Effects of Combination Therapy with *Bunium persicum* and *Foeniculum vulgare* Extracts on Patients with Polycystic Ovary Syndrome

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Abstract

Background: Considering the side effects of common drugs used to treat polycystic ovary syndrome (PCOS), researchers have turned their attention to natural compounds, including medicinal plants. *Foeniculum vulgare* has estrogenic properties and has been traditionally used to treat gynecological disorders. *Bunium persicum* has medical aspects that have not yet been evaluated, so the aim of this study was to evaluate the effects of combination therapy with these extracts on clinical symptoms of women with PCOS.

Materials and Methods: In this double-blind clinical trial study, 70 women with PCOS referred to infertility clinics, were selected and randomly divided into two groups. The intervention group received *B. persicum* capsule 60 mg plus *F. vulgare* capsule 25 mg) twice daily for 4 months and the control groups received routine intervention. Before and after the intervention, levels of luteinizing hormone (LH), follicle-stimulating hormone, progesterone, prolactin, testosterone and dehydroepiandrosterone sulfate (DHEAS) levels, hirsutism score, and menstrual pattern were recorded and endometrial thickness and follicle count were determined by ultrasound. Data were analyzed by the SPSS21 software.

Results: Treatment with *B. persicum* and *F. vulgare* extracts significantly decreased LH and DHEAS levels, hirsutism score, and significantly increased menstrual duration compared to the control group. Before the intervention, 5.7% of the intervention and control groups had the normal menstrual pattern, while after the intervention 31.4% of the intervention group and 25.7% of the control group had the normal pattern.

Conclusion: Regarding the effect of these extracts combination and because they have no side-effects, which is a great advantage over chemical drugs, using of these plants recommend.

Keywords: *Bunium persicum*, *Foeniculum vulgare* extracts, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases of women of childbearing age with the symptoms of nonovulation with clinical or biochemical evidence of elevated androgen levels (hirsutism, acne, and alopecia) appears. According to the Rotterdam criteria, for at least two of the three criteria for oligomenorrhea or amenorrhea, hyperandrogenism, and polycystic ovary morphology, PCOS must be matched for ultrasound evaluation in the individual, after excluding other medical conditions leading to the abnormal menstrual cycle.[1]

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Prevalence estimates ranged from 6% to 26%, depending on the population under study and the diagnostic criteria used.[2] A recent study by Tehrani *et al.*, on 1266 women randomly selected from women of childbearing age from different geographical areas of Iran, indicates that the prevalence of this complication in Iran, as defined by the National Institutes of Health, is 1/7. Percentage based on androgen association criteria (Androgen Excess Society), 11.7%, and based on the Rotterdam criteria, 14.6% reported.[3]

Women with PCOS have numerous hormonal abnormalities and metabolic problems that affect their health.[4] Infertility affects 4% of PCOS patients. Approximately 95%–90% of women with no ovulation who have referred to an infertility clinic have PCOS.[5,6]

PCOS syndrome can be a source of psychological distress for a variety of reasons. Studies have shown that the quality of life of women with PCOS is lower than that of healthy people and even compared to those with other gynecological diseases. Therefore, PCOS requires special medical attention apart from hormonal and reproductive disorders.[7]

The most well-known treatment for PCOS is the use of drugs such as clomiphene citrate, metformin, letrozole, spironolactone, and tamoxifen.[8] Given the side effects of these drugs, identifying and preparing alternative drugs is of great importance.[9] Traditional medicine and herbs have been used to treat a wide variety of gynecological diseases besides being cost-effective and less side effects.

Many herbal remedies have been found to have beneficial effects on many diseases today.[9] The beneficial effects of several medicinal herbs, including *fennel*,[9] tea,[10] and five-fingered plant[11] on PCOS symptoms have already been shown in animal models.

Fennel or anise (*Foeniculum vulgare*) belongs to the genus *Foeniculum*.[12] It is rich in compounds similar to the female hormone estrogen (phytoestrogens).[13] *Fennel* contains 4%–6% essential oils, the most important of which is anethole (50%–80%), fenshon (8%), and limonene (5%). *Fennel* also contains flavonoids, phenolic acids, hydroxy acids, coumarin, and tannins.[14] *F. vulgare* has been implicated in increasing milk secretion, treatment of dysmenorrhea, ease of birth, and sexual desire due to its phytoestrogens.[15]

The black *cumin* or *cumin*, scientifically named *Bunium Persicum Boiss* belongs to the family Apiaceae. *Cumin* contains significant amounts of essential oil (9%) which is widely used in the pharmaceutical, food, health, and cosmetics industries.[16] Several therapeutic effects are explained for this plant in traditional and modern medicine. *B. persicum* is used for treating gastrointestinal and urinary disorders such as stomatitis stimulant, flatulent indigestion, dyspeptic headache, relieve of heartburn, colic, and diarrhea as well as dyspepsia, hysteria, and for improving live[17] but still needs further research to isolate the specific phytoconstituent to target the specific chronic disease.[16] Despite a variety of phytochemical

and experimental research on it, there is no considerable update on all related outcomes. Many of the experimental and pharmacological studies on *B. persicum* have not evaluated the medical aspects also despite various experimental studies, few trials on remarked activities of *B. persicum* is still remained to be covered.[18]

The clinical efficacy of *fennel* extract was compared with echinophora-platyloba in the primary dysmenorrhea. The clinical trial was carried out on students with dysmenorrhea in Shahrekord. There was no significant difference in the mean of dysmenorrhea severity during the two cycles before the intervention between the two groups, but during the two cycles after the intervention, both drugs could reduce the severity of dysmenorrhea pain but *fennel* extract showed more significant.[19]

Given to the differences reported in the essential oil composition of this plant, and the lack of study on the combination of *B. persicum and F. vulgare* for PCOS the current study was done.

MATERIALS AND METHODS

This study was a double-blind clinical trial (ethical code: IR.SKUMS.REC.1397.162). The study population consisted of 70 women with PCOS who referred to Imam Ali Women's Clinic and Shahrekord Infertility Clinic, Shahrekord, Iran. A sample size of 35 prospectively enrolled participants in each randomization arm will yield a statistical power of 80 at a significance level of 0.01. Inclusion criteria were the age range of 16–40 years and having normal body mass index (BMI) (18.5–24.9) and PCOS-based ultrasound findings and criteria included the presence of 12 follicles or more in each ovary of 2–9 mm or ovarian volume >10 ml, presence of oligomenorrhea or amenorrhea. Clinical or biochemical signs of hyperandrogenism and hirsutism were rated by a Freeman-Gallway score of 8 or higher. Secondary causes of hyperandrogenism and ovulation dysfunction will be excluded before a PCOS diagnosis is confirmed, such as ovarian interstitial tumor or adrenal tumor, congenital adrenal hyperplasia, hyperprolactinemia, and thyroid dysfunction. The women who have previously been diagnosed with a uterine disorder or have experienced recurrent spontaneous abortions or had medical conditions that contraindicate assisted reproductive technology and/or pregnancy, such as poorly controlled type 1 or type 2 diabetes mellitus; undiagnosed liver disease or dysfunction (based on serum liver enzyme test results); renal disease or abnormal serum renal function; significant anemia; history of deep venous thrombosis, pulmonary embolus, or cerebrovascular accident; uncontrolled hypertension or known symptomatic heart disease; history of (or suspected) cervical carcinoma, endometrial carcinoma, or breast carcinoma; and undiagnosed vaginal bleeding and the women who were are unable to comply with the study procedures were excluded from the study.

Method of preparation of capsules

B. persicum and *F. vulgare* seeds are prepared from a local Atari in Shahrekord and after approval by the botanist, they are powdered by electric grinding and powdered using 96% ethanol by soaking three times a night without using heat, extract, and solvent were gently heated and vacuum removed. The extract was dried at a gentle temperature (below 40°C) and mixed with starch.

The extract is thoroughly mixed with starch (as a filler in capsules) to obtain a uniform powder mixture and to have the same consumption in individuals. Peel capsules were made and each capsule containing 25 mg of black *cumin* (based on the dose of *cumin* soft capsule made by Barij Essence Pharmaceuticals) and 60 mg of *fennel* (based on the dose of the soft phenolic capsule made by Barij Essence Pharmaceuticals) or starch (as a placebo) filled with an electric filling capsule device without the use of a hand.[19]

Sampling

Participants ($n = 70$) will be allocated randomly into one of the two study groups at a ratio of 1:1 using a random number table. Individual characteristics, hirsutism score of patients (according to Freeman and Gallway criteria),[20] and menstrual pattern (amenorrhea or oligomenorrhea) were recorded in the attached checklist for each patient. Age and weight were matched and divided into two groups.

The first group received a herbal capsule and the second group a placebo filled with starch and resembled a herbal capsule, given twice daily for 4 months. Patients continued to receive routine medications for the treatment of PCOS. The participants were evaluated monthly for regular drug use, hirsutism status, and menstrual pattern. Questionnaires and checklists were completed at the end of each month.

After 4 months of drug use, ultrasonography of ovarian volume and follicle count was again performed and according to the obtained data, the checklist was completed. The study was a double-blinded study, with the intervention and data analyzer blinded to the groups (pretestosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were checked on day 3 of the cycle, and ultrasonography was performed on day 13 for dominant follicles. These tests were repeated at the same time and the results were reviewed. An ultrasound was performed before treatment and once at the end of the study and the results were compared.

Data analysis

Data were analyzed by the SPSS 21 (IBM Crop., Armonk, NY) software and analyzed using descriptive statistics (including mean, standard deviation, frequency, and percentage) and inferential statistics (including independent *t* and paired *t*). The significance level was considered $P < 0.05$.

RESULTS

In the present study, 70 women with PCOS were randomly divided into two groups of intervention (*Fennel* and *Cumin*) and control groups [Figure 1]. The mean age, number of

pregnancies, number of births, number of live births, number of stillbirths, abortion, and molar pregnancy rates were not significantly different between the intervention and control groups [Table 1]. Based on the results of Table 2 after the intervention, the mean FSH and testosterone levels were not significantly different between the intervention and control groups ($P > 0/05$).

After intervention, the mean and standard deviation of LH and dehydroepiandrosterone sulfate (DHEAS) levels were significantly decreased in the intervention group ($P < 0.001$ and $P < 0.05$), whereas in the control group, there was no significant change ($P > 0.05$). After intervention, the mean and standard deviation of TSH and prolactin levels were significantly decreased in the control group ($P < 0.05$ and $P < 0.01$), whereas in the intervention group there was no significant change ($P > 0.05$). After intervention, the mean and standard deviation of progesterone levels were significantly increased in the control group ($P < 0.05$), whereas in the intervention group there was no significant change ($P > 0.05$).

According to the results of Table 3, the mean uterine endometrial thickness after intervention was not significantly different
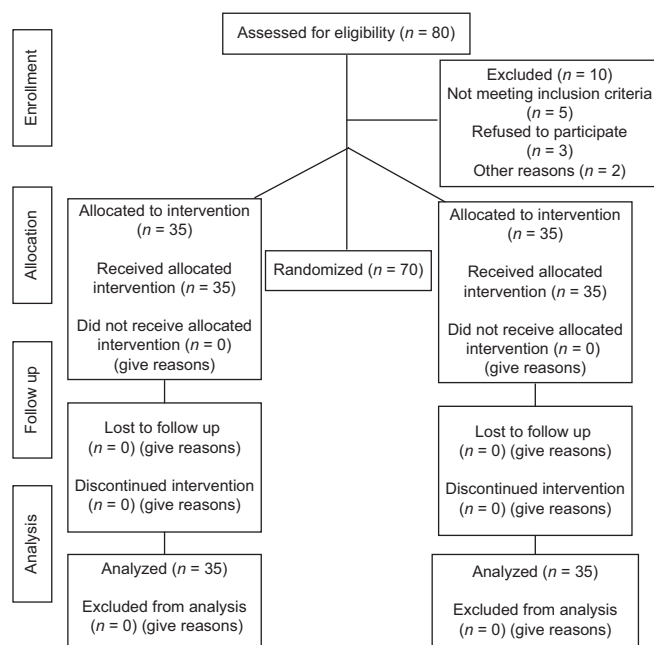
Figure 1: Consort diagram

Table 1: Demographic variable in two groups

Variable	Groups (SD±mean)		P
	Intervention	Control	
Age (years)	30.11±6.22	28.83±5.38	0.358
Pregnancy number	1.14±0.94	0.74±0.92	0.11
Child birth	0.89±0.90	0.63±0.83	0.230
Live child	0.89±0.87	0.66±0.91	0.285
Death child	0.06±0.24	0.03±0.17	0.564
Abortion	0.17±0.62	0.06±0.24	0.312
Molar pregnancy	0.03±0.17	0.0±0.0	0.324

SD: Standard deviation

between the intervention and control groups (*P* > 0.05). After the intervention, the mean number of follicles in the intervention and control groups was significantly increased (*P* < 0.001 and *P* < 0.05) and the increase in the intervention group was significantly higher than the control group (*P* < 0.05).

According to the results of Table 4, after the intervention, the mean score of hirsutism in the intervention group was significantly decreased (*P* < 0.01) but in the control group there was no significant change. Furthermore, after the intervention, the mean menstrual intervals were significantly decreased in the intervention and control groups (*P* < 0.05) and its changes were not significantly different between the two groups (*P* > 0.05). After the intervention, the

mean menstrual duration was significantly increased in the intervention group (*P* < 0.01), while in the control group there was no significant change (*P* > 0.05). The mean BMI was significantly decreased in the intervention and control groups (*P* < 0.01); however, the decrease in the intervention group was significantly higher than the control group (*P* < 0.05).

According to the results of Table 5, 2 (5.7%) of the intervention group had normal menstrual pattern before intervention, while 11 (31.4%) had normal pattern after intervention (*P* < 0.01). Furthermore, 2 (5.7%) of the control group had normal pattern

Table 2: Comparison of mean of different hormones in the study groups before and after the intervention

Variable	Groups (SD±mean)		*P*
	Intervention	Control	
FSH			
Before	2.83±3.53	3.30±1.86	0.391
After	2.69±1.98	3.19±1.78	0.275
P	0.558	0.482	
Before and after changes	0.14±1.44	0.11±0.89	0.898
LH			
Before	8.56±5.38	8.46±4.29	0.932
After	6.55±3.65	7.10±2.52	0.542
P	<0.001	0.072	
Before and after changes	2.01±2.71	1.46±4.63	0.539
DHEAS			
Before	2.41±1.27	2.35±0.33	0.591
After	2.24±0.98	2.28±0.51	0.180
P	0.021	0.340	
Before and after changes	0.18±0.43	0.07±0.45	0.339
TSH			
Before	3.56±1.37	2.86±0.91	0.014
After	3.40±1.28	2.62±0.77	0.003
P	0.185	0.029	
Before and after changes	0.16±0.70	0.23±0.61	0.633
Prolactin			
Before	7.96±4.91	11.59±10.33	0.067
After	7.29±5.91	10.27±9.28	0.115
P	0.172	0.006	
Before and after changes	0.67±2.85	1.32±2.67	0.328
Total testosterone			
Before	0.70±1.19	0.36±0.07	0.100
After	0.53±0.26	0.43±0.45	0.290
P	0.328	0.321	
Before and after changes	0.17±1.01	−0.08±0.46	0.191
Progesterone			
Before	1.01±1.33	0.92±1.14	0.767
After	0.91±1.10	0.96±1.20	0.856
P	0.177	0.015	
Before and after changes	0.10±0.42	−0.04±2.67	0.064

SD: Standard deviation, TSH: Thyroid stimulant hormone,
LH: Lutenizing hormone, DHEAS: Dehydroepiandrosterone sulfate,
FSH: Follicle-stimulating hormone

Table 3: Comparison number of follicles and endometrial thickness in the study groups before and after the intervention

Variable	Groups (SD±mean)		*P*
	Intervention	Control	
Endometrial thickness			
Before	10.19±3.63	10.33±2.87	0.856
After	9.80±3.57	10.06±2.93	0.743
P	0.183	0.201	
Before and after changes	0.39±1.86	0.27±1.23	0.898
Number of follicles			
Before	11.91±1.98	13.37±2.91	0.042
After	14.4±3.32	14.29±2.53	0.840
P	<0.001	0.011	
Before and after changes	−2.3±2.54	−0.91±2.01	0.019

SD: Standard deviation

Table 4: Comparison of mean of hirsutism and menstrual cycle in the study groups before and after the intervention

Variable	Groups (SD±mean)		*P*
	Intervention	Control	
Hirsutism score			
Before	7.94±1.71	8.17±0.95	0.493
After	7.32±1.83	7.94±1.21	0.110
P	0.002	0.160	
Before and after changes	0.60±1.60	0.23±0.94	0.126
Interval between periods			
Before	42.11±2.24	36.51±5.52	0.257
After	32.11±5.90	35.34±5.71	0.113
P	0.038	0.006	
Before and after changes	9.00±24.65	1.17±2.36	0.070
Menstrual cycle			
Before	4.63±0.97	4.14±0.73	0.021
After	5.03±0.79	4.29±0.99	0.001
P	0.004	0.419	
Before and after changes	−0.40±0.43	−0.14±1.03	0.243
BMI			
Before	24.10±2.80	24.47±2.95	0.591
After	23.31±2.31	24.18±3.01	0.180
P	<0.001	0.009	
Before and after changes	0.79±1.14	0.29±0.6	0.026

SD: Standard deviation

Table 5: Comparison of menstrual pattern frequency distribution in the study groups before and after the intervention

Groups	Before		After		P
	Normal, *n* (%)	Hypo menorrhea, *n* (%)	Normal, *n* (%)	Hypo menorrhea, *n* (%)	
Intervention	2 (5.7)	33 (94.3)	11 (31.4)	24 (68.6)	0.004
Control	2 (5.7)	33 (94.3)	9 (25.7)	25 (74.3)	0.016

before intervention, while 9 (25.7%) had normal pattern after intervention ($P < 0.05$).

Discussion

In the present study, treatment with *B. persicum* and *F. vulgare* extract significantly decreased the levels of LH and DHEAS, but did not change significantly the levels of testosterone, FSH, prolactin, and progesterone. In PCOS, the levels of female hormones (such as estrogen, progesterone, LH, and FSH) are unbalanced and increase the levels of male hormones (androgens), prolactin, and insulin.[21]

Similar studies have been reported in studies on *cumin and fennel* extract. Concerning *fennel* extract, in a 2014 study by Karampoor *et al.*, it was observed that the treatment of PCOS with *fennel* extract by Wistar rats increased serum levels of FSH and decreased LH and testosterone.[9] In a 2018 study by Shirdel *et al.*, treatment of PCOS female mice with *fennel* extract reduced LH and increased FSH.[22] In another study of PCOS female rats, *fennel* extract reduced estrogen and increased serum progesterone.[23] In a preclinical study by Ghavi *et al.*, 2015, the treatment of 15 PCOS patients with 90 mg of *fennel* extract for 3 months did not cause significant changes in TSH, LH, and DHEAS, but significantly increased FSH. The inadequate efficacy of *fennel* extract in this study was attributed to the low dose of the extract and the limited number of samples.[24]

Fennel is rich in compounds similar to the female hormone estrogen (phytoestrogens). Phytoestrogens have a functional mechanism for binding to estrogen receptors due to their structural similarity to estradiol, so they can act as agonists with estrogen receptor antagonists. Thus, phytoestrogens in *fennel* extract appear to decrease estrogen and testosterone levels in PCOS mice through negative feedback effects on LH.[22]

A study of male Wistar rats also found that treatment with an aqueous extract of *fennel* significantly reduced the levels of LH, FSH, and testosterone compared with the control group. The researchers reported that the phytoestrogens present in *fennel* (anethole and photosantoin) increase estrogen due to their estrogenic role, thereby reducing testosterone and decreasing sperm production in the seminal tube.[25]

Phytosterols are other compounds found in *fennel* that have a structure similar to cholesterol and can interfere with cholesterol absorption and lower serum levels.[26] Concerning *cumin* extract, a study by Thakur *et al*. found that treatment with *cumin* extract reduced the levels of FSH and LH hormones and increased estrogen levels,[27] which is in line with the

present study. The effects of cholesterol-lowering by *cumin* have also been observed in animal models[28] and it seems that *cumin* extract can inhibit the synthesis of androgens such as DHEAS by lowering cholesterol.

Based on the results of the present study, after the intervention, the mean BMI in the intervention and control groups was significantly reduced; however, the decrease in the intervention group was significantly higher than the control group.

High insulin levels increase fat storage and lead to overweight. Increased testosterone levels in women with PCOS are also associated with abdominal obesity.[1] Given that in the present study, *cumin* and *fennel* extract reduced LH and testosterone, this hormonal modulation may have an anti-obesity effect. Previous studies have also shown the anti-obesity effects of *cumin* and *fennel* extracts in animal models as well as in clinical trials. Concerning black cumin, in a clinical trial of Kazemipoor *et al*. In 2013, a daily intake of 30 mg of *cumin* extract was associated with a significant reduction in body weight, BMI, body fat percentage, and waist-to-hip ratio.[29]

Animal studies have also shown that *cumin* compounds exert anti-obesity effects by altering the expression of genes associated with inflammation and adipogenesis.[30] An experimental study with *fennel* extract also found that treatment of a high-fat diet with *fennel* extract reduced food intake and BMI and improved dyslipidemia, trypanosomes, and hyperglycemia.[31]

According to the results of the present study, the mean endometrial thickness after the intervention was not significantly different between the intervention and control groups, but the mean number of follicles in the intervention and control groups was significantly increased and the increase in the intervention group was significantly higher than the control group. Consistent with the present findings, in a 2011 study by Khazaei *et al*., the treatment of female rats with *fennel* extract increased the number of graphenes, antral, and multilayer follicles.[32]

In the present study, after the intervention, the mean score of hirsutism was significantly decreased in the intervention group, but it did not change significantly in the control group. In a 2014 trial of women with idiopathic hirsutism, Akha *et al*. found that topical application of 3% *fennel* extracts significantly reduced hair thickness compared to the control group.[33] Another study of women with idiopathic hirsutism found that applying 1% and 2% *fennel* extract reduced the hirsutism score by 7.8% and 18.3%, respectively, while control group's hirsutism score was 0.5%.[34]

In the present study, after the intervention, the mean menstrual intervals were significantly reduced in the intervention and control groups, and its changes were not significantly different between the two groups. However, after the intervention, the mean menstrual duration was significantly increased in the intervention group, while the control group did not change significantly. Before intervention 2 (5.7%) of the intervention group had the normal menstrual pattern, while after intervention 11 (31.4%) had the normal pattern. Furthermore, 2 (5.7%) of the control group had a normal pattern before the intervention, while 9 (25.7%) had a normal pattern after the intervention.

These results show that the combination of *lemongrass* and *cumin* extract has improved menstrual duration and improved menstrual pattern compared to the control group. A review of the studies did not find a study evaluating the effectiveness of *B. persicum* and *F. vulgare* extracts on menstrual pattern; however, studies in women with dysmenorrhea[35] and premenstrual syndrome[36] have found that *fennel* extract improves pain, symptoms of premenstrual syndrome, and reduces menorrhagia.

CONCLUSION

In the present study, the treatment of women with PCOS by the combination of *fennel* and *cumin* extract decreased LH and DHEAS levels, significantly decreased hirsutism score, significantly decreased BMI and increased menstrual duration so this combination can be used as a cost-effective and safe combination to improve PCOS symptoms. Positive results from such trials would confirm the medicinal usefulness of traditional medicines.

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Conflicts of interest

There are no conflicts of interest.

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