Effects of Ferula on Polycystic Ovary Syndrome

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Research

Keywords: Ferula, Asafoetida, Polycystic ovarian syndrome, PCOS, Stein-Leventhal Syndrome

Posted Date: February 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-117187/v2>

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Abstract

Background: Polycystic ovarian syndrome is the most common endocrine disorder in reproductive aged women. As a result of side effect of pharmaceutical medications women are interested in using alternative medicines to treat. To determine the comparative effects of *Ferula assa-foetida* on androgenic hormone levels and ovarian features in patient with polycystic ovarian syndrome (PCOS).

Methods: In this triple-blinded controlled clinical trial, 34 student participants were randomly divided in two groups. Intervention group received 100 mg of oleo-gum resin of *Ferula assa-foetida*, control group received oral paraffin (Placebo) twice daily for 3 months. The efficacy of this herbal medicines was measured after the 3-month intervention. Hormonal assay for evaluating Testosterone, DEHAS, Prolactin, TSH, FSH, LH levels and also trans abdominal ultrasound for evaluating ovarian volumes, number of follicles of both ovaries, and endometrial thickness. Were measured before and after the study.

Results: In this study, significant changes in DEHAS and TSH level were observed (p value <0.03). The greatest reduction in the number of ovarian follicles was reported in the *Ferula* group (p value <0.00).

Conclusion: Use of *Ferula assa-foetida* can be effected in decrease of DHEAS, TSH levels, and ovarian follicles number in young girls with PCOS.

Background

PCOS is a problem with hormones that affects women during their childbearing years, Androgen disturbances increase the prevalence of several comorbidities, including insulin resistance, diabetes mellitus, hyperlipidemia, and cardiovascular disease (1). In addition, these features are accompanied by hirsutism, acne, and an ovulatory cycles leading to menstrual irregularities and infertility (2).

Several treatments are recommended for PCOS such as life style modification(3), drug therapy(4) and herbal medicine(5).

In Iran, some women with gynecological disorder such as dysmenorrhea (6) and oligomenoreha (7) use herbal medicines such as *Ferula assa-foetida*, that is locally known as Anghuzeh. Owing to its anti hirsutism, antibacterial, anthelmintic, and anticancer properties (8), this herbal medicine has been traditionally used for different purposes: abdominal pain, cancer and colic in children (9) and also for treatment of vaginal infection(10). This medicinal plant belong to the Umbelliferae (Apiaceae) family. The biochemical activities of Umbelliferae which are attributed to terpenoids such as ferutinin, may modulate estrogen signaling in the same way as phytoestrogens. Due to the potential selectivity of ferutinin for Estrogen receptor Alpha (ER α) and Estrogen Receptor Beta (ER β), they may be useful as elective Estrogen Receptor Modulators (SERMs) (11). Some study evaluated the effects of *Ferula assa-foetida* in histopathology of testis in male wistar rat and showed a significant decreasing trend in terms of testosterone hormones (12-14). Polycystic ovary syndrome is a disorder primarily characterized by signs

and symptoms of androgen excess(15), and based on some study results that Ferula can decrease testosterone in gonad and blood (13, 14).

Since the effect of Ferula on human polycystic ovary syndrome has not been studied and its effectiveness in reducing animal testosterone has only been proven, this study was conducted as in a group of students at a university center.

Methods

Participants: This study was conducted on students who were studying in Jahrom University of Medical Sciences.

Sample size estimation: There was no previous comparable study in Ferula on which to base data for a Sample size calculation, then based on FG score results in another similar article (16) with this formula:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2} \quad \mu_1 = -0.2 \quad \mu_2 = -1.1 \quad \sigma_2^2 = 0.9 \quad \sigma_1^2 = 0.8$$

And significance level of 0.05, a power level of 0.80, with a 10% attrition rate investigated that 18 samples should enroll to study. Due to the samples available to, 17 samples were included in the study.

Inclusion criteria: In this study, the participants were young girls aged 18-30 years that diagnosed PCOS based on Rotterdam criteria (table 1)

The exclusion criteria were medical conditions such as androgen-secreting tumors, hyper prolactinemia, thyroid disorders and Cushing's syndrome (determined by suitable laboratory assay), pregnancy and lactation.

Random allocation: simple or finite random sequences with table of random number was Created. Based on this step, each participant was given a unique identifier. In concealment random allocation step, boxes were coded of identical shape and size numbered randomly containing herbal medicine or placebo. Based on this step, participants assigned randomly to one of two groups. Each Participant in intervention group received active compounds in capsular form (each capsule contained 100 mg of oleo-gum resin of Ferula assa-foetida) twice daily for 3 months. In the same way, participants in placebo group received capsules of 100 mg prepared from oral paraffin.

Blinding: The participants, and all investigator, were unaware of the capsule contents. After 3 months interventions, the contents of the capsules given to each group were revealed by the pharmacist. After study was completed, the researchers received information about the numbers and the nature of each drug.

In the execution of a randomized specialized process, S.A is the person who created the random sequence, F.GH is person who has evaluated and registered the samples in terms of include and exclude criteria. F.SH is the person who assigns the samples to the groups. M.T is the who, analyzed of data.

Preparation of Capsules: Root and Stem of *Ferula assa foetida* L. (gum) was purchased from a medicinal plant market (Tabib daru), a supplier of herbal medicines, Kashan Iran. In Department of phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences with Herbarium Voucher Number 981, *Ferula assa foetida* essence was produced by distilling the Root and Stem with steam and then for this study they were formed into pearl-shaped pills (100 mg). The major components of *Ferula assa foetida* included 65% oleo gum resin, 20% essence, 25% stem(17). *Ferula assa foetida* drug toxicity was assessed in a past study and its safety had been reported, Based on systematic review study, *Ferula* may be cause the skin allergic sign and do not recommended for infant(9).

The placebo contained 100 mg soya produced by the Barij Essence Company. In order to isotropy, each pearl was placed inside a capsule and was coded.

Data Collection: The primary outcome was clinical parameters (BMI, FG score, Menstruation periods), that data were obtained at the beginning of the study and at the end of the study period. Secondary outcome were hormonal (Dehydroepiandrosterone sulfate (DHEAS), Free testosterone (FT), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH) and Prolactin(PRL)) and ultrasound parameters (Endometrial thickness, ovarian volume and Number of follicle in both Ovary). A venous blood sample was obtained from the studied population to evaluate the changes in the level of biochemical factors. Plasma was separated and kept at -20°C until it was assayed for DHEAS, FT, FSH, and LH using immunoassay kits (Monobind Inc, CA, US) according to the manufacturer's instructions.

Testosterone, DEHAS, Prolactin, TSH, FSH and LH were measured by using the enzyme-linked immune sorbent assay method using the Eliza Kit (Monobind Inc., Germany).

In all groups, Participants underwent Trans abdominal ultrasound for evaluating ovarian volumes, number of follicles of both ovaries, and endometrial thickness at 4.4-MHz (Alpinion, Seoul, South Korea) by a one sonographer in the follicular phase of menstrual cycle except in participants with oligo or amenorrhea

Ethics Consideration: The study was approved by the Ethics and Research Committee of Jahrom University of Medical Sciences (reference number: ums.REC.1393.023) and registered in the Iranian Randomized Clinical Trial (**IRCT2016040427207N1**).

Statistical Analysis: All statistical analysis was performed using SPSS statistical software version 14 and Graph pad Prism (version 6). Quantitative variables were reported as mean and standard (95% confidence Interval). The normal distribution of the data was tested by Kolmogorov–Smirnov test and a non-parametric test was conducted to evaluate the objectives. clinical, hormonal and ultrasound parameters

were analyzed by using Man Whitney tests to intergroup comparison before and after 3 months and Wilcoxon test for comparison between groups before and after 3 months interventions.

Results

Off the 32 participants recruited into this study, four subjects did not complete the trial and were excluded from the analysis. Finally 28 students completed 3 months of the intervention (Fig1).

The mean ages in this study were 22.93 ± 1.5 years in the Ferula group and 23.14 ± 2.7 years in the placebo groups, respectively.

To compare mean between the groups before and after 3 months interventions results showed FG score ($p < 0.02$), DHEAS ($p = 0.005$), Free testosterone ($p = 0.02$), TSH ($p = 0.013$) in Ferula group and free testosterone ($p = 0.01$), FSH ($p = 0.007$) and right ovarian volume ($p = 0.039$) in placebo group significantly changes.

To compare mean intergroup Ferula and placebo result showed DHEAS ($p = 0.03$), TSH ($p = 0.004$), number of follicles in right and left ovary ($p = 0.00$) significantly change. No significant differences were shown between the two groups before and after the intervention in Clinical parameters (BMI, FG score and menstruation) (table 2). Hormonal parameters (FSH, LH, Prolactin, and free testosterone) before and after intervention was no significantly different between the two groups (table 3). The both ovarian volume and endometrial thickness was not significant after intervention in the Ferula group vs. placebo group (table 4).

Discussion

This randomized, placebo-controlled clinical trial was conducted to evaluate the efficacy of Ferula assa-foetida in improving the features of PCOS.

In our study, BMI in both groups was not significantly different before and after the intervention, and this might be related to the duration of intervention, which was three months. Based on recent PCOS international guidelines, a six month intervention duration is optimal to reduce the BMI in PCOS women (18) some studied reported that Soy protein diet can decrease weight in obese women (19, 20). Also, the meta-analysis reported by Zhang *et al.* (2013) concluded that Soy Isoflavone supplementation could improve glucose metabolism and insulin control in non-Asian postmenopausal women (21).

Although result showed that F-G score for the hirsutism severity significant after intervention in Ferula group, but in compare men intergroup of Ferula and placebo, this change was not significantly. In one study result, that idiopathic hirsutism with creams containing 1% and 2% fennel extract over 12 weeks were treated (22) but oral fennel used in PCOS women was not change in FG score (23).

In this study, Ferula was not effective on the length of the menstruation cycle in PCOS women, and this could be related to the dosage and duration of treatment which is comparable to the results of treatment

with fennel in PCOS. However, the use of another herbals such as Vitex (24), Cinnamon (25), Mentha longifolia (26) Trigonella foenum-graecum(27) have been effective for oligomenorrhea treatment.

Animal Studies showed pharmacological effects of Ferula on testosterone level(12, 14), gastrointestinal function, blood pressure, anti-cancer and anti-parasite(9).

Hormonal level in this study did not significantly change after intervention except in DHEAS and TSH and this was in accordance with following studies. One study investigated the efficacy of fenugreek seed extract on PCOS that decrease in the LH to FSH ratio was reported (28). In another study, use of fennel in women with PCOS was not significantly change blood hormonal level(23). Use of Urtica dioica in hyper-androgenic women was effective in testosterone level decrease after treatment(29). Also, serum levels of luteinizing hormone (LH), triglyceride (TG), low density lipoprotein cholesterol (LDL), dehydroepiandrosterone sulfate (DHEAS) and testosterone were significantly decreased after 3 months therapy in Genistein group (30). Vitex agnus-castus after three months can decrease prolactin level in women (31).

Ovarian characteristics such as ovarian follicular numbers in this study were significantly improved after intervention such as metformin therapy in PCOS women that decrease both ovarian volume (32, 33). Also, use of fennel in PCOS women could decrease follicular number of both ovarian(23). Trigonella foenum-graecum decreased significantly polycystic-appearing ovaries in ultrasound scans (27)and decreased both ovarian volume (28).

In this study, some result of mean comparison between group such as significantly decrease in free testosterone, FSH level and ovarian volume in placebo group after 3 months, Indicates the presence of confounder factors such as the absence of a stable follicular phase in patients with oligomenorrhea and the inaccuracy of trans-abdominal ultrasound can change the results.

Some of the limitations of this study were small sample size, poor generalizability and the short duration of treatment. Thus, we suggest for future studies, use a greater sample size with a longer treatment to evaluate long term efficacy of Ferula in PCOS management and ovarian cysts by Trans-vaginal ultrasound.

Conclusion

The results of this study showed that Ferula exhibited effects on decrease in the DHEAS, TSH levels, and the number of ovarian follicles in women with PCOS after three months intervention.

Abbreviations

PCOS: polycystic ovarian syndrome

LH: Luteinizing hormone

FSH: Follicle-stimulating hormone

PRL: Prolactin

DHEAS: Dehydroepiandrosterone sulphate

F- G: Ferriman–Gallwey

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics (reference number: ums.REC.1393.023) and Research Committee of Jahrom University of Medical Sciences and registered in the Iranian Randomized Clinical Trial (22343).

The informed consents were obtained from all of university students above 18 years.

Consent for publication

Informed consent from participants included consent to the publication of anonymised data.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Authors Contributions

S.A and F.GH were involved in study design, preparation of intervention.

F.SH contributed to critical discussion and manuscript drafting. All authors read and approved the final manuscript.

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Acknowledgment:

We would like to express special thanks of gratitude to Dr. [Mohammad M Zarshenas](#), in Medicinal Plants Processing Research Center, and Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran to help us for preparing of Ferula capsule.

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Tables

Table 1. Rotterdam diagnostic criteria for PCOS
Rotterdam (2003) Diagnostic criteria for PCOS - two out of three of:
Clinical Hyperandrogenism (Ferriman-Gallwey Score >9) or Biochemical Hyperandrogenism (Elevated Total/Free Testosterone)
Oligomenorrhea (Less Than 6-9 Menses per Year) or Oligo-Ovulation
Polycystic Ovaries on Ultrasound (≥ 12 Antral Follicles in One Ovary or Ovarian Volume $\geq 10\text{ cm}^3$)

Table 2: compare clinical parameters in patients treated with Ferula and placebo before and after intervention.

Parameters	Group	Mean $\pm$ SD (95%CI)	Mean $\pm$ SD(95%CI)	P. value*
		Before intervention	After intervention	
	Ferula	23.8 $\pm$ 1.1	23.37 $\pm$ 4.25	0.117
	placebo	25.3 $\pm$ 1.2	25.24 $\pm$ 4.6	0.859
	P. value**	0.427	0.376	
Gallwey	Ferula	7.21 $\pm$ 6.81	3.92 $\pm$ 4.23	0.02
	placebo	6.57 $\pm$ 4.9	6.30 $\pm$ 4.23	0.918
	P. value**	0.91	0.137	
tion periods	Ferula	40.29 $\pm$ 18.63	39.50 $\pm$ 23.65	0.83
	placebo	49.36 $\pm$ 19.62	39.14 $\pm$ 11.61	0.564
	P. value**	0.541	0.210	

*** Wilcoxon**

**** Mann-Whitney**

Table 3: compare hormone parameters in patients treated with Ferula and placebo before and after intervention.

Parameter	Group	Mean ± SD(95%CI) Before intervention	Mean ± SD(95%CI) After intervention	P. value*
Estradiol (pg/ml)	Ferula	2.28±0.29	1.51±0.865	0.005
	placebo	2.38±0.24	2.96±1.01	0.490
	P. value**	0.667	0.03	
Testosterone (pg/ml)	Ferula	3.7±0.84	1.52±1.615	0.02
	placebo	3.8±0.6	2.06±1.5	0.019
	P. value**	0.454	0.376	
LH (U/ml)	Ferula	4.11±0.27	3.742±2.53	0.221
	placebo	5.34±0.55	3.91±1.34	0.007
	P. value**	0.50	0.227	
FSH (U/ml)	Ferula	10.96±2.34	11.1±6.14	0.638
	placebo	5.34±0.55	7.57±4.5	0.925
	P. value**	0.511	0.104	
Estrone (pg/ml)	Ferula	1.93±0.20	1.25±0.43	0.013
	placebo	1.57±0.23	1.92±0.72	0.124
	P. value**	0.05	0.004	
Progesterone (ng/ml)	Ferula	17.65 ±1.98	14.25±8.35	0.109
	placebo	19.69±1.93	19.05±14.7	0.594
	P. value**	0.376	0.178	

* Wilcoxon

** Mann-Whitney

Table 4: compare ultrasound parameters in patients treated with Ferula and placebo before and after intervention.

Abdominal ultrasound	Group	Mean $\pm$ SD(95%CI)	Mean $\pm$ SD(95%CI)	P. value *
		Before intervention	After intervention	
Endometrial thickness	Ferula	6.79 $\pm$ 0.74	6.28 $\pm$ 2.43	0.573
	placebo	5.46 $\pm$ 0.44	5.82 $\pm$ 1.81	0.609
	P. value**	0.178	0.667	
Ovarian volume	Ferula	11.31 $\pm$ 1.75	9.42 $\pm$ 5.8	0.64
	placebo	9.04 $\pm$ 0.87	9.91 $\pm$ 3.58	0.039
	P. value**	0.511	0.511	
Uterine volume	Ferula	10.18 $\pm$ 1.73	11.11 $\pm$ 6.95	0.505
	placebo	8.73 $\pm$ 0.61	8.88 $\pm$ 3.08	0.655
	P. value**	0.946	0.603	
Number of follicle in right Ovary	Ferula	10.93 $\pm$ 1.98	6.35 $\pm$ 1.49	0.002
	placebo	11.50 $\pm$ 0.76	11.29 $\pm$ 1.20	0.145
	P. value**	0.178	0.00	
Number of follicle in left Ovary	Ferula	11.50 $\pm$ 1.87	7.14 $\pm$ 1.51	0.002
	placebo	11.86 $\pm$ 0.66	11.07 $\pm$ 2.5	0.459
	P. value**	0.910	0.00	

* Wilcoxon

** Mann-Whitney

Figures

Figure 1

CONSORT flow diagram