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Review article

Impact of phytoestrogens on treatment of urogenital menopause symptoms: A systematic review of randomized clinical trials

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ABSTRACT

Objective: Menopause symptoms affect the various dimensions of women's lives and they can lead to reduction of their quality of life. Phytoestrogens can be used as an approach to diminish these symptoms. The aim of this systematic review was to investigate the effect of phytoestrogens on the treatment of urogenital menopause symptoms.

Study design: PubMed, EMBASE, Web of Science, Cochrane library,Scopus and ProQuest were systematically searched from 2000–2020. All randomized clinical trials were included. The quality of the selected papers was evaluated by the CONSORT checklist.

Results: 33 eligible high-quality papers were reviewed. Various forms of phytoestrogens such as Pueraria Mirifica, fennel, Hop plant(Humuluslupulus L.), Glycine Max (L.) Merr, soy, red clover, black cohosh, ginsing, cimicifugaracemosa, genistein, diadzein, glycitein and isoflavone in the form of oral capsules and pill, food supplement, enriched powder, vaginal gel, cream and suppository could improve menopausal urogenital symptoms. The recovery rate in vaginal use of these phytoestrogens was greater than other consumptions.

Conclusions: After using a variety of phytoestrogens in different forms indicators of urogenital atrophy and urinary disorders improved and women's sexual function improved after treatment. The use of phytoestrogens as a safe, low-risk compared to hormone therapy and almost accessible method for women can relieve urogenital symptoms and promote the sexual satisfaction and quality of life.

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Introduction

Menopause, which is defined as the absence of menstruation periods for at least 12month(mth), is a multidimensional evolutionary process with major effects on women's quality of life and risk of developing particular diseases and the related mean age is 51 years in women [1,2]. In addition, menopause can be attained through surgery, chemotherapy, or radiation therapy [3]. Although recent medical advances and the consequent rise in life expectancy have increased the number of postmenopausal women, the age of menopause has remained almost constant, i.e. postmenopausal years still constitute about one-third of women's lives. Postmenopausal women experience different physical and psychological symptoms after menopause [4]. Such symptoms are very different in women and it often involves hot flashes, sleep disorders, anxiety, and depression [5]. The pathophysiological changes associated with the urogenital atrophy occurs due to decreased estrogen synthesis during the period of menopause and its most common diagnostic symptoms are vaginal dryness, burning, dyspareunia and urinary incontinence.

The pathogenesis of a urogenital atrophy is directly related to estrogen deficiency and the presence of estrogen receptors in vaginal epithelium, proximal and distal urinary tract, bladder trigone and supporting tissues of pelvic floor, such as pubococcygeus muscle [6].

In recent studies, much attention has been paid to phytoestrogens as a plant with estrogenic effects [7].Phytoestrogens, with the four main categories of flavonoids, coumestans and lignin are plant compounds with estrogenic activity. Their chemical structure consists of 2 phenolphthalein that can be attached to the estrogen receptor. Phytoestrogens diminish the risk of cardiovascular disease, breast and endometrial cancer, osteoporosis and menopausal symptoms [8]. The metabolism of phytoestrogens is complex in humans and their bioavailability is largely determined by intestinal flora [9].

Phytoestrogens have been shown to be effective in improving the urogenital symptoms associated with menopause and vaginal performance indicators that indicate the growth and proliferation of vaginal colonies, such as maturation value and karypycnotic indices as well as increase in vaginal acidity [10–12]. The latest systematic review of herbal medicines, both phytoestrogens and non-phytoestrogens, on the sexual function of postmenopausal women was conducted between 2000 and 2020, and 31 studies included all effective herbal medicines in this field were analyzed [13]. The main advantage of this study over other studies is the present study assessed the effect of phytoestrogens not only urogenital menopause symptoms but also sexual functions.

Material and methods

Literature search strategy

The guidelines of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) were followed while reporting the study protocol [14,15]. Also, in accordance with the PRISMA guidelines the following steps were taken: a systematic literature search, organization of documents for the review, abstracting and quality assessment of each empirical study, synthesizing data, and writing the report [16]. PubMed, EMBASE, Web of Science, Cochrane library, Scopus, Google Scholar and ProQuest were systematically searched between 2000–2020 by using the Mesh keywords as follow (Appendix A):

' menopause' [tiab], OR' menopausal syndrome' [tiab] OR' menopausal symptoms' [tiab], urogenital syndrome [tiab], 'urogenital atrophy' [tiab], OR 'atrophy' [tiab], OR 'dyspareunia' [tiab] OR 'Dysuria' [tiab] 'OR 'urogenital symptoms '[tiab], OR ' Urogenital Syndrome of Menopause' [tiab], OR 'GSM' [tiab]AND 'phytoestrogen ' [tiab] OR 'phytoestrogens' [tiab] OR ' Plant Estrogen' [tiab] OR ' Plant Estrogens' [tiab], OR ' Estrogen Like Plant Extract, [tiab], OR ' Estrogen-Like Plant Extracts' [tiab] OR ' Phyto-Estrogen' [tiab], OR ' Estrogen, Plant' [tiab], OR ' Plant Extracts, Estrogen-Like' [tiab], OR ' Fennel' [tiab], OR ' Pueraria Mirifica' [tiab], OR "Hop plant (Humuluslupulus L.)'[tiab], OR Hops[tiab] OR' Glycine Max (L.) Merr' [tiab], OR ' Soy' [tiab], OR ' red clover' [tiab], OR 'Cimicifugaracemosa' [tiab], OR 'Genistein' [tiab], OR 'Diadzein' [tiab], OR 'Isoflavone'[tiab].

Inclusion and exclusion criteria

Randomized clinical trials conducted between 2000 and 2020 were included in this review. Letters, comments, and observational studies, as well as case reports, were excluded. There are no language restrictions to using and entering articles in this study. If the language used in an article is other than Persian or English, we asked a translator to translate the article.

The studies were selected if their participants were healthy women over 40 who have naturally experienced menopause, those who had amenorrhea for one year and increased level of follicular stimulatory hormones (FSH) greater than or equal to 40 IU / L, women who were sexually active who reported symptoms of urogenital atrophy such as dryness, irritation of the vulva and vagina, irritability, abnormal discharge, dyspareunia and other urinary problems, ones who did not have underlying illness and tend to participate in interventions and to comply with medical protocols. Placebo or another drug could be prescribed to the control group. In case less than 70 % of the participants were present at the end of the research, the study would be excluded.

Population, Intervention, Comparators, Outcomes, Study Design (PICOS) criteria for this study:

- Population: menopausal women
- Intervention: phytoestrogens
- Comparison: placebo /conventional treatment
- Outcome: urogenital symptoms
- Study design: Randomized clinical trials

Study selection

The two authors(FAR and FA) independently reviewed qualified articles and any disagreements by consulting a third author. Finally

the papers which were agreed upon by both authors were analyzed (Fig. 1).

Quality assessment

The CONSORT checklist, as an authoritative tool that proposes 25 items for reporting or evaluating different sections of interventional studies, was used for assessing the quality of the present research [17].

Data extraction

The selection of papers and their evaluation was done by two researchers. After agreement on 34 eligible articles in form of Table 2 and 3, items including author's name, publication year and country, study design, sample size, participants' symptoms, intervention and control group's characteristics, comparison and measures and outcomes were extracted and analyzed.

Results

The process of the literature search is depicted in Fig. 1. The abstracts and titles of the initial search results were evaluated. After the review of the full texts of potentially eligible papers, 33 papers, which met the inclusion criteria and adhered to all seven items of the CONSORT checklist (i.e. had high quality), entered the analysis. According to the Table 3, the number of samples is between 10 and 248, and a total of 2972 individuals entered into the selected interventions. The location of the selected studies has been geographically diverse so that the mentioned research were done in different countries such as Iran [10], Brazil [6], Italy [6], Thailand [4], India [3], United States [1], South Korea [1], Romania [1] And Australia [1]. The quality of the studies was assessed using the CONSORT checklist. The average score of CONSORT for studies varied from 16 to 24.

Phytoestrogens

Fennel

The effect of fennel in form of vaginal cream, powder or oral capsule alone or mixed with chamomile and saffron on the female sexual function index (FSFI) and the symptoms of vaginal atrophy compared with placebo was investigated in three studies with a total of 180 postmenopausal women [11,18–21].The impact of fennel vaginal cream on women's sexual function index and symptoms of vaginal atrophy such as dryness, burning, itching, dyspareunia and cytological indices of vaginal epithelium such as vaginal PH and the maturation vaginal index (MVI) had clearly positive consequences and the outcomes indicated the improvement all the above mentioned indices in the intervention group. However, no improvement was observed ultimately in a study in which the effect of the fennel capsule on vaginal atrophy was examined.

The results of a study indicated that daily use of Fennel seed significantly improved menopausal symptoms in postmenopausal women over 8 weeks.And other study showed that a 12 weeks extracts treatment, there were significant improvement urogenital domains in group high dose (chamomile1000 mg, fennel120 mg, saffron60 mg).

Pueraria Mirifica

The effect of Pueraria Mirifica as a vaginal gel or oral pill on menopausal urogenital symptoms was investigated in two studies

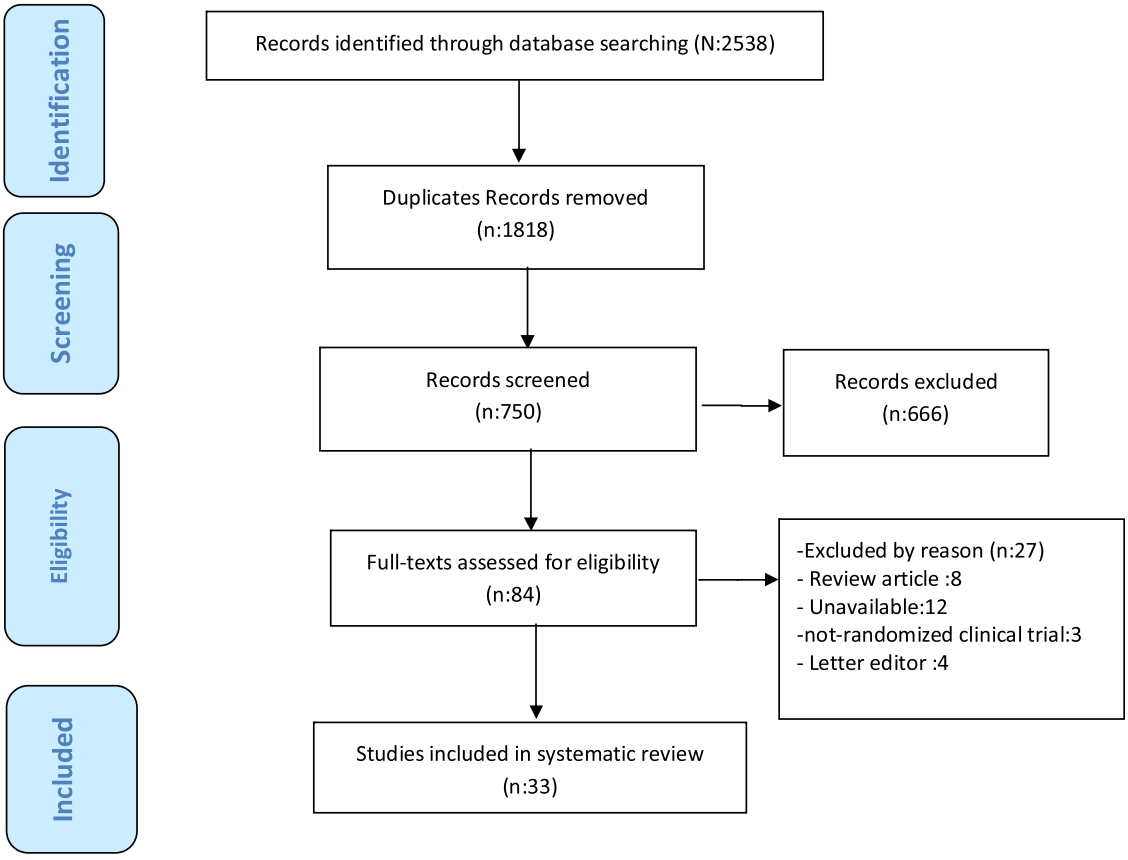

Fig. 1. PRISMA diagram for searching resources.

Table 1
Overview of all studies included in the systematic review.

ID	Author,year(ref)	Location	Sample size(n)	Age (years)	Symptoms	Intervention	Comparison	Measurement Tools	Follow up	Quality Score
1	Sritonchai2020, [22]	Thailand	60	50–70	- Dryness - Burning - Irritation - Lack of lubrication - Sexual discomfort or pain - Urinary urgency - Dysuria - Recurrent UTI	Pueraria mirifica vaginal gel 5 g/day in the first 2 wk then reduced to 3 times / wk for 12 wk	Placebo	GSM specific questionnaire	12 wk	23
2	Padmapriya2020 (28)	India	125	40–60	Sexual Domain	Soymilk200 ml/day for 6 wk	Control group	MENQOL	6 wk 10 wk	17
3	Ghaffari2020(18)	Iran	80	>45	Desire	Fennel capsule 500 mg (4 capsules/ day for 8 wk	Placebo	KMI HISD	4 wk 8 wk	21
4	Sadeghi2019(29)	Iran	135	45–64	Atrophy	- Black Cohosh tablet 6.5 mg/day - Vitagnus tablet 4.8 mg/day for 8 wk	Control group	MRS	4 wk 8 wk	19
5	Ribeiro2019(30)	Brazil	58	40–60	- Urogenital Symptoms - SD - Bladder problems - Dryness	- Isoflavone capsule 150 mg/day - Isoflavone capsule 150 mg + one pack of probiotic/day - HT(estradiol 1 mg +	HT group	MRS	16 wk	24
6	Palma2019(31)	Italy	75	> 45	Atrophy	norethisterone acetate0.5 mg) /dayfor 16 wk - Oral HT (CEE 0.3 mg + MPA 1.5 mg,)/day - soy isoflavones - Oral 75 mg twice/ day - Acupuncture once a week for 6 mth	HT and Acupuncture group	MenQoL MGCS	3 mth 6 mth	22
7	Mahdavian2019(19)	Iran	120	45–65	Atrophy	chamomile (1000, 500, 250 mg)+fennel (120, 60, 30 mg) +saffron(60, 30, 15 mg)/day for 12 wk	Placebo	MRS	6 wk 12 wk	22
8	Khayatan2019(32)	Iran	76	45–65	- Desire - Arousal - Lubrication - Orgasm - Sexual satisfaction - Dyspareunia	Red clover vaginal cream 2%/day for 8 wk	Placebo	FSFI	8 wk	19
9	Ghorbani2019(33)	Iran	62	45–60	- Desire - Arousal - Lubrication - Orgasm - Satisfaction - Dyspareunia	Ginseng capsules 500 mg twice/day for 4 wk	Placebo	-MENQOL -FSFI - MGCS	4 wk	23
10	Abedi2018(20)	Iran	60	45–65	-SD	Fennel vaginal cream 5 g/day for 8 wk	Placebo	FSFI	8 wk	20
11	Suwanvesh2017 (23)	Thailand	76	45–60	- dryness - soreness - irritation - dyspareunia - abnormal discharge	Puerariamirifica6%, Vaginal gel 0.5 g/day for 2 wk and then decreased to 3 times/ wk for 10 wk	conjugated estrogen vaginal cream0.5 g, at the same frequency as intervention group	- Atrophy symptom questionnaire - Vaginal health assessment questionnaire	6 wk 12/ wk	17
12	Lee2017(34)	South Korea	84	45–60	Atrophy	isoflavones tablets 400 mg (contained 336.0 mg of soy extract (isoflavones 10.5 %)) two tablet/ day for 12 wk	Placebo	-KMI -MENQOL	6 wk 12 wk	18

Table 1 (*Continued*)

ID	Author,year(ref)	Location	Sample size(n)	Age (years)	Symptoms	Intervention	Comparison	Measurement Tools	Follow up	Quality Score
13	Ghazanfarpour 2017(21)	Iran	52	45–65	Atrophy	Fennel capsules 100 mg(30 % fennel) three times / day for 4 wk	Placebo	Assessment of MV and vaginal PH	Every wk for 4 wk	19
14	Davinelli2017(9)	Italy	60	50–55	Atrophy	dietary supplement containing200 mg of fermented soy (isoflavone aglycones 80 mg + equol 10 mg) + resveratrol from Vitisvinifera 25 mg / day for 12 wk	Placebo	MRS HRQoL	1 mth 3 mth	23
15	Yaralizadeh2016 (11)	Iran	60	45–65	Atrophy	Fennel vaginal cream 5% /day(5 g/day) for 8 wk	Placebo	- urogenital atrophy subscale	2 wk 4 wk 8 wk	21
16	Aghamiri2016(8)	Iran	120	40–60	Atrophy	Hop Plant tablet 500 mg /day for 90 days	Placebo	MGCS	4 wk 8 wk 12 wk	22
17	Carmignani2015 (35)	Brazil	60	40–60	Atrophy	- HT (estradiol 1 mg + 0.5 mg of norethisterone acetate)/day - Soy dietary supplement)isoflavone 90 mg /day) for 16 wk	Placebo	-MRS -urogenital subscale	16 wk	17
18	Lima2014(25)	Brazil	55	>45	Atrophy	Glycine max (L.)Merr. 4% vaginal gel/day for 12 wk	Placebo	Individual average symptom	4 wk 12 wk	21
19	Tit2013(36)	Romania	230	34–58	Atrophy	Phytoestrogens derived from soy, red clover Cimicifugaracemosa or plant combinations in different doses for 12 mth	Control group	MRS	3 wk 6 wk 12 wk	16
20	Lima2013(26)	Brazil	75	>45	- dryness and/or pruritus - pain/soreness - vulvar or vaginal burning - dyspareunia	- Glycine max - (L.) Merr. Isoflavone vaginal gel 4% /day for 12 wk - Conjugated equine estrogens (CEE) 0.625 mg /day for 12 wk	Placebo	Individual average symptom scores	4 wk 12 wk	22
21	Tedeschi2012(37)	Italy	186	53.7 ± 5.0	Vaginal dystrophy and receiving oral soy isoflavones 60 mg + Lactobacillus sporogenes (Estromineral) 1 tablet/day	EG (vaginal gel containing aglicon isoflavones 10 mg, L. sporogenes109 CFU, Calendula officinalis125 mg and lactic acid 20 mg	Control group	Individual average symptom scores	2 wk 4 wk	16
22	Le Donne2011(38)	Italy	62	58	Atrophy	Genistein 97 μg Intra vaginal suppository/ day for 15 days continuously per month for 3 mth	Placebo	KMI and Individual average symptom scores	3 mth	20
23	Levis2010(39)	USA	248	45–60	Atrophy	Soy isoflavone 200 mg/ day for 2 years	Placebo	WHQ	10 meetings during 2 years	20
24	Radhakrishnan2009 (40)	India	100	49	Atrophy	- Isoflavone rich soy protein isolate 25 g containing 75 mg of isoflavones in powder form /day for 6 mth	Placebo	KMI	3 mth 6 mth	18

Table 1 (*Continued*)

ID	Author,year(ref)	Location	Sample size(n)	Age (years)	Symptoms	Intervention	Comparison	Measurement Tools	Follow up	Quality Score
25	Hanachi 2008(41)	Iran	37	52.2 ± 4.6	Atrophy	- Soy milk)12.5 mg soy protein with Genistein, 13 mg, Diadzein 4.13 mg) - Soy milk + exercise(one hour walking/day) for 3 mth	Control group	KMI	3 mth	17
26	Nahas 2007(27)	Brazil	76	>45	Atrophy	Standardized soy isoflavone extract (Glycine max AT) capsule 250 mg twice/day	Placebo	KMI	10 mth	19
27	D'anna2007(42)	Italy	209	50–70	Atrophy	Genistein tablets 54 mg/day	Placebo	Assessment of MV	12 mth	19
28	Chandeying 2007 (24)	Thailand	8	>40	Atrophy	Puerariamirifica oral 50 and 100 mg / day for 6 mth	Before-after	MGCS	Every mth for 6 mth	16
29	Shah 2006 (43)	India	58	49.4	Atrophy	soy isoflavones, lignans, antioxidants and plant-based ingredients one capsule twice a day for 6 mth	Placebo	KMI	6 mth	16
30	Manonai 2006(6)	Thailand	36	45–70	Atrophy	soy-rich diet (soy protein25 g in various forms of soy food containing more than 50 mg/day of isoflavones substituted for an equivalent amount of animal protein) for 12 wk	control diet (soy-free diet) for 12 wk	Questionnaire based on ICS for urinary symptoms and RWJMS for vaginal health index	12 wk	18
31	Kaari2006(44)	Brazil	68	>45	Atrophy	Isoflavone 300 mg of the standardized soy extract with a medium dose of 120 mg isoflavones twice a day for 6 mth	Conjugated estrogen 0.625 mg One capsule and other capsule with glucose 0.625 mg (placebo) for 6 mth	KMI	3 mth 6 mth	19
32	Chiechi2003(10)	Italy	94	39–60	Atrophy	-Phytoestrogen rich diet(to provide an isoflavone intake of at least 20–30 mg/day) -HRT	Control group with habitual daily diet	Assessment of KI and MV	6 mth	18
33	Kotsopoulos2000 (45)	Australia	94	50–75	Atrophy	isoflavones118 mg/ day (daidzein, genistein, glycitein and their respective glycosides)	Placebo	Individual average symptom scores	3 mth	20

SS: sample size, CEE: conjugated equine estrogens, MPA: medroxyprogesterone acetate, UTI: Urinary tract infection, GSM: Genitourinary Syndrome of Menopause, MENQOL: Menopause specific quality of life questionnaire, MRS: Menopause Rating Scale, FSFI: female sexual function index, WHQ: Women's Health Questionnaire, KMI: Kupperman Menopausal Index, MGCS: Greene climacteric scale, HEQoL: health related quality of life, ICS: International Continence Society, RWJMS: Robert Wood Johnson Medical School, HISD: Hurlbert Index of Sexual Desire, HRT: hormone replacement therapy,SD: sexual dysfunction, Wk:week, mth:month.

in total on 144 postmenopausal women and it was perceived that such phytoestrogen can be used as a safe and non-complicated approach, such as estrogenic methods, to improve the mentioned symptoms [22–24].

Hop plant (Humuluslupulus L.)

The impact of noted phytoestrogen on the symptoms of menstruation was only examined in one study. The research was performed on 120 eligible postmenopausal women according to the Greene index and the amount of unwillingness to have sexual relations was also measured in this criterion. Significant improvements were observed after intervention in this parameter compared to placebo group [8].

Glycine max (L.) merr

The effect of this substance as a vaginal gel or a capsule containing its extract on menopausal symptoms related to estrogen deficiency was investigated in four studies on 308

postmenopausal women. At the end of the interventions, the positive effect of this substance on the recovery of symptoms was observed, which was more satisfactory in form of the vaginal gel [25–27].

A total of 22 studies were conducted about using the soy, red clover, black cohosh, ginsing, Cimicifugaracemosa, genistein, diadzein, glycitein and isoflavone [6,9,10,28–45].

Soy, Red clover, black cohosh (Cimicifugaracemose)

In a study in which the impact of combination of soy, red clover, Cimicifugaracemose was investigated on 230 postmenopausal women, it was observed at the end of the intervention that women were satisfied with improving their urogenital symptoms compared with the control group [36]. Another study of 76 postmenopausal women found that red clover had beneficial effects on sexual dysfunction in postmenopausal women [32].

In other three studies, the effect of soy milk (containing soy protein, Genistein and Diadzein) with exercise [28,41] or a soy-rich diet with the goal of receiving high levels of isoflavone was investigated [6] on a total of 236 women with menopausal symptoms. In the end, it was also observed that the severity of vaginal menopausal symptoms was reduced while vaginal performance indicators were improved.

Considering the effect of Vitagnus plant and black cohosh on improving the menopausal symptoms of 135 postmenopausal women, their use can be considered according to the growth in the desired area [29].

Ginsing

Ginseng improved sexual function and quality of life of 62 postmenopausal women [33].

Genistein

In two studies, the specific goal was to receive certain amounts of Genistein alone in form of vaginal suppository or tablet which were taken to a total of 271 postmenopausal women with symptoms of urogenital atrophy and it was observed that vaginal suppository has been more effective in improving such symptoms [38,42].

Isoflavone

Exclusive influence of Isoflavone was investigated in studies on the symptoms of urogenital atrophy of menopause [9,10,27,30,31,34,35,37,39,40,43–45]. The interventions were in forms of vaginal gel, capsule and powder alone or mixed with probiotics and compared with placebo, estrogen or acupuncture. Total interventions were performed on 1000 postmenopausal women and the resulting data indicated that various forms of this substance can be effective in the treatment of urogenital atrophic symptoms. Also probiotics improved the metabolism of isoflavones after 16 weeks of treatment and Isoflavones were less involved in improving urogenital symptoms than acupuncture. However, according to a study on 186 women during two-year follow-up, it was observed that the combination of vaginal gel and the oral form of this substance would be effective in improving the symptoms of urogenital atrophy as much as hormone therapy.

There was a statistically significant difference in urogenital symptoms of women who used black cohosh, red clover and ginseng. Data from the analysis of all studies are presented in Tables 1 and 2.

Discussion

Considering the impact of phytoestrogens on urogenital symptoms in postmenopausal women and as a result, affecting their sexual lives as well as reducing their quality of life, it was elected to examine and analyze the outcomes of research conducted in this area based on a systematic study. The results indicate that treatment with a variety of phytoestrogens improved the indices which are indicative of urogenital atrophy and increased female sexual performance after treatment.

Approximately 75–80 % of women experience menopausal symptoms, and almost half of them consider such indications painful which can affect their quality of life in various psychosocial areas [36]. To this end, numerous treatments have been taken into account to reduce or improve the mentioned symptoms as well as to boost the quality of life of postmenopausal women in different areas. Although Hormone Replacement Therapy (HRT) is used as an effective treatment to reduce moderate to severe degrees of urogenital atrophy during menopause, it has many side effects such as breast cancer, venous thromboembolism and stroke [46]. However, the use of processed phytoestrogens can have beneficial effects on the recovery of urogenital symptoms with less complications [47].

The positive effect of phytoestrogens on vaginal atrophy in comparison with premarin or conjugated equine estrogen (CEE) in postmenopausal women have been examined and confirmed in some studies [48–50]. In terms of safety, concerns have been expressed about the possible adverse effects of phytoestrogens because of their affinity for the ERs. These concerns have focused primarily on estrogen sensitive tissues, particularly the breast and endometrium. However, recent clinical studies involving menopausal women have not shown an increase in risk of breast cancer or increase in endometrial hyperplasia following equal treatment [51–55]. Also in a systematic review of 11 RCTs was observed that phytoestrogens have different effects on the vaginal atrophy based on administration route and type [56].

In the past, the estrogenic effects of Puerariamirifica on vaginal tissue and the ability to improve the symptoms of vaginal epithelium atrophy have been indicated in healthy postmenopausal women. The effects of Puerariamirifica on the health of vaginal epithelium was also investigated in a study by Suwanvesh et al. (2017), [23]. Puerariamirifica is a specific plant in Thailand which is the source of phytoestrogen [57].

Puerariamirifica gel and its estrogenic effects on vaginal epithelium were investigated and it was observed that symptoms of vaginal atrophy were relieved. Moreover, atrophied epithelium of vagina was also restored in healthy postmenopausal women [23].

Foeniculumvulgare or fennel is a plant which has estrogenic effects. This plant can improve milk secretion, promote menstruation, and decrease postmenopausal symptoms in women and it serves as a major source of flavonoids [58,59]. 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 placed into three groups randomly including one control group and two ovariectomized groups. One ovariectomized sample group received 5 mg/kg subcutaneous estradiol daily while the other received700 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 was 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 [60]. Abedi et al.(2018) in their clinical trial exhibited that all areas of sexual performancewas improved significantly in the fennel group compared to the control group [20].

Table 2
Characteristics of the included randomized clinical trials.

ID	Author, year,(ref),	Score of intervention group		Score of control group		Results
		Before N(%) /Mean(SD)	After N(%) /Mean(SD)	Before N(%) /Mean(SD)	After N(%) /Mean(SD)	
1	Sritonchai2020(22)	- Dryness: 27 (90.0 %) - Burning: 3 (10.0 %) - Irritation: 9 (30.0 %) - Lack of lubrication: 19 (63.3 %) - Sexual discomfort/pain: 1 (3.3%) - Urinary urgency: 5 (16.7 %) - Dysuria: 2 (6.7 %) - Recurrent UTI: 1 (3.3 %)	- Dryness: 15 (50 %) - Burning: 1 (3.3 %) - Irritation: 6 (20.0 %) - Lack of lubrication: 7 (23.3 %) - Sexual discomfort / pain: 0 (0.0 %) - Urinary urgency: 3 (10.0 %) - Dysuria: 2 (6.7 %) - Recurrent UTI: 1 (3.3 %)	- Dryness: 28 (93.3 %) - Burning: 7 (23.3 %) - Irritation: 8 (26.7 %) - Lack of lubrication: 13 (43.3 %) - Sexual discomfort /pain: 3 (10.0 %) - Urinary urgency: 5 (16.7 %) - Dysuria: 1 (3.3 %) - Recurrent UTI: 0 (0.0 %)	- Dryness: 15 (50 %) - Burning: 4(13.3 %) - Irritation: 5(16.7 %) - Lack of lubrication: 6 (20.0 %) - Sexual discomfort/pain: 2 (6.7 %) - Urinary urgency: 1 (3.3 %) - Dysuria: 1 (3.3 %) - Recurrent UTI: 0 (0.0 %)	NS
2	Padmapriya2020 (28)	2.10 ± 0.09	- 6 wk: 1.91 ± 0.10 - 12 wk: 1.71 ± 0.11	2.00 ± 0.12	6 wk: 1.91 ± 0.09 12 wk:1.96 ± 0.10	Significant
3	Ghaffari2020(18)	desire:26.4 ± 10.7 menopausal symptoms: 30.8 ± 6	**desire:** - 4 wk: 29.1 ± 10.2 - 8 wk: 31.3 ± 10.1 **menopausal symptoms:** - 4wk: 23.6 ± 5.7 - 8wk: 19 ± 5.5	desire:26.1 ± 8.8 menopausal symptoms: 31.2 ± 6.5	**desire:** - 4 wk: 27.1_8.5 - 8 wk: 28.5_8.5 **menopausal symptoms:** - 4wk: 28.7 ± 6.3 - 8wk: 26.4 ± 6.2	NS
4	Sadeghi2019(29)	- Black cohosh:6.21 ± 2.90 - Vitagnus: 6.87 ± 3.34	NR	5.53 ± 2.62	NR	Significant
5	Ribeiro2019(30)	**Isoflavone:** - Total urogenital subscale: 2.88 ± 3.2 - Sexual problems: 1.21 ± 1.6 - Bladder problems: 0.37 ± 1.0 - dryness: 1.42 ± 1.6 **Isoflavone+probiotic:** - Total urogenital subscale: 4.68 ± 3.6 - Sexual problems: 2.05 ± 1.7 - Bladder problems: 1.15 ± 1.7 - dryness: 1.50 ± 1.6 **HT:** - Total urogenital subscale: 4.94 ± 3.5 - Sexual problems: 2.21 ± 1.6 - Bladder problems: 1.00 ± 1.2 - dryness: 1.74 ± 1.6	**Isoflavone:** - Total urogenital subscale: 2.23 ± 2.5 - Sexual problems: 0.76 ± 1.5 - Bladder problems: 0.59 ± 1.1 - Vaginal dryness: 0.88 ± 1.2 **Isoflavone+probiotic:** - Total urogenital sub-scale:3.05 ± 2.2 - Sexual problems: 1.21 ± 1.5 - Bladder problems: 0.79 ± 1.4 - dryness: 1.05 ± 1.4 **HT:** - Total urogenital sub-scale:2.26 ± 2.4 - Sexual problems: 1.05 ± 1.3 - Bladder problems: 0.63 ± 1.1 - dryness: 0.58 ± 1.0	–	–	Significant for HT
6	Palma2019(31)	MGCS: 25.2 ± 10.2 MENQOL: 4.3 ± 1.1	- MGCS(3 mth-baseline): _3.4 ± 4.3 - MENQOL(3 mth-baseline): _1.0 ± 1.3 - MENQOL(6 mth baseline): _0.6 ± 1.1 - MENQOL(6 months-3 months): 0.4 ± 0.7	–	–	Significant
7	Mahdavian2019(19)	-High dose: 1.88I -Median dose: 2 -Low dose: 2.83 (IQR)	**6wk**: -High dose: 1.78 -Median dose: 1.95 -Low dose: 1.97 (IQR) **12wk:** -High dose: 2.33 -Median dose: 2.05 -Low dose: 1.20 (IQR)	3(IQR)	- 6 wk: 1.82 - 12 wk: 1.18 - (IQR)	Significant in high dose group
8	Khayatan2019(32)	- Desire:1.62 ± 0.39 - Arousal:1.56 ± 0.19 - Lubrication: 1.77 ± 0.38 - Orgasm:1.36 ± 0.22 - Satisfaction: 1.53 ± 0.50 - Dyspareunia:1.97 ± 0.35 - FSFI:9.91 ± 0.41	- Desire: 4.29 ± 0.58 - Arousal: 4.38 ± 0.48 - Lubrication:5.35 ± 0.43 - Orgasm: 5.07 ± 0.55 - satisfaction: 4.67 ± 0.33 - Dyspareunia: 5.07 ± 0.60 - FSFI: 28.98 ± 1.72	- -Desire:1.50 ± 0.38 - Arousal: 1.46 ± 0.22 - Lubrication: 1.67 ± 0.45 - Orgasm: 1.30 ± 0.17 - Sexual satisfaction: 1.73 ± 0.53 - Dyspareunia:2.09 ± 0.34 - FSFI: 9.77 ± 0.28	- Desire: 2.90 ± 0.40 - Arousal:2.71 ± 0.34 - Lubrication: 2.89 ± 0.39 - Orgasm: 2.76 ± 0.27 - Satisfaction:3.1 ± 0.41 - Dyspareunia: 3.09 ± 0.47 - FSFI: 17.59 ± 0.51	Significant

Table 2 (*Continued*)

ID	Author, year,(ref),	Score of intervention group		Score of control group		Results
		Before N(%) /Mean(SD)	After N(%) /Mean(SD)	Before N(%) /Mean(SD)	After N(%) /Mean(SD)	
9	Ghorbani2019(33)	- Desire: 1.72 ± 0.75 - Arousal: 2.53 ± 1.16 - Lubrication: 3.16 ± 1.16 - Orgasm: 2.83 ± 1.39 - Satisfaction: 2.88 (1.29) - Dyspareunia: 3.75 ± 1.76 - FSFI: 16.82 ± 5.66 - MENQOL: 72.65 ± 21.54	- Desire: 2.69 ± 0.78 - Arousal: 3.47 ± 1.12 - Lubrication: 3.63 ± 0.01 - Orgasm: 3.35 ± 1.32 - Satisfaction: 3.97 ± 1.14 - Dyspareunia: 4.62 ± 1.45 - FSFI: 21.73 ± 5.45 - MENQOL: 50.62 ± 16.46	- Desire: 2.11 ± 0.89 - Arousal: 2.65 ± 0.90 - Lubrication: 3.19 ± 1.00 - Orgasm: 2.90 ± 0.94 - Satisfaction: 2.98 ± 0.98 - Dyspareunia: 4.39 ± 1.46 - FSFI: 18.08 ± 4.39 - MENQOL: 68.90 ± 27.64	- Desire: 2.32 ± 0.80 - Arousal: 2.23 ± 1.51 - Lubrication: 2.53 ± 1.66 - Orgasm: 2.33 ± 1.62 - Satisfaction: 2.81 ± 1.25 - Dyspareunia: 3.76 ± 2.23 - FSFI: 15.99 ± 7.72 - MENQOL: 66.97 ± 27.37	Significant
10	Abedi2018(20)	FSFI: 9.4 ± 2.8	FSFI: 33.79 ± 0.78	FSFI: 10.36 ± 8.03	FSFI: 18.9 ± 1.09	Significant
11	Suwanvesh2017 (23)	- Dryness: 1.53 ± 0.93 - Soreness: 0.81 ± 0.88 - Irritation: 0.91 ± 0.92 - Discharge: 0.27 ± 0.45 - Dyspareunia (sexually active): 1.34 ± 1.04	**After 6 wk:** - Dryness: 0.51 ± 0.63 - Soreness: 0.16 ± 0.48 - Irritation: 0.30 ± 0.51 - Discharge: 0.11 ± 0.39 - Dyspareunia (sexually active): 0.62 ± 0.77 **After 12 wk:** - Dryness: 0.23 ± 0.57 - Soreness: 0.11 ± 0.44 - Irritation: 0.16 ± 0.43 - Discharge: 0.07 ± 0.25 - Dyspareunia (sexually active): 0.45 ± 0.68	- Dryness: 1.40 ± 0.80 - Soreness: 0.76 ± 0.79 - Irritation: 1.02 ± 0.84 - Discharge: 0.38 ± 0.66 - Dyspareunia (sexually active): 1.29 ± 0.99	**After 6 wk:** - Dryness: 0.45 ± 0.70 - Soreness: 0.11 ± 0.39 - Irritation: 0.33 ± 0.52 - Discharge: 0.14 ± 0.35 - Dyspareunia (sexually active): 0.54 ± 0.88 **After 12 wk:** - Dryness: 0.21 ± 0.56 - Soreness: 0.04 ± 0.31 - Irritation: 0.19 ± 0.45 - Discharge: 0.09 ± 0.30 - Dyspareunia (sexually active): - 0.25 ± 0.67	NS
12	Lee2017(34)	Sexual score: 1.56 ± 1.64 KMI: 34.05 ± 5.82 MENQOL: 1.00 ± 0.64	**Sexual score:** 6 wk: 1.25 ± 1.46 12 wk: 0.91 ± 1.40 **KMI:** 6 wk: 28.20 ± 14.65 12 wk; 27.10 ± 15.91 **MENQOL:** 6 wk: 0.66 ± 0.48 12 wk: 0.57 ± 0.51	Sexual score: 2.08 ± 1.73 KMI: 34.60 ± 5.04 MENQOL: 1.33 ± 0.83	**Sexual score:** 6 wk: 1.40 ± 1.70 12 wk: 0.95 ± 1.04 **KMI**: 6 wk: 30.28 ± 14.91 12 wk: 28.28 ± 14.49 **MENQOL:** 6 wk: 0.76 ± 0.64 12 wk: 0.58 ± 0.43	Significant
13	Ghazanfarpour 2017(21)	Vaginal pH: 5.6±0.7 MV: 43.1±7.6	Vaginal pH: 5.3±0.94 MV: 47.1±4.3	Vaginal pH: 5.8±0.87 MV: 45.1±4.5	Vaginal pH: 5.7±1.1 MV: 47.6±4.4	NS
14	Davinelli2017(9)	- Sexual problems (Moderate):100% - Dryness (Moderate): 93.3 % - Bladder problems (Mild): 66.7 %	- Sexual problems (1 mth): 76.7 % - Sexual problems (3mth): 26.7 % - Dryness (1mth): 76.6 % - Dryness (3mth): 13.3 % - Bladder problems (1mth): 33.4 % - Bladder problems (3mth): 13.3 %	- Sexual problems (Moderate): 100 % - Dryness (Moderate):93.3 % - Bladder problems (Mild): 83.3 %	- Sexual problems (1 mth):80 % - Sexual problems (3mth): 97.7 % - Dryness (1mth): 89.9 % - Dryness (3mth): 89.9 % - Bladder problems (1mth): 76.6 % - Bladder problems (3mth): 63.3 %	Significant
15	Yaralizadeh2016 (11)	- Burning: 6(20 %) - Itching:5(16.7 %) - Dryness:4(13.3 %) - Pallor:7(23.3 %) - Dyspareunia:3(10 %)	- Burning (2 wk):14(46.7 %) - Burning (4wk):0 - Burning (8 wk):0 - Itching(2 wk):3(10 %) - Itching(4 wk):0 - Itching(8 wk):0 - Dryness (2 wk): 21(70 %) - Dryness (4wk):0 - Dryness (8 wk):0 - Pallor (2 wk):9(30 %) - Pallor (4 wk):1(3.3 %) - Pallor (8 wk):0 - Dyspareunia(2 wk):21(70 %) - Dyspareunia(4 wk):1(3.3%) - Dyspareunia(8 wk):0	- Burning: 7(23.3 %) - Itching: 3(10 %) - Dryness: 5(16.7 %) - Pallor: 6(20 %) - Dyspareunia: 4(13.3 %)	- Burning (2 wk):7(23.3 %) - Burning (4 weeks):8(26.7 %) - Burning (8 wk):7(23.3 %) - Itching(2 wk): 2(6.7 %) - Itching(4 wk):3(10 %) - Itching(8 wk):2(6.7 %) - Dryness (2 wk): 15(50 %) - Dryness (4 wk):15(50 %) - Dryness (8 wk):17(56.7 %) - Pallor (2 wk):6(20 %) - Pallor (4 wk):6(20 %) - Pallor (8 wk):6(20 %) - Dyspareunia(2 wk): 18(60 %) - Dyspareunia(4 wk): 18(60 %) - Dyspareunia(8 wk):22 (73.3 %)	Significant
16	Aghamiri2016(8)	Loss of interest in sex: 2.3 ± 0.8	4wk: 2.0 ± 0.8 8wk: 1.4 ± 0.7 12wk: 1.1 ± 0.7	2.1 ± 0.9	4wk: 2.1 ± 0.9 8wk: 2.1 ± 0.8 12wk: 2.2 ± 0.8	Significant
17	Carmignani2015 (35)	- Vaginal pH(HT) : 5.7 ± 1.1 - Vaginal pH(soy) : 5.8 ± 1.0	- Vaginal pH(HT): 4.6 ± 0.8 - Vaginal pH(soy): 5.9 ± 1.2	- Vaginal pH :5.8 ± 1.2 - MV: 43.4 ± 27.2	- Vaginal pH :5.5 ± 1.3 - MV: 46.7 ± 25.6	NS

Table 2 (*Continued*)

ID	Author, year,(ref),	Score of intervention group		Score of control group		Results
		Before N(%) /Mean(SD)	After N(%) /Mean(SD)	Before N(%) /Mean(SD)	After N(%) /Mean(SD)	
		- MV(HT): 41.2 ± 23.4 - MV(soy): 41.9 ± 23.6	- MV(HT): 59.3 ± 11.8 - MV (soy): 41.3 ± 22.5			
18	Lima2014(25)	- dryness:3 (3–1)* - Dyspareunia: 3 (3–0)* - Vaginal pH:7.1 ± 0.9	- Dryness(4week):2 (3–0)* - Dyspareunia(4wk):2 (3–0)* - dryness(12 wk):1 (2–0)* - Dyspareunia(12wk): 0 (3–0)* - vaginal PH(12 wk):5.4 ± 0.8	- dryness(12wk): 2 (3–1)* - Dyspareunia(12wk): 2 (3–0)* - vaginal PH:7.4 ± 0.8	- dryness(4wk):2 (3–0)* - Dyspareunia(4wk):1 (3–0)* - dryness(12wk): 2 (3–0)* - Dyspareunia(12wk): 1 (3–0)* - vaginal PH(12 wk:7.1 ± 0.8	Significant
19	Tit2013(36)	Severe cases of Urogenital symptoms : 43.5%	After 3 mth: 37.1 % After 6 mth: 29 % After 12 mth: 19.3 %	Severe cases of Urogenital symptoms: 41.5%	After 3 mth: 41.5 % After 6 mth: 41.5 % After 12 mth: 39.6 %	Significant
20	Lima2013(26)	- dryness(Isoflavone): 70% intense/30%moderate - dryness(CEE):60 %intense/40 %moderate - Dyspareunia(Isoflavone): 60 %intense/40 %moderate - Dyspareunia(CEE):55 %intense/45 %moderate - MV(isoflavone): 3.7 - MV(CEE):0	- dryness(isoflavone,4wk): 10%intense/66.7%moderate/23.3%mild - dryness(CEE,4wk):50 % moderate/40 %mild/5%intense - dryness(isoflavone,12wk):56.7 %mild/3.3 % moferate/40 %none - dryness(CEE,12wk):35 % mild/65 %none - Dyspareunia(isoflavone/4wk):10 %intense/46.7 % moderate/33.3 %mild - Dyspareunia(CEE/4wk):15 %intense/25 %moderate/60%mild - Dyspareunia(isoflavone,12wk):56.7 %mild/3.3 % moderate/40 %none - Dyspareunia (CEE,12wk):5%moderate/55 %mild/40 %none - MV(isoflavone,4wk): 27.5 - MV(CEE,4wk):30 - MV(isoflavone,12wk): 46.2 - MV(CEE,12wk):50	- dryness:72 %intense/28 % moderate - Dyspareunia: 72 %intense/28 %moderate -MV:0	- dryness(4wk):12 %intense,64 %moderate/24 % mild - dryness(12wk):36 %moderate/44 %mild/20 %none - Dyspareunia(4wk): 12 % mild/60 %moderate/24 % intense - Dyspareunia(12wk):40 % moderate/56 %mild/4% none - MV(4wk):10 - MV(12wk):20	Significant
21	Tedeschi2012(37)	- Itching: 1.7 - Burning :1.8 - vulvo-vaginal erithema:1.5 - dryness:2.6 - dyspareunia:2.3	- Itching(2wk): 51.1 % - Burning(2wk) :-34.9 % - vulvo-vaginal erithema (2wk): -62.8 % - dryness(2wk):-45.3 % - dyspareunia(2wk):-31.7 % - Itching(4wk): -32.2 % - Burning(4wk) :-79 % - vulvo-vaginal erithema (4wk):-82.1 % - dryness(4wks):-70.1% - dyspareunia(4wk):-62.3 %	- Itching:1.4 - Burning:1.3 - vulvo-vaginal erithema:1.4 - dryness:2.4 - dyspareunia:2	- Itching(2wk): -43.8 % - Burning(2wk) :-31.5 % - vulvo-vaginal erithema (2wk): -27.4 % - dryness(2wk):-21.6 % - dyspareunia(2wk):-16.9 % - Itching(4wk): -22.9 % - Burning(4wks) :-73.1 % - vulvo-vaginal erithema (4wks): -72.6 % - dryness(4wks):-38.7 % - dyspareunia(4wk):-41.4 %	Significant
22	Le Donne2011(38)	- Genital score:3 - Colposcopy score:0 - MV:0	- Genital score:1 - Colposcopy score:2 - MV:2	- Genital score:3 - Colposcopy score:0 - MV:0	- Genital score:2 - Colposcopy score:1.5 - MV:1.5	Significant
23	Levis2010(39)	- dryness: 50 % - Menopause symptoms: 6.2 ± 2.8	- MV:40. 7 ± 18.9 - Menopause symptoms:12.15 ± 6.61	- dryness: 50 % - Menopause symptoms: 6.2 ± 2.8	- MV:43.0 ± 19.3 - Menopause symptoms:12.95 ± 7.10	Significant
24	Radhakrishnan2009 (40)	- MV: 48.11 ± 26.93 - KMI: 24.63 ± 27.51	- MV: 52.62 ± 23.42 - dryness: -60 % - KMI: 27.49 ± 28.77	- MV: 50.0 ± 28.65 - KMI: 33.26 ± 31.43	- MV: 51.7 ± 24.51 - dryness:-15 % - KMI: 29.01 ± 29.93	Significant
25	Hanachi 2008(41)	–	- Reduction of 70 % of vaginal symptoms and 62.5 % of sexual symptoms in the soy milk group - 50% reduction of vaginal symptoms and 45% of sexual symptoms in the soy-milk + exercise group	–	–	Significant

Table 2 (*Continued*)

ID	Author, year,(ref),	Score of intervention group		Score of control group		Results
		Before N(%) /Mean(SD)	After N(%) /Mean(SD)	Before N(%) /Mean(SD)	After N(%) /Mean(SD)	
26	Nahas 2007(27)	- MV: 50 (0–52)* - Vaginal pH: 6 (5.5–7)* - KMI: 23.3 ± 7.0	No significant change was observed in MV and Vaginal pH	- MV: 50 (2.8–51)* - Vaginal pH: 6 (5.5–6.5)* - KMI: 22.4 ± 7.4	No significant change was observed in MV and Vaginal pH	Significant for KMI
27	D'anna2007(42)	MV: 22.9 ± 1.71	MV: 22.2 ± 1.52	MV: 23.7 ± 1.60	MV: 20.6 ± 1.67	NS
28	Chandeying 2007 (24)	- Dryness:2.5 - Dyspareunia:1.6 - Loss of sex satisfaction:2.2 - Loss of interest in sex:2.6 - Urinary frequency: 2.6 - UI:2	- Dryness(1 mth): 1.2 - Dryness(3 mth): 0.6 - Dryness(6 mth): 0.2 - Dyspareunia(1 mth):0.8 - Dyspareunia(3mth):0.3 - Dyspareunia(6mth):0.3 - Loss of sex satisfaction (1mth):1 - Loss of sex satisfaction (3mth):0.8 - Loss of sex satisfaction (6mth):0.5 - Loss of interest in sex (1mth):1.2 - Loss of interest in sex (3mth):1 - Loss of interest in sex (6mth):0.6 - Urinary frequency(1 mth):2 - Urinary frequency(3 mth):1.6 - Urinary frequency(6 mth):1.1 - UI:(1mth):2 - UI:(3mth):0.8 - UI:(6 mth):1.1	–	–	Significant
29	Shah 2006 (43)	- sexual desire:62.9 % - dryness and dyspareu-nia:75.9 % - Urinary urgency /UI:60 %	- the recovery rate of urinary symptoms: 35.7 % - the recovery rate of sexual symptoms: 21.4 %	- sexual desire:60.4 - dryness and dyspareu-nia:71.8 - Urinary urgency /UI:59.3 %	- the recovery rate of urinary symptoms: 26.7 % - the recovery rate of sexual symptoms: 40 %	NS
30	Manonai 2006(6)	- dryness: 0.81 ± 0.71 - Dyspareunia: 1.10 ± 0.88 - Vaginal pH: 7.06 ± 0.72 - MV: 38.68 ± 32.66 - SI: 0.67 ± 0.68 - UI: 0.17 ± 0.38 - Urgency: 0.64 ± 0.72 - Frequency: 0.67 ± 0.76	- dryness: 0.72 ± 0.74 - Dyspareunia: 1.05 ± 1.13 - Vaginal pH: 7.11 ± 0.88 - MV: 30.83 ± 30.39 - SI: 0.72 ± 0.66 - UI: 0.19 ± 0.47 - Urgency: 0.64 ± 0.68 - Frequency: 0.61 ± 0.80	- dryness: 0.61 ± 0.84 - Dyspareunia: 1.16 ± 1.01 - Vaginal pH: 7.15 ± 0.77 - MV: 32.99 ± 32.18 - SI: 0.75 ± 0.65 - UI: 0.35±.014 - Urgency: 0.58 ± 0.65 - Frequency: 0.56 ± 0.61	- dryness: 0.92 ± 0.99 - Dyspareunia: 0.95 ± 0.85 - Vaginal pH: 7.43 ± 0.63 - MV: 29.58 ± 28.12 - SI: 0.72 ± 0.74 - UI: 0.25 ± 0.50 - Urgency: 0.64 ± 0.68 - Frequency :- 0.61 ± 0.69	Significant
31	Kaari2006(44)	- vaginal PH:5.1 - Parabasal cells:30 % - Intermediate cells:55% - -Superficial cells:10 %	- vaginal PH(3 mth): 5.6 - vaginal PH(6 mth):5.6 - Parabasal cells(3mth):35% - Intermediate cells (3mth):55 % - Superficial cells(3mth):8% - Parabasal cells(6mth):35 % - Intermediate cells (6mth):58 % - Superficial cells(6mth):5%	- vaginal PH: 5.6 - Parabasal cells:50 % - Intermediate cells:40 % - Superficial cells:5%	- vaginal PH(3 mth): 4.6 - vaginal PH(6 mth): 4.8 - Parabasal cells(3mth):0 % - Intermediate cells (3mth):20 % - Superficial cells(3mth):30 % - Parabasal cells(6mth):5% - Intermediate cells (6mth):23 % - Superficial cells(6mth):25 %	NS
32	Chiechi2003(10)	- MV(diet group): 31.8 ± 29.5 - MV(HRT group): 36 ± 29.8 - KI(diet group):7.9 ± 9.1 - KI(HRT group):12.8 ± 26.08	- MV(diet group): 44.4 ±30.0 - MV(HRT group): 75.1 ± 16.2 - KI(diet group): 23.4 ± 26.2 - KI(HRT group):47.1 ± 28.6	- MV: 47.1 ± 27.8 - KI: 21.4 ± 18.9	- MV: 50.1 ± 28.0 - KI:22.1 ± 21.5	Significant
33	Kotsopoulos2000 (45)	- dryness: 0.91 ± 0.19 - Dyspareunia: 0.27 ± 0.16 - Libido: 0.97 ± 0.16	- dryness: 0.56 ± 0.18 - Dyspareunia: 0.35 ± 0.13 - Libido: 0.53 ± 0.15	- dryness: 1.00 ± 0.16 - Dyspareunia: 0.54 ± 0.20 - Libido: 0.54 ± 0.20	- dryness: 0.85 ± 0.16 - Dyspareunia: 0.34 ± 0.16 - Libido: 0.34 ± 0.16	Significant for vaginal dryness and libido

Wk:week, mth:month; KI: karyopycnotic index, MV: maturation value, NS: not significant, UTI: Urinary tract infection, HT: Hormone therapy, HRT: hormone replacement therapy, NR: Not reported, NS; not significant, *:median (maximum–minimum values), UI: Urinary incontinence, SI: Stress incontinence.

In a clinical trial, Ghazanfarpour et al.(2016) examined the effect of fennel pills on vaginal atrophy in postmenopausal women but they did not observe any positive effect on vaginal atrophy (vaginal PH variations and vaginal cytology) [21].

Yaralizadeh et al.(2016) also studied the effect of fennel vaginal cream on vaginal atrophy in postmenopausal women.

After the end of the intervention and comparison of the results with the placebo group, they observed that the symptoms including burning, itching, and dyspareunia were reduced in the intervention group after 8 weeks of treatment [11].

Isoflavone was studied more than other phytoestrogens and it was examined in both oral and topical conditions [61–64].

Lee et al.(2017)evaluated the effect of isoflavone on climacteric signs and quality of life in postmenopausal women in a double-blind, placebo-controlled study and they observed that daily use of 70 mg of isoflavone supplementation improve the Kupperman index after 6 weeks and 12 weeks of treatment was effective compared to the pre-intervention scores [34].

Davinelli et al(2017) in their double-blind study to determine the effect of daily isoflavone supplement on the health related to the quality of life in postmenopausal women, perceived that symptoms associated with sexual problems, bladder disorders and vaginal dryness in the intervention group indicated a higher percentage of decrease after 3 mth of intervention [9].

The most important effect of estrogen deficiency on the urogenital system is the development of symptoms such as vaginal dryness, dysuria, dyspareunia and burning. Vaginal alkalization may also occur, causing urogenital infections [63,65]. Carmignani et al. (2015) revealed that isoflavone 90 mg / day in the form of food supplement powder, which contains soy protein, is effective in improving vaginal dryness.

Other urinary and sexual problems in the treatment groups were unaltered, and this may be due to the multifactorial etiology of these problems [35].

The effect of isoflavones derived from Glycine max (L.) Merr.in the treatment of vaginal atrophy by topical gel compared to placebo was evaluated. Systemic hormone therapy with natural estrogens issued for the relief of menopausal symptoms. However, a substantial proportion of women with urogenital complaints and changes in sexuality have no clinical improvement from systemic hormone treatment, where the combination of local treatment for relief of symptoms is required in this group [25,66].

Tedeschi and Benvenuti(2012) in a study compared symptoms of vaginal atrophy in women who received oral vaginal gel in addition to oral isoflavone and women who did not use any vaginal treatment.

A significant improvement in vaginal dryness and dyspareunia was seen after 4 weeks of treatment [37]. In the case of consuming Genistein, Diadzein, similar outcomes were also reported in some studies [6,38,42].

Lima et al.(2014) in a study on the morphology of vaginal epithelium and the occurrence of estrogen receptors in postmenopausal women, observed that average scores of dryness of the vagina, dyspareunia and pH of vagina in the intervention group decreased after 12 weeks of treatment, while the maturation value and thickness of the epithelium of the vagina increased [25].

They also studied the effect of isoflavone vaginal gel, vaginal gel of conjugated estrogens and placebo on vaginal atrophy and observed that common complaints of women such as vaginal dryness and dyspareunia were diminished in both groups of isoflavone and conjugated estrogens, but the percentage of reduction was reported to be higher in conjugated estrogen group [26].

Soy isoflavones have gained a lot of interest in last two decades as a natural approach to the management of menopause and many studies have been conducted with conflicting results using soy isoflavones either as a part of protein supplement or as purified extract tablet. A 25 g soy supplement containing 75 mg of isoflavones may be an effective alternative therapy for menopausal symptoms such as sex hormones, vaginal cytology, uterine endometrium and etc. [40].

According to the observations of Kaari et al.(2006) in their 6-month trial, there was a decrease in the symptomatology in both estrogen and isoflavone groups. There was also a significant decline in vaginal pH, an increase in superficial vaginal cells and endometrium proliferation after 3 and 6 mth of treatment in the estrogen group, but no differences were observed in the isoflavone group for these variables [44].

Among other plants containing Prenylnaringenin phytoestrogens, it can be referred to the Hop Plant, which has been one of the strongest phytoestrogens up to now [67]. In this regard, the study by Aghamiri et al(2016) about the effect of phytoestrogen pill on menopausal symptoms showed that the rate of unwillingness to have sex compared to the placebo group at the end of the research declined [8]. Enhancing the diet of postmenopausal women with food containing phytoestrogens such as soybean and soy milk can also have a beneficial effect on urogenital problems of menopausal women [10,36,41].

Conclusion

Phytoestrogens as a safe and uncomplicated method in various forms of gel, vaginal cream, vaginal suppository, capsule, extract or enriched diet can improve the urogenital symptoms of menopause as effective as hormone therapy and they can promote the quality of life of postmenopausal women.

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Ethics approval

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Contributor ship

FA and FAR conceived the study, interpreted the data, and drafted the manuscript. NR,RP acquired the data and interpreted the data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Search strategy

ID	Search term
#1	' menopause' [tiab], OR ' menopausal symptoms' [tiab], urogenital syndrome [tiab], 'urogenital atrophy' [tiab], OR 'atrophy' [tiab], OR 'dyspareunia' [tiab] OR 'Dysuria' [tiab] 'OR 'urogenital symptoms '[tiab], OR ' Urogenital Syndrome of Menopause' [tiab], OR 'GSM' [tiab]
#2	'phytoestrogen ' [tiab] OR 'phytoestrogens' [tiab] OR ' Plant Estrogen' [tiab] OR ' Plant Estrogens' [tiab], OR ' Estrogen Like Plant Extract, [tiab], OR ' Estrogen-Like Plant Extracts' [tiab] OR ' Phyto-Estrogen' [tiab], OR ' Estrogen, Plant' [tiab], OR ' Plant Extracts, Estrogen-Like'

(*Continued*)

ID	Search term
	[tiab], OR ' Fennel' [tiab], OR ' Pueraria Mirifica' [tiab], OR "Hop plant (Humuluslupulus L.)'[tiab], OR ' Glycine Max (L.) Merr' [tiab], OR ' Soy' [tiab], OR ' red clover' [tiab], OR 'Cimicifugaracemosa' [tiab], OR 'Genistein' [tiab], OR 'Diadzein' [tiab], OR 'Isoflavone'[tiab]
#1 AND #2	

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