. There are various pharmacological and non-pharmacological treatment approaches to reduce vaginal atrophy; however, no comprehensive study on a convenient, affordable, inexpensive, and noninvasive treatment with fewer complications has been conducted so far. Thus, the current study aimed to provide a systematic review of pharmacological treatment for vaginal atrophy in postmenopausal women in Iran. In this systematic review, all Iranian articles published in Persian or English during 2009 to 2019 were collected and analyzed by searching the Scopus, PubMed, Web of Science, Magiran, Iranian Registry of Clinical Trials (IRCT), and Cochrane Library databases. The inclusion criteria were clinical trials for vaginal atrophy and menopause. Based on the selection criteria, articles with a Jadad scale score of 3 and above were included in the study and qualitatively analyzed. Overall, 15 clinical trials met the inclusion criteria. In total, 12 articles examined the efficacy of pharmacological treatments (including three herbal medicines, three vitamins and dietary supplements, and two chemical drugs) in treating vaginal atrophy in postmenopausal women. Various types of medication have been used to improve vaginal atrophy, and effective treatments include licorice, chamomile, royal jelly, vitamin E, vitamin D, hyaluronic acid, and Vagifem; however, the results of studies on fennel have been inconsistent. However, considering the small number of studies reviewed, further studies with a stronger methodology are needed to confirm the efficacy of these medications.

Key Words: Atrophic vaginitis, Menopause, Systematic review

INTRODUCTION

Menopause is a physiological period in women's lives. Menopause with structural changes in ovarian tissue and disruption of their activity results in a decrease in the level of estrogen secretion in the body [1]. The main consequences in menopause are largely dependent on estrogen levels. Low levels of estrogen have adverse effects on the genitourinary tract and sexual function [2]. However, vaginal atrophy is one of the most important

factors affecting sexual function and the genitourinary system [3]. Vaginal atrophy is one of the most common menopausal complications associated with thinning, drying, and inflamed vaginal walls and increased vaginal pH levels [4]. It is estimated that 90% of women are affected by its symptoms such as dryness, itching, burning of urine and painful intercourse [3].

Vaginal atrophy is often overlooked and, unlike other menopausal symptoms that diminish over time, vulvovaginal symptoms are progressive and persistent

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unless they are treated [4]. However, there are various treatments to reduce vaginal atrophy [5]. Estrogen and hormone drugs have a major role in improving vaginal atrophy. Estrogen can improve menopausal complications by increasing tissue thickness, polysaccharides, and Hyaluronic acid, and maintaining the functional properties of vaginal epithelial cells [6]. However, the acceptance of treatment with hormonal drugs is low and the major cause is concern about the side effects of these drugs. Hormone drugs increase the risk of cardiovascular events, thrombosis, breast cancer, and endometrial hyperplasia, thereby increasing the tendency for alternative treatments and use of complementary therapies [7-9].

Women are more likely to seek natural replacement therapies to relieve menopause complications [8]. Therefore, it is essential to use the materials with less complications and a therapeutic effect on vaginal atrophy and at the same time less side effect. In this regard, the use of nonhormonal methods has been considered. Nonhormonal methods include the use of herbal remedies, vitamins, vaginal softeners and certain lifestyle changes that improve vaginal atrophy [10-13].

Numerous studies have been conducted on the use of chemical and herbal medicines and vitamins for the treatment of vaginal atrophy in Iran and worldwide. The results of a study in 2018 on vaginal atrophy therapies indicate that timely detection of vaginal atrophy and proper treatment can prevent the disease progress and significantly improve the quality of life and quality of sexual life for women [14].

Given the Iranian tendency to herbal remedies, traditional and complementary medicine, and the variety of complementary therapies used to treat vaginal atrophy, various studies have been reported in Iran.

Finding convenient, affordable, inexpensive, and non-invasive treatment with fewer complications is of great importance. Therefore, a systematic review was conducted to evaluate the therapeutic treatments of vaginal atrophy in postmenopausal women in Iran.

MATERIALS AND METHODS

Search strategy

This study is a systematic review of all clinical trials conducted on different types of treatment that affect vaginal atrophy.

All Iranian articles published in Persian or English in the period 2009 to 2019 were collected and reviewed

by searching the Scopus, PubMed, Web of Science, Magiran, Iranian Registry of Clinical Trials (IRCT), Cochrane Library databases. Inclusion criteria included clinical trial for vaginal atrophy and menopause. Exclusion criteria for articles included: Lack of access to the full text of the article, the results of irrelevant, duplicate articles, and trials on animal were excluded. In order to search for articles in Persian electronic resources, for maximizing comprehensiveness in the search, the general keywords including “vaginal atrophy, menopause, treatment, Iran” and their possible combinations in the title and abstract were used. “And” and “OR” operators were used for this purpose. In searches in electronic English databases, the Latin equivalent of MeSH “vaginal atrophy, menopause, treatment, Iran” were performed using the AND, OR operators in combination.

Evaluating the quality of articles

Jadad scale was used to evaluate the quality of clinical trial articles. The Jadad scale examines the existence of bias in randomization, patient follow-up, and blindness. In this case, in the randomization part, if there is no randomization or the method is wrong, the scale is zero; if there is randomization, the scale is 1, and if the randomization method is correctly explained, the scale is 2. In the blinding part, if the blinding is not done or the method is wrong, the score is zero, if the blinding is done, it is 1, and if the blinding method is correctly explained the scale is 2. The scale will be assigned a score of 0 if the patient follow-up is not explained, and a score of 1 is assigned if follow-up is stated. The minimum score required to confirm the quality of articles is 3 and a maximum of 5.

Data extraction

In order to prevent bias, search and evaluation of the articles were carried out by two project partners. Data were collected using a checklist consisting of authors' names, year of publication, study location, sample size, duration of follow-up, type of treatment, dose of intervention evaluation tool and quality of articles evaluation score.

RESULTS

There were 15 clinical trials that met the inclusion criteria. Finally, 12 articles examined the efficacy of pharmacological treatments (including three herbal medicines, three vitamins and dietary supplements, and two

chemical drugs) in treating postmenopausal atrophic vaginitis.

Figure 1 illustrates the process of selecting studies. Table 1 shows the characteristics of the studies eligible for systematic review and the quality of the articles under review.

Herbal

In this group, four articles examine the effects of three herbal remedies (fennel, licorice, chamomile) (Table 1).

Fennel

There have been two studies on the fennel plant that the study of Yaralizadeh et al. [15] have shown positive effects of this plant on vaginal atrophy symptoms (dryness, pallor, itching and dyspareunia) in postmenopausal women, which may be due to the presence of a biologically active compound called Phytoestrogen. In this study, vaginal cream form had been used for research, but postmenopausal women were followed up for only 8 weeks, and further studies with longer follow-up and larger sample sizes are recommended. On the other hand, in the study of Ghazanfarpour et al. [16], fennel was not effective in improving vaginal atrophy (Maturation Vaginal Index and maturation values).

Licorice

There was only one study in the field of licorice. In the study of Sadeghi et al. [17], the effect of licorice vaginal cream was compared with placebo. The results showed that licorice vaginal cream significantly improved the mental symptoms of vaginal atrophy (itching, burning, dyspareunia and dryness) compared to placebo [17].

Chamomile

There was only one study in the field of chamomile. In the study of Bosak et al. [18], the effects of chamomile gel, conjugated estrogen and placebo gel were compared. Results showed that chamomile vaginal gel cream and conjugated estrogen vaginal cream both significantly improved mental symptoms of vaginal atrophy (burning, itching, intercourse pain, vaginal dryness) compared to placebo, but no significant difference was observed between the two groups [18].

Vitamins and supplements

In this group, five papers have examined the effects of two vitamins and one dietary supplement (royal jelly, vitamin E, vitamin D) (Table 1).

Royal jelly

Concerning the effect of royal jelly, only one study by Seyyedi et al. [19] has been done, in which the effects of vaginal estrogen and royal jelly cream were compared. The results showed that Royal jelly cream is significantly more effective than vaginal estrogen cream in symptoms of vaginal atrophy (vaginal cytology), sexual-urinary problems and quality of life [19].

Vitamin E

There have been two studies regarding the effect of vitamin E on vaginal atrophy in postmenopausal women, both of which show the effectiveness of this vitamin on vaginal atrophy [20,21].

In a study by Parnan Emamverdikhan et al. [20], the effect of this vitamin on vaginal atrophy was less than that of vaginal estrogen cream. Although estrogen is mostly absorbed locally, in some areas it can also have systemic uptake and cause endometrial growth, with complications such as bleeding, cervical allergy, increased cervical secretions, and growth of the uterine myomas [22,23]. In long-term use, vitamin E can be effective in postmenopausal women who are estrogen-deficient or have shown reaction to other therapies because it has no complications. Less effectiveness of

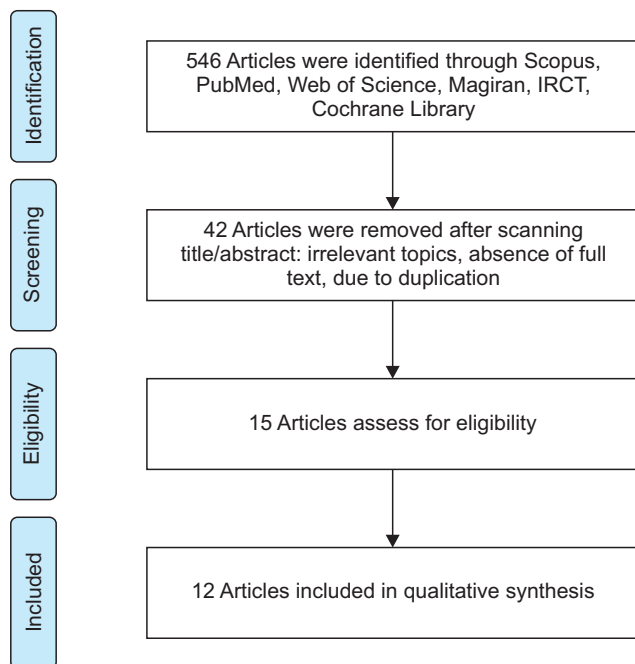


Fig. 1. Flowchart of article selection. IRCT: Iranian Registry of Clinical Trials.

Table 1. Characteristics of studies of different types of medication for vaginal atrophy in postmenopausal women in Iran

Category	Study (y)	Number of subjects (intervention/control)	City	Duration (wk)	Intervention	Group	Control	Assessment tool	Adverse effect	Jadad scale score
Herbal	Ghazanfarpour et al. (2017) [16]	30/30	Mashhad	12	100-mg soft capsules containing 30% fennel, three times a day	Capsules were filled with sunflower oil only		Maturation Vaginal Index and maturation values	Mentioned	5
	Yaralizadeh et al. (2016) [15]	30/30	Ahvaz	8	Fennel 5% vaginal cream, one application per day for 8 weeks	Placebo, one application per day for 8 weeks		Vaginal pH and maturation vaginal index	Mentioned	4
	Bosak et al. (2019) [18]	32/32/32	Ahvaz	12	5% vaginal chamomile gel, conjugated vaginal estrogen cream	Placebo gel		Likert self-report questionnaire	Mentioned	5
Vitamins and supplements	Sadeghi et al. (2018) [17]	35/35	Ahvaz	8	Licorice 2% vaginal cream for every night (5 mg) for 8 weeks	Placebo every night (5 mg) for 8 weeks		Self-assessment Likert scale	-	4
	Seyyedi et al. (2016) [19]	30/30/30	Shahrekord	12	Vaginal estrogen 0.625 mg / vaginal cream of royal jelly 15% in lubricant Base, 1-2 week: an applicator per night; 3-4 week: an applicator for every other night; 5-12: an applicator, two nights per week	Placebo (KY Jelly), 1-2 week: an applicator per night; 3-4 week: an applicator for every other night; 5-12: an applicator, two nights per week		Vaginal cytology assay	-	4
	Ziaghham et al. (2013) [21]	20/22	Ahvaz	8	Vaginal suppository containing 1 mg vitamin E	Placebo suppository		Vaginal pH and maturation value	-	4
	Rad et al. (2015) [24]	22/22	Ahvaz	8	Vitamin D suppositories 1,000 IU	Placebo suppositories consisted of Suppocire AM-15, a semi-synthetic fatty acid glyceride		Vaginal pH and vaginal Maturation value	-	3
	Parnan Emamverdikhan et al. (2016) [20]	26/26	Mashhad	12	100 IU of vitamin E suppositories	0.5 g of conjugated estrogen cream		Vaginal maturation value	-	4
	Tadayon et al. (2012) [11]	22/22	Ahvaz	8	Vaginal suppository of vitamin D, two weeks each night and six weeks later one night	Placebo suppository		pH and maturation index of superficial cells	Mentioned	3
Chemical	Ziaghham et al. (2012) [25]	20/20	Ahvaz	8	Vaginal suppositories of either 5 mg hyaluronic acid sodium salt	1 mg vitamin E		Self-assessed	Mentioned	5
	Jokar et al. (2016) [26]	28/28	Shiraz	8	Conjugated estrogen 0.625 mg cream, one applicator of drug (0.058 mg) every night before sleep for a period of two weeks and two times a week for the next six weeks	Hyaluronic acid vaginal cream (containing 5 mg sodium salt), one applicator 5 (mg) every night before sleep for a period of 8 weeks		Visual analogue scale	Mentioned	5
	Hosseinzadeh et al. (2015) [28]	80/80	Isfahan		Vaginal estrogen cream of Actoverco company, one tube every night for 14 nights; then, one tube 2 nights in 1 week (two tubes every week) for 10 weeks	Vaginal estrogen cream from Novo Nordisk was replaced with Vagifem 25 g		Visual analogue scale	Mentioned	3

vitamin E than estrogen can be due to its form, administration, and effective dose.

Vitamin D

Studies have shown the positive effects of this vitamin on vaginal atrophy [11,24]. In the study of Rad et al. [24], the effect of vitamin D suppository with placebo was investigated. The results showed that vitamin D significantly improved the symptoms of vaginal atrophy, puberty index, dryness of the vaginal atrophy and decreased pH compared to the placebo group [24]. Tadayon et al. [11] evaluated the effect of vitamin D suppository with placebo. The results showed that vitamin D was more effective than placebo in proliferation of vaginal superficial cells, lowering vaginal pH, and improvement of dyspareunia [11].

Chemical

In this group, three papers examined the effects of two chemical drugs (hyaluronic acid, Vagifem) (Table 1).

Hyaluronic acid

Two studies have investigated the effect of vaginal hyaluronic acid suppository on vaginal atrophy [25,26]. The results of the study by Ziaghham et al. [25] showed that hyaluronic acid and vitamin E both significantly increased cell maturation and vaginal epithelium but the improvement was more in hyaluronic acid group [25]. Jokar et al. [26] compared hyaluronic acid and conjugated estrogen gels. Based on their study, hyaluronic acid and conjugated estrogen both decrease dryness, irritability, improve cellular maturation and improve vaginal pH, but only hyaluronic acid gel improves urinary incontinence in postmenopausal women. The overall symptom score was better in the hyaluronic acid group and, as a result, the overall effect of the gel was greater than that of conjugated estrogen, and could be a good substitute for conjugated estrogen, given its nonhormonal properties [27].

Vagifem

One study investigates the effect of Vagifem on vaginal atrophy. In the study of Hosseinzadeh et al. [28], the effect of Vagifem was compared with vaginal estrogen cream. The results showed that both treatment groups significantly led to treatment of vaginal atrophy but no significant difference was observed between the two groups [28].

DISCUSSION

The purpose of this study was to evaluate the effective treatment methods for vaginal atrophy in Iran. A review of studies on the treatment of vaginal atrophy indicates that few herbs and drugs have been studied in Iran and further studies with a stronger methodology are recommended for their application.

Fennel is a plant of the umbrella family with trans-anthole, limonene and fenchone compounds. Fennel is rich in phytoestrogens, including lignans, and is also a rich source of one of the phytoestrogens called isoflavones. The ability of attachment of fennel isoflavone to beta estrogen receptors may have a positive effect on vaginal mucosa [27,29].

In a study by Yaralizadeh et al. [15], the positive effects of this plant on vaginal atrophy in postmenopausal women may be due to the presence of a biologically active compound called phytoestrogens. In the study of Ghazanfarpour et al. [16], one of the reasons for the ineffectiveness of fennel is related to its usage as orally. Therefore, further studies can be useful to obtain the effective form, dose and usage way of fennel [16].

In the field of licorice, only one study was conducted, while licorice is one of the herbs that has plant estrogen and is effective in hormonal balance of the body. Its estrogen is a steroid type, similar to estrogen and estradiol, which is produced in the body [29]. Licorice, with increasing the blood circulation, increases the vaginal mucosa metabolism, thereby increasing the moisture and flexibility of the vaginal wall. In the study of Sadeghi et al. [17], licorice had a positive and significant effect, but since Vaseline had been used in its cream compound, it is recommended to consider the potential impact of these compounds in the design of future studies.

There was only one study in the field of chamomile. Chamomile (*Matricaria chamomilla* L.) is a plant from the orchid or Asteraceae family. There are reports that apigenin and chrysin flavonoids in chamomile extract have phytoestrogenic effects [30-32]. A study by Bosak et al. [18] found that chamomile vaginal gel can have the same effect as conjugated estrogen cream, as it increases vaginal discharge and vaginal dryness, but is not superior to estrogen cream. Due to the limitations of the literature in this area, it is not possible to comment on the effectiveness of this method and further research is recommended in this regard.

There has been only one study on the effect of royal

jelly that showed the effect of royal jelly on the reduction of atrophy symptoms in postmenopausal women was greater than vaginal estrogen cream [19]. Royal jelly contains 60% to 70% water, 12% to 15% protein, 10% to 12% carbohydrate, 3% to 7% fat, 1.5% mineral salt and various vitamins. Water increases moisture inside the vagina and temporarily reduces vaginal dryness [33,34].

Since the royal jelly is nonhormonal and more effective than vaginal estrogen cream, it can be an effective alternative to vaginal estrogen. Since this study is the first and only study to investigate the effect of royal Jelly on vaginal atrophy and has only done on 24 postmenopausal women, further studies with larger sample sizes are recommended. In this study, postmenopausal women were re-examined one month after taking the royal jelly, suggesting longer investigations to identify possible side effects.

Vitamin E is one of the fat-soluble vitamins, has antioxidant properties, and protects the body's cells against damage. The primary function of vitamin E is to maintain the integrity of the body's intracellular membrane by preserving its physical stability and providing a line of defense against the physical damage caused by oxidation. This vitamin keeps the arteries flexible and elastic and allows the blood to flow freely. Vaginal moisturizers can have beneficial short-term and long-term effects on improving vaginal atrophy by improving intracellular fluid balance in the vaginal epithelium and improving tissue growth [2,35].

Studies have shown that this vitamin has positive effects on vaginal atrophy, which may be due to its effect on vaginal cell maturation [11,24]. In relation to vitamin D, vitamin D binds to intracellular receptors that are actually similar to the thyroid receptor family. Vitamin D and its receptors form a compound that binds to the genes that respond to vitamin D, resulting in the positive and negative effects of those genes. Vitamin D is also effective in vaginal cell maturation [36,37].

Sodium hyaluronic acid is a high molecular weight material belonging to the glycosaminoglycan group, and contains repeating disaccharide units of glucuronic acid and N-acetyl glucosamine. Hyaluronic acid, an example of moisturizers, can store large amounts of water molecules. It is non-greasy and water-permeable [2]. Hyaluronic acid is an important part of the extracellular matrix of the skin and cartilage, and has properties such as creating and maintaining extracellular swelling, moisturizing the skin and maintaining water balance

that can greatly affect vaginal atrophy [38]. The results of studies on hyaluronic acid have shown that this compound is well tolerated by patients without adverse effects and complications are only seen when it is used as an injectable royal jelly that causes allergy at injection sites [39].

Vagifem pill is a small vaginal pill containing 25 micrograms of 17 beta estradiol. It is inserted into the vagina with the applicator and adheres to the vaginal mucosa [40]. Vagifem is associated with a greater reduction in health problems and is widely accepted by consumers due to being nonhormonal. Due to the limited number of studies in this field, more research with a larger sample size and longer duration is recommended.

This systematic review had some limitations that should be considered. The most important limitation was the lack of access to all published articles and non-published reports. The next problem was the lack of accurate, high quality, and usable report by some articles, which limited the ability to make more accurate and complete comparisons and analyzes. Finally, because of the scarcity of studies on each intervention, it was not possible to draw definitive conclusions about a particular method. The results of this study can be used to improve the health and quality of life of postmenopausal women and improve the quality of health services.

CONCLUSION

Various types of medication have been used to improve vaginal atrophy. Effective treatments for improving vaginal atrophy include licorice, chamomile, royal jelly, vitamin E, vitamin D, hyaluronic acid, Vagifem, and the results of studies on fennel have been inconsistent. However, in order to confirm the efficacy of these methods, given the small number of studies reviewed, further studies with a stronger methodology are needed.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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