

# Effects of Ferula Assa-Foetida on Clinical, Hormonal and Sonography Parameters in Young Girls with Polycystic Ovary Syndrome: Pilot Randomized, Placebo Controlled, Triple-Blinded

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## Research

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

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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 abdominal sonography for evaluating ovarian volumes, number of follicles of both ovaries, and endometrial thickness. were measured before and after the study.

**Results:** In this study, no significant hormonal changes were observed ( $p$  value $>0.5$ ). Although the greatest reduction in the number of ovarian follicles and ovarian volume was reported in the *Ferula assa-foetide* group ( $p$  value  $<0.01$ ).

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

**Trial registration:** the Iranian Randomized Clinical Trial (**IRCT2016040427207N1**).

url: <https://www.irct.ir/trial/22343>

## Background

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder affecting 6%-20% of reproductive-aged women according to various diagnostic criteria (1), AYOUBI, ARSHAMI (2). The 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam, describe PCOS as fulfilling two of the following three criteria; anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound (Rotterdam consensus)(3). Androgen disturbances increase the prevalence of several comorbidities, including insulin resistance, diabetes mellitus, hyperlipidemia, and cardiovascular disease (4). In addition, these features are accompanied by hirsutism, acne, and an ovulatory cycles leading to menstrual irregularities and infertility (5).

Several treatments are recommended for PCOS such as life style modification(6), drug therapy(7) and herbal medicine(8).

In Iran, some women with gynecological disorder such as dysmenorrhea (9) and oligomenoreha (10) use herbal medicines such as *Ferula assa-foetida*, that is locally known as Anghuzeh. Owing to its anti hirsutism, antibacterial, anthelmintic, and anticancer properties (11), this herbal medicine has been

traditionally used for different purposes: abdominal pain, cancer and colic in children (12) and also for treatment of vaginal infection(13). 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 $\alpha$ ) and Estrogen Receptor Beta (ER $\beta$ ), they may be useful as elective Estrogen Receptor Modulators (SERMs) (14). 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 (2, 15, 16).

Since Polycystic ovary syndrome is a disorder primarily characterized by signs and symptoms of androgen excess(17), and based on some study results that Ferula can decrease testosterone in gonad and blood (2, 16), then use of Ferula is one way for PCOS improving in patients, the present study aimed to investigate the effect of Ferrula assa-foetida on PCOS symptoms.

## 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 on which to base data for a

Sample size calculation, then to estimate an acceptable sample size, the Cohen's table was used (17). For sample size Calculation, a significance level of 0.05, a power level of 0.80, an effect size of 1.05 based on blood Testosterone changes and SD = 2, were determined. The minimum sample size was determined 17.

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

Table 1  
Rotterdam diagnostic criteria for PCOS

<b>Rotterdam (2003) Diagnostic criteria for PCOS - two out of three of:</b>
Clinical Hyperandrogenism (Ferriman-Gallwey Score > 8) 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 >= 10 cm <sup>3</sup> )

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.

**Randomization:** After being informed about the research methods and objectives, each participant gave written informed consent prior to data collection. Each participant was given a unique identifier and

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 manufacturer produced 17 *assafoetida* boxes that contain 180 Capsules (100 mg) and 15 placebo boxes. The subjects were requested to use that drug for 12 weeks, twice a day (each 12 hours) after meals. Each box was assigned a number from 1 to 30 and each participant received one box according to table randomization. Participant groups received the capsule from the container that had the same label. Therefore, the participants, and investigator, were all 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 researcher received information about the numbers and the nature of each drug.

**Preparation of Capsules:** Root and Stem of *Ferula assa foetida* L. (gum) was purchased from a medicinal plant market (Adonis Gol Darou), a supplier of herbal medicines, Tehran, 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 (18). *Ferula assa foetida* drug toxicity was assessed in a past study and its safety had been reported (12). The placebo contained 100 mg paraffin. 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 sonography 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 (reference number: 725090), 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 abdominal sonography 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). Data are presented as mean and standard deviation. 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 sonography parameters were analyzed by using Kruskal Wallis tests to compare the efficacy of the Ferula with the placebo before and after 3 months interventions. P values less than 0.05 were considered significant.

## Results

Off the 34 participants recruited into this study, six subjects did not complete the trial and were excluded from the analysis. Finally 28 students completed 3 months of the intervention (Fig. 1).

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

No significant differences were shown between the two groups before and after intervention in Clinical parameters (BMI, FG score and menstruation) (Table 2).

Table 2

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

clinical parameters	Group	Mean $\pm$ SD	P. value	Mean $\pm$ SD	P. value
		Before intervention		After intervention	
BMI	Feula	$23.8 \pm 1.1$	0.557	$23.37 \pm 4.25$	0.278
	placebo	$25.3 \pm 1.2$		$25.24 \pm 4.6$	
Ferriman-Gallwey Score	Feula	$7.21 \pm 6.81$	0.569	$10.5 \pm 5.30$	0.597
	placebo	$6.86 \pm 5.11$		$7.22 \pm 3.54$	
Menstruation période	Feula	$40.29 \pm 18.63$	0.144	$39.50 \pm 23.65$	0.399
	placebo	$49.36 \pm 19.62$		$39.14 \pm 11.61$	

All of hormonal parameters (TSH, FSH, LH, DHEAS, PROLACTIN, and free testosterone) before and after intervention were no significantly different between the two groups (Table 3).

Table 3

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

Hormone parameter	Group	Mean $\pm$ SD	P. value	Mean $\pm$ SD	P. value
		Before intervention		After intervention	
DHEAS (g/ml)	Feula	2.28 $\pm$ 0.29	0.144	1.51 $\pm$ 0.865	0.06
	placebo	2.38 $\pm$ 0.24		2.96 $\pm$ 1.01	
Free Testosterone (pg/ml)	Feula	3.7 $\pm$ 0.84	0.289	1.52 $\pm$ 1.615	0.37
	placebo	3.8 $\pm$ 0.6		2.06 $\pm$ 1.5	
FSH (mIU/ml)	Feula	4.11 $\pm$ 0.27	0.076	3.742 $\pm$ 2.53	0.29
	placebo	5.34 $\pm$ 0.55		3.91 $\pm$ 1.34	
LH (mIU/ml)	Feula	10.96 $\pm$ 2.34	0.312	11.1 $\pm$ 6.14	0.37
	placebo	5.34 $\pm$ 0.55		7.57 $\pm$ 4.5	
TSH (mIU/ml)	Feula	1.93 $\pm$ 0.20	0.479	1.25 $\pm$ 0.43	0.011
	placebo	1.57 $\pm$ 0.23		1.92 $\pm$ 0.72	
Prolactin (g/ml)	Feula	17.65 $\pm$ 1.98	0.823	14.25 $\pm$ 8.35	0.57
	placebo	19.69 $\pm$ 1.93		19.05 $\pm$ 14.7	
LH/FSH	Feula	2.65 $\pm$ 0.54	0.225	3.88 $\pm$ 3.3	0.351
	placebo	1.57 $\pm$ 0.20		1.99 $\pm$ 1.19	

All of sonography parameters in two groups before intervention were not significantly different but 3 months after intervention. There were remarkable reductions in the ovarian volume and number of follicles in both ovaries in the Ferula group vs placebo group endometrial thickness was not significant after intervention between two groups (Table 4).

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

Sonography Parameters	Group	Mean $\pm$ SD	P. value	Mean $\pm$ SD	P. value
		Before intervention		After intervention	
Endometrial thickness	Feula	6.79 $\pm$ 0.74	0.237	6.28 $\pm$ 2.43	0.632
	placebo	5.46 $\pm$ 0.44		5.82 $\pm$ 1.81	
right ovary volume	Feula	11.31 $\pm$ 1.75	0.408	9.42 $\pm$ 5.8	0.003
	placebo	9.04 $\pm$ 0.87		9.91 $\pm$ 3.58	
left ovary volume	Feula	10.18 $\pm$ 1.73	0.460	11.11 $\pm$ 6.95	0.009
	placebo	8.73 $\pm$ 0.61		8.88 $\pm$ 3.08	
Number of follicle in right Ovary	Feula	10.93 $\pm$ 1.98	0.079	6.35 $\pm$ 1.49	0.001
	placebo	11.50 $\pm$ 0.76		11.29 $\pm$ 1.20	
Number of follicle in left Ovary	Feula	11.50 $\pm$ 1.87	0.058	7.14 $\pm$ 1.51	0.012
	placebo	11.86 $\pm$ 0.66		11.07 $\pm$ 2.5	

## 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 (19) some studied reported that Soy protein diet can decrease weight in obese women (20, 21). 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 (22).

Result showed that F-G score for the hirsutism severity was not significant after intervention, same as result of oral fennel used in PCOS women(23) and in consist with Javidnia et al. result that idiopathic hirsutism patients were treated with creams containing 1% and 2% fennel extract over 12 weeks (24).

In this study, *assa-foetida* 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* (25), *Cinnamon* (26), *Mentha longifolia* (27) *Trigonella foenum-graecum*(28) have been effective for oligomenorrhea treatment.

The findings of this study showed that *Ferula assa-foetida* exhibited effects on ovarian volumes and the number of ovarian follicles in women with PCOS. To the authors' knowledge there has been no study that has evaluated the effects of *assa-foetida* in patients with PCOS.

Animal Studies showed pharmacological effects of *assa-foetida* on testosterone level(2, 15), gastrointestinal function, blood pressure, anti-cancer and anti-parasite(12).

Hormonal level in this study did not significantly change after intervention 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 (29). 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(30). Also, serum levels of luteinizing hormone (LH), triglyceride (TG), low density lipoprotein cholesterol (LDL), dehydroepiandrostrone sulfate (DHEAS) and testosterone were significantly decreased after 3 months therapy in Genistein group (31).

Ovarian characteristics such as ovarian volume and 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 (28)and decreased both ovarian volume (29).

Some of the limitations of this study were small sample size, poor generalizability and the Duration of treatment. Thus, we suggest a greater sample size with a longer treatment time for future studies to evaluate this herbal drug. According to budget limitations the effect size which

The authors used where determined to high, so the study was unable to detect small differences.

Due to the short duration of our study and small sample size, we detected no improvement in androgen hormone levels and clinical manifestations such as menstrual cycle and hirsutism. Further studies are suggested to evaluate long term efficacy of this herbal medicine in PCOS treatment and to evaluate the biochemical efficacy of *Ferula* on ovarian cysts.

## Conclusion

the results of this study showed that *Ferula assa-foetida* exhibited effects on decrease of ovarian volumes 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.

## **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 and M.T contributed to critical discussion and manuscript drafting. All authors read and approved the final manuscript.

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## References

1. Yildiz BO, Bozdogan G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Human reproduction*. 2012;27(10):3067-73.
2. AYOUBI A, ARSHAMI J, VALIZADEH R, MOUSAVI Z, MOUSAEI A. THE EFFECT OF ASAFETIDA GUM EXTRACT ON BLOOD PARAMETERS AND HISTOPATHOLOGY OF TESTES IN MALE WISTAR RAT. *IRANIAN JOURNAL OF ANIMAL SCIENCE RESEARCH*. 2013;4(4):-.
3. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and sterility*. 2004;81(1):19-25.
4. Wild RA. Long-term health consequences of PCOS. *Human reproduction update*. 2002;8(3):231-41.
5. Jalilian A, Kiani F, Sayehmiri F, Sayehmiri K, Khodae Z, Akbari M. Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis. *Iranian journal of reproductive medicine*. 2015;13(10):591.
6. Abdolahian S, Tehrani FR, Amiri M, Ghodsi D, Yarandi RB, Jafari M, et al. Effect of lifestyle modifications on anthropometric, clinical, and biochemical parameters in adolescent girls with polycystic ovary syndrome: a systematic review and meta-analysis. *BMC Endocrine Disorders*. 2020;20(1):71.
7. Lashen H. Role of metformin in the management of polycystic ovary syndrome. *Ther Adv Endocrinol Metab*. 2010;1(3):117-28.
8. Kwon C-Y, Lee B, Park KS. Oriental herbal medicine and moxibustion for polycystic ovary syndrome: A meta-analysis. *Medicine (Baltimore)*. 2018;97(43):e12942-e.
9. Jahangirifar M, Taebi M, Dolatian M. The effect of Cinnamon on primary dysmenorrhea: A randomized, double-blind clinical trial. *Complementary therapies in clinical practice*. 2018;33:56-60.
10. Akha O, Rabiei K, Kashi Z, Bahar A, Zaeif-Khorasani E, Kosaryan M, et al. The effect of fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, A randomized placebo controlled clinical trial. *Caspian journal of internal medicine*. 2014;5(1):26-9.
11. Iranshahy M, Iranshahi M. Traditional uses, phytochemistry and pharmacology of asafoetida (*Ferula assa-foetida* oleo-gum-resin)—A review. *Journal of ethnopharmacology*. 2011;134(1):1-10.
12. Zare AR A, Omid M, Fallah Hoseini H, Yazdani D, Rezazadeh S, Irvani N, et al. A Review on Pharmacological Effects of *Ferula assa-foetida* L.: a Systematic Review. *Journal of Medicinal Plants*. 2011;4(40):17-25.
13. Bagherinasab S, Tafazoli M, Mirteimouri M, Hamedi S, Berenji F, Mazloun SR. Comparing the effect of ferula oral capsule and metronidazole oral pill on improvement of clinical signs of infection by

- Trichomonas Vaginalis: A Controlled Clinical Trial. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2019;22(9):55-63.
14. Ikeda K, Arao Y, Otsuka H, Nomoto S, Horiguchi H, Kato S, et al. Terpenoids found in the umbelliferae family act as agonists/antagonists for ER(alpha) and ERbeta: differential transcription activity between ferutinine-liganded ER(alpha) and ERbeta. Biochemical and biophysical research communications. 2002;291(2):354-60.
  15. Bagheri SM, Yadegari M, Porentezari M, Mirjalili A, Hasanpor A, Dashti RM, et al. Effect of Ferula assa-foetida oleo gum resin on spermatic parameters and testicular histopathology in male wistar rats. Journal of Ayurveda and integrative medicine. 2015;6(3):175-80.
  16. Bagheri SM, Yadegari M, Porentezari M, Mirjalili A, Hasanpor A, Dashti RMH, et al. Effect of Ferula assa-foetida oleo gum resin on spermatic parameters and testicular histopathology in male wistar rats. J Ayurveda Integr Med. 2015;6(3):175-80.
  17. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P T. 2013;38(6):336-55.
  18. PURE NATURAL ASAFOETIDA OIL [Available from: <http://adonisherb.ir/en/Asafoetida-oil.aspx>.
  19. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertility and sterility. 2018;110(3):364-79.
  20. Bosello O, Cominacini L, Zocca I, Garbin U, Compri R, Davoli A, et al. Short- and long-term effects of hypocaloric diets containing proteins of different sources on plasma lipids and apoproteins of obese subjects. Annals of nutrition & metabolism. 1988;32(4):206-14.
  21. Yamashita T, Sasahara T, Pomeroy SE, Collier G, Nestel PJ. Arterial compliance, blood pressure, plasma leptin, and plasma lipids in women are improved with weight reduction equally with a meat-based diet and a plant-based diet. Metabolism: clinical and experimental. 1998;47(11):1308-14.
  22. Zhang YB, Chen WH, Guo JJ, Fu ZH, Yi C, Zhang M, et al. Soy isoflavone supplementation could reduce body weight and improve glucose metabolism in non-Asian postmenopausal women—a meta-analysis. Nutrition (Burbank, Los Angeles County, Calif). 2013;29(1):8-14.
  23. Ghavi F, Taghizadeh M, Taebi M, Abdolahian S. Effect of Foeniculum vulgare essence on symptoms of Polycystic ovarian syndrome (PCOS): A Randomized Double-Blind, Placebo-Controlled Trial. Journal of Herbal Medicine. 2019:100277.
  24. Javidnia K, Dastgheib L, Mohammadi Samani S, Nasiri A. Antihirsutism activity of Fennel (fruits of Foeniculum vulgare) extract. A double-blind placebo controlled study. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2003;10(6-7):455-8.
  25. Arentz S, Abbott JA, Smith CA, Bensoussan A. Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. BMC complementary and alternative medicine. 2014;14:511.

26. Kort DH, Lobo RA. Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial. *American journal of obstetrics and gynecology*. 2014;211(5):487.e1-6.
27. Mokaberinejad R, Zafarghandi N, Bioos S, Dabaghian FH, Naseri M, Kamalinejad M, et al. *Mentha longifolia* syrup in secondary amenorrhea: a double-blind, placebo-controlled, randomized trials. *Daru*. 2012;20(1):97-.
28. Hassanzadeh Bashtian M, Emami SA, Mousavifar N, Esmaily HA, Mahmoudi M, Mohammad Poor AH. Evaluation of Fenugreek (*Trigonella foenum-graceum* L.), Effects Seeds Extract on Insulin Resistance in Women with Polycystic Ovarian Syndrome. *Iran J Pharm Res*. 2013;12(2):475-81.
29. Swaroop A, Jaipuria AS, Gupta SK, Bagchi M, Kumar P, Preuss HG, et al. Efficacy of a novel fenugreek seed extract (*Trigonella foenum-graecum*, Furocyst™) in polycystic ovary syndrome (PCOS). *International journal of medical sciences*. 2015;12(10):825.
30. Najafipour F, Rahimi AO, Mobaseri M, Agamohamadzadeh N, Nikoo A, Aliasgharzadeh A. Therapeutic effects of stinging nettle (*Urtica dioica*) in women with Hyperandrogenism. *Int J Current Res Acad Rev*. 2014;2(7):153-60.
31. Khani B, Mehrabian F, Khalesi E, Eshraghi A. Effect of soy phytoestrogen on metabolic and hormonal disturbance of women with polycystic ovary syndrome. *J Res Med Sci*. 2011;16(3):297-302.
32. Farimani Sanoee M, Neghab N, Rabiee S, Amiri I. Metformin therapy decreases hyperandrogenism and ovarian volume in women with polycystic ovary syndrome. *Iranian journal of medical sciences*. 2011;36(2):90-5.
33. Bayrak A, Terbell H, Urwitz-Lane R, Mor E, Stanczyk FZ, Paulson RJ. Acute effects of metformin therapy include improvement of insulin resistance and ovarian morphology. *Fertility and sterility*. 2007;87(4):870-5.

## Figures

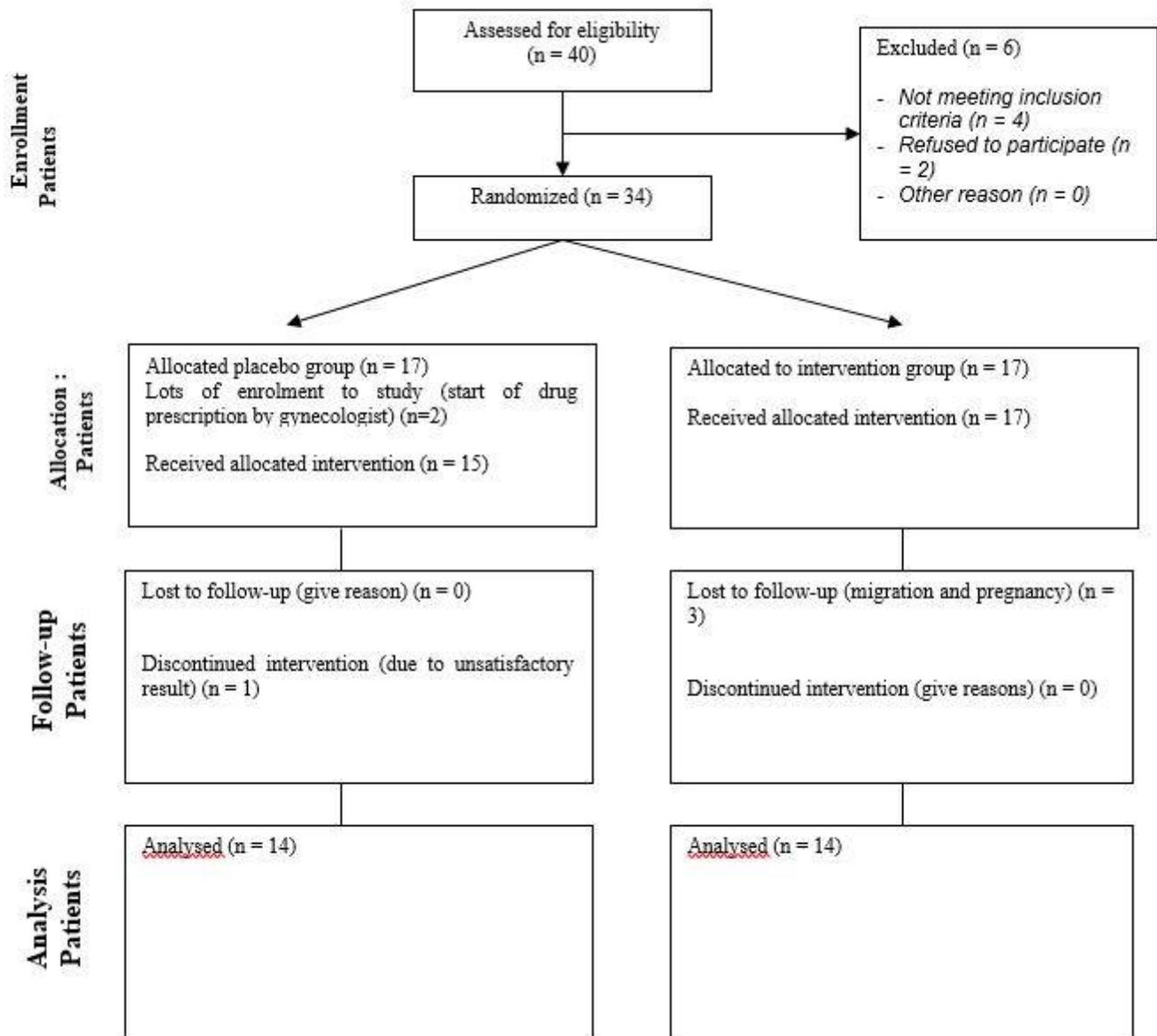


Figure 1

CONSORT flow diagram

## Supplementary Files

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