The Role of medicinal herbs in treatment of insulin resistance in patients with Polycystic Ovary Syndrome: A literature review

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Abstract: Background: Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine abnormalities in women. Due to the side effects of drugs, the tendency to use natural antioxidants and anti-inflammatory agents to regulate metabolism, hyperinsulinemia, and hyperlipidemia in PCOS patients has been increased. This review aimed to investigate the role of herbal substances on the treatment of PCOS.

Methods: The present review was carried out using keywords such as polycystic ovary syndrome and/or PCOS and/or herb. Databases including Web of Science, PubMed, and Science Direct were used to collect all related articles published from 1990 to 2019. We excluded studies unrelated to the PCOS and medical herbs.

Results: Overall, 361 records were identified through database searching. After primary screening and the full-texts assessment, 323 records were excluded, and 38 articles were finally included. The results indicate that some medicinal herbs may have a key role in treating PCOS. The compounds in these medical herbs can affect lipid profiles (Aloe vera, chamomile, and cinnamon), insulin resistance (cinnamon, chamomile, Aloe vera, and Camellia sinensis), blood glucose (Aloe vera, cinnamon, and Camellia sinensis), hormones (Aloe vera, silymarin, chamomile, fenugreek, Camellia sinensis, Heracleum persicum, Potentilla, Mentha spicata, Foeniculum vulgare, licorice, and Marrubium), and ovarian tissue (Aloe vera, chamomile, Camellia sinensis, Mentha spicata, and silymarin).

Conclusion: Natural substances such as Aloe vera, cinnamon, green tea, fenugreek, and silymarin can be used as a new supportive care for PCOS. Further clinical trials are warranted to confirm their benefits and safety.

Keywords: medical herbs; PCOS; Polycystic Ovary Syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder related to elevated androgens (male hormones) in females in reproductive age. PCOS is associated with various clinical symptoms such as irregular menstruation, infertility, androgen growth, hirsutism, insulin resistance, acne, weight gain, and ovarian cyst [1]. The prevalence of PCOS has been reported to be 2.2–26% in different societies [2].

Some factors appear to play an important in PCOS development including hypothalamic-pituitary dysfunction, ovarian dysfunction, and increased insulin level [3]. PCOS is a disorder characterized by abnormal gonadotropin secretion including Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH), and increased secretion of ovarian steroids that may be associated with insulin resistance [4]. Insulin stimulates androgens synthesis and increases LH function. The ovaries produce too much testosterone androstenedione and dehydroepiandrosterone in PCOS patients [3, 4].
Excess adrenal precursor androgen secretion is demonstrated in PCOS women [5]. Hyperandrogenism may play a major pathological role in the development of the severe endocrine and metabolic disturbances associated with PCOS. Sex hormone-binding globulin (SHBG) is a glycoprotein that can regulate the bioavailability of sex steroid hormone and SHBG levels are correlated with the risk of PCOS. PCOS women with low SHBG levels were more likely to have hyperandrogenism, diabetes type 2, insulin resistance, glucose intolerance, obesity, infertility, and cardiovascular disease (CVD) [6] due to existed insulin resistance [7]. PCOS has been divided into 3 phenotypes that include Classic PCOS (Phenotypes A and B), Ovulatory PCOS (Phenotype C), and Nonhyperandrogenic PCOS (Phenotype D) [8]. Treatment should be tailored to each patient’s phenotype and expectations, such as a desire for pregnancy [9].

Different treatment strategies have been tried for patients with PCOS, such as lifestyle modification, ovulation induction, high testosterone therapy, insulin sensitizer, supplementation with myoinositol, folic acid, and vitamin D, assisted reproductive technology therapy, and surgical treatment [10, 11]. The main treatment for insulin resistance and glucose intolerance of women with PCOS is metformin [7, 11, 12], but a study reported that pioglitazone improved the menstrual cycle and ovulation of PCOS patients better than metformin [13]. Another drug prescribed is Clomiphene Citrate (CC). CC is a non-steroidal selective estrogen receptor modulator, and although it has efficient stimulation on ovulation, but the pregnancy rate is not satisfactory [14]. However, because of the side effects of drugs, the tendency to use of herbal drugs as the natural antioxidants and anti-inflammatory agents to regulate metabolism and control of hypertension and hyperlipidemia has increased [13, 14]. Medical herbs may be an important role in PCOS treatment. These medical herbs have a steroidogenic response and express estrogen receptor protein, reduce androgens, increase estrogens, and ultimately improve the conditions of PCOS patients [15, 16].

This study aimed to assess the effects of natural antioxidants and herbal substances on PCOS-IR by a systematic review in in patients with PCOS.

Methods

Search Strategy

The present research reviews the studies that focus on PCOS, herb, medical herbs, antioxidant, and nutrition by searching international databases of PubMed, Google Scholar, ISI, Embase (Elsevier) from 1990 to 2019. The current research was performed using the terms of medical subject headings and combinations of the keywords using the following search strategy: “polycystic ovary syndrome” or “PCOS” and “medical herbs” or “herb” or “antioxidant” or “nutrition” or “ovarian cysts” or “hyperandrogenism” or “hirsutism” or “botanical medicine”, or “insulin resistance”. All articles collected in the electronic search process, as well as the references used in these articles, were reviewed. Irrelevant, non-English, and inappropriate articles were excluded from the review process. Studies that have quantitatively investigated the association between polycystic ovary syndrome and herb or medical herbs were included in our review.

Assessment of methodological rigor

At this stage, studies conducted to investigate the association between medicinal herbs, insulin resistance, and polycystic ovary syndrome were selected. The quality of the studies was independently assessed by 2 persons (SD and MGh), and if two assessors do not agree with each other, the assessment was completed as a discussion with a third person (SAMJ). The irrelevant articles were excluded from the intended articles. The full text of the articles known as appropriate in this study was investigated. Figure 1 reported the selection process of articles. In the initial search, 361 articles were collected. After investigating the title and abstract, 221 articles were excluded from the study. Additionally, 102 articles were excluded after studying the full text of the articles, and finally 38 eligible articles were identified and included in the review study. The main characteristics of the studies are presented in table 1.

Aloe vera

_Aloe vera_ is a medicinal plant with hypoglycemic effects [13, 15, 16]. _Aloe vera_ is rich in fiber which accelerates gastrointestinal transit, absorption, and modulation of hemostasis [15–17]

_Aloe vera_ contains many compounds with different potential biological activities. Phytosterols in the _Aloe vera_ can alter the steroidogenic response and express estrogen receptor protein, reduce androgens, increase estrogens, and ultimately improve the conditions of the PCOS. _Aloe vera_ phytosterols such as sitosterol reduce serum cholesterol levels and normalized
(3β-Hydroxysteroid dehydrogenase) 3βHSD activity in PCOS rats [15, 17, 18].

One study by Radha et al. was conducted to investigate the effect of Aloe vera gel on rats with PCOS. In this study, Aloe vera was administered to rats of each group at different doses (5 mg/kg, 10 mg/kg, and 15 mg/kg) for 60 days, and it was found that Aloe vera can improve glucose tolerance in a dose-dependent manner. Although all dosages of Aloe vera may cause changes in the structure of the ovary, high dose treatment decreases atretic follicles and 3βHSD and 17β- Hydroxysteroid dehydrogenase (17βHSD) activates. Serum insulin levels and insulin resistance were significantly decreased in all groups and the doses of 10 and 15 mg significantly decreased the testosterone levels [17].

A clinical trial examined the endocrine effects of 1 mL of Aloe vera gel for 45 days in rats; as a result, Aloe vera did not change the biomarker enzymes and weight but improved the insulin sensitivity and 3βHSD and 17βHSD activity [18]. Some studies reported that Aloe vera can reduce Triglyceride (TG) and low-density lipoprotein (LDL-C) levels, decrease atretic follicles, and improve glucose intolerance and lipid metabolizing enzyme activities [15, 18, 19].

Faisal [20] reported a significant reduction in plasma glucose, insulin, and TG to high-density lipoprotein (HDL) ratio after oral supplementation with Aloe vera in mice. Aloe vera is an insulin sensitizer and influence on pancreatic β-cells [21].

Cinnamon

Cinnamomum is an herbaceous plant belonging to the Lauraceae family. Cinnamomum grows in tropical Southern India and Sri Lanka. Many studies have reported...
### Table 1:

| Author and year | Country | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|-----------------|---------|----------------------|-------------------------------|----------------------------------|----------------------|---------------|------------------|
| Desai BN et al, 2011 | India  | AVG formulation (1 ml (10 mg/day) orally | 30 days + The carboxymethyl cellulose and AVG control groups had 6 to 8 animals and PCOS group had 32 animals | Animal | Aloe vera reduced TG and LDL-C levels, increase HDL-C, improved glucose intolerance and lipid metabolizing enzyme activities. The Aloe vera derivatives have anti-hyperlipidemic effects. | None | Aloe vera exert influence on PCOS. It can manage PCOS and dyslipidemia. |
| Maharjan et al, 2014 | India  | Aloe vera gel (1 ml dose daily for 45 days) | 45 days + 8 control and 8 PCOS group that received Aloe vera gel | Animal | Aloe vera gel formulation exerts have a protective effect in PCOS and high dose Aloe treatment decrease atretic follicles and reverting ovary to normalcy. Restoring the ovarian steroid status, by modulation of key steroidogenic enzymes activities. | None | Aloe vera had exerted influence on PCOS. |
| Radha et al, 2014 | India  | Aloe vera gel (5 mg, 10 mg, 15 mg of dry weight for 60 days each group) | 60 days + 20 rats were divided into 2 groups | Animal | It was found that more effective doses are 10 mg/kg and 15 mg/kg and all doses could improve glucose tolerance. Serum insulin levels ($P < 0.001$) and insulin resistance (HOMA IR < 3) were significantly decreased in all groups and the doses of 10 and 15 mg had a significant decrease in testosterone levels. | None | Aloe vera had exerted influence on PCOS. |
| Moniruzaman 2012 | Malaysia | five groups: (1) water (WC), (2) libenclamide, (3) concentrated gel extract (Gel-C), (4) ethanol (80%) gel extract (Gel-Et), and (5) ethanol (80%) skin extract of Aloe vera (Skin-Et) | 4 weeks + 34 female rats were divided into 5 groups: group 1 (n = 7), WC rats; group 2 (n = 7), libenclamide-treated rats; group 3 (n = 6), concentrated gel extract; group 4 (n = 7), ethanol (80%) gel extract; and group 5 (n = 7), ethanol (80%) skin extract of Aloe vera | Animal | The rats treated with Gel-C, Gel-Et and Skin-Et had a significant reduction in fasting serum glucose levels, total cholesterol levels and LDL cholesterol. | None | Aloe vera had exerted influence on PCOS. |
| Author and year | Country        | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|----------------|----------------|----------------------|--------------------------------|----------------------------------|----------------------|---------------|-------------------|
| Ho-Chun Choi 2012 | South Korea | Aloe Vera (100 mg/g) or metformin (100 mg/g) for 3 weeks | 3 weeks + rats divided in to 2 group (group1 received (100 mg/g Aloe vera and group 2 received metformin) | Animal | After oral supplementation with Aloe vera fasting blood glucose decrease in mice. Aloe vera is insulin sensitizer that influence on pancreatic β-cells. | None | Aloe vera had exerted influence on PCOS. |
| Kim et al, 2018 | Republic of Korea | Aloe Vera (100 mg/g) or metformin (100 mg/g) | 8 weeks + 6 subjects in the control group and 8 in the intervention group | People with obese prediabetes and early non-treated diabetic patients | Body weight (P = 0.02), body fat mass (p = 0.03) and insulin resistance were significantly lower in the intervention group. FBG reduced in the intervention group (P = 0.02). | None | Aloe vera had exerted influence on PCOS. |
| Wang et al, 2007 | Colombia | 3 cinnamon capsules (each one contained 333 mg cinnamon) or placebo daily | 8 weeks + 15 women with PCOS | Women with PCOS | Cinnamon supplementation improved significant reduction in fasting glucose and insulin resistance. | None | Cinnamon had exerted influence on PCOS. |
| Kort et al, 2014 | USA | 1.5 g/d cinnamon supplements | 6 months + 45 women with PCOS receive cinnamon supplements or placebo for 6 months. | Women with PCOS | During 6 month intervention, menstrual cycles were more frequent in patients received cinnamon compared with patients received placebo. Luteal phase progesterone concentration confirmed ovulatory menses. Insulin resistance and serum androgen did not change. | None | Cinnamon had exerted influence on PCOS. |
### Cinnamon

**Hajimonfarednejad, Iran 2017**
- **Type of intervention**: Cinnamon powder capsules 1.5 g/day in 3 divided doses for 12 weeks
- **Time of experiment, and number**: 12 weeks + 66 women participated in the clinical trial 33 women receive cinnamon and 33 women received placebo
- **Study design and tested material**: Women with PCOS
- **Significant outcomes**: Fasting insulin, LDL-C, and insulin resistance were reduced after 12 weeks in intervention group compared with control group.
- **Adverse effect**: There was Observed of rash and itchiness in one patient.
- **Influence on PCOS**: Cinnamon had exerted influence on PCOS.

**Borzoei, Iran 2017**
- **Type of intervention**: 3 cinnamon capsules (each one contained 500 mg cinnamon) or placebo daily
- **Time of experiment, and number**: 8 weeks + 84 overweight or obese PCOS patients (42 subjects in cinnamon and 42 subjects in placebo groups)
- **Study design and tested material**: Overweight or obese PCOS patients
- **Significant outcomes**: Serum total antioxidant capacity significantly increased and malondialdehyde decreased in intervention group. Cinnamon supplementation significantly improved serum level of total cholesterol, LDL, and HDL-C, and decreased serum fasting blood glucose, insulin, and homeostatic model assessment for insulin resistance.
- **Adverse effect**: None
- **Influence on PCOS**: Cinnamon had exerted influence on PCOS.

**Wiweko, Indonesia 2017**
- **Type of intervention**: 1500 mg metformin divided into two doses or 100 mg DLBS3233 (including cinnamon) for 6 months
- **Time of experiment, and number**: 6 months + 20 received metformin, and 18 patients received
- **Study design and tested material**: Women with PCOS
- **Significant outcomes**: Decrease in anti-Müllerian hormone (AMH) level was higher in the metformin group compared to the Cinnamon group. AMH can reduced follicle sensitivity to FSH.
- **Adverse effect**: More side effects were observed in the metformin group compare with cinnamon group.
- **Influence on PCOS**: Cinnamon had exerted influence on PCOS.

**Dou et al, 2018**
- **Type of intervention**: The control group received 0.1 ml sesame oil and 100 μL 0.5% methylcellulose+ the DHEA group received 6 mg/100 g body weight dissolved in 0.1 ml of sesame oil and the DHEA + cinnamon group received 10 mg/100 g body weight mixed in 100 μL 0.5% methylcellulose
- **Time of experiment, and number**: 20 days + the animal randomly divided into 3 groups (control group (n=10), DHEA group (n=25), DHEA + cinnamon group (n=25))
- **Study design and tested material**: Animal
- **Significant outcomes**: Cinnamon down-regulate serum testosterone and insulin level, reduced insulin-like growth factor-1 and increase IGF-binding protein 1 level in plasma as well as in the ovary in PCOS mice.
- **Adverse effect**: None
- **Influence on PCOS**: Cinnamon had exerted influence on PCOS.
### Table 1: Medicinal Herbs and Polycystic Ovary Syndrome

| Author and year | Country | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|-----------------|---------|----------------------|--------------------------------|---------------------------------|----------------------|---------------|------------------|
| **Camellia sinensis (Green Tea)** |         |                      |                                 |                                 |                      |               |                  |
| Chan et al, 2006 | China   | Green tea capsules or placebo for 3 months | 3 months + 34 obese women with PCOS | Women with PCOS                  | The body weight in intervention group decreased, whereas the body weight, BMI, and body fat in the control group were significantly higher after 3 months. There were no differences in any of the hormone levels measured in either group. The triglyceride level in intervention group was increased. | None         | Green tea does not exert influence on PCOS |
| Allahdadian et al, 2015 | Iran    | 500 mg green tea twice a week for 12 weeks or placebo | 12 weeks + 60 obese women with PCOS | Women with PCOS                  | After 12 weeks intervention with green tea weight loss decreased fasting insulin levels and testosterone concentration were significantly higher in the intervention group than in the control group. The green tea combinations inhibited the production of the base and stimulated testosterone. | None         | Green tea exerts influence on PCOS |
| Tomatis 2015 | United States | Tablets providing 2093 mg green tea, catechins and 220 mg chlorogenic acids/day | 16 weeks + women divided in to 2 group | Women with PCOS | The nitric oxide production did not improve, but the intervention reduced waist circumference, changed eicosanoid profile, and reduced diastolic blood pressure, total cholesterol, and LDL cholesterol. | None         | Green tea exerts influence on PCOS |
| Author and year | Country | Type of intervention | Time of experiment, number and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|----------------|---------|----------------------|---------------------------------------|--------------------------------|----------------------|--------------|------------------|
| Ghafernian 2014 | Iran    | 50, 100 & 200 mg/kg green tea extract | 10 days + 96 mature Wistar rats | Wistar rats | Significant changes in the number of follicles and theca layer thickness. Reduction in LH serum level, body weight and ovarian weight between the green tea extract treated-groups. Reduction in insulin resistance index was seen in the treatment groups related to PCOS. | None | Green tea exerts influence on PCOS. |
| Gasemi Tehrani 2017 | Iran | Green tea in tablet produced by DINEH IRAN | 12 weeks + 60 overweight women suffering from PCOS (30 received green tea and 30 placebo) | Women with PCOS | Weight lost, decrease in fasting insulin, and level of free testosterone. | None | Green tea exerts influence on PCOS. |
| Mombaini 2007 | Iran | The four tablets of green tea containing 500 mg green tea and placebo group received the same number of placebo tablets contain (corn starch) | 45 days + women randomly allocated into two groups receiving green tea tablets or placebo | Women with PCOS | Green tea tablets intake did not change inflammation biomarkers in PCOS women but it may be effective as a complementary treatment for weighting control. | None | Green tea exerts influence on PCOS. |
| Bashtian et al, 2012 | Iran | Three tablets of metformin 500 mg and 2 tablets containing 500 mg foenum and placebo group received 3 tablets of metformin 500 mg and 2 tablets of placebo for 2 months. | 8 weeks + 58 women with PCOS (30 women in intervention group and 28 women in control group) | Women with PCOS | The fasting glucose, insulin sensitivity and hormonal concentrations were not significantly different between two groups. Improved the sonographic results and menstrual cyclicity. | None | Fenugreek exerts influence on PCOS. |
| Swaroop 2015 | USA | Trigonella foenum-graecum seed extract 500 mg/day | 90 days + 50 premenopausal women with PCOS | Women with PCOS | The LH and FSH levels increased and ovarian volume, cyst size, and the number of ovarian cysts decreased. | None | Fenugreek exerts influence on PCOS. |
### Table 1:

| Author and year | Country | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|----------------|---------|----------------------|-------------------------------|---------------------------------|----------------------|---------------|------------------|
| **Silymarin**  |         |                      |                               |                                 |                      |               |                  |
| Kayedpoor 2017 | Iran    | 100 & 200 mg/kg silymarin | 14 consecutive days + 144 adult female Wistar | Animal                          | Different doses of silymarin caused a significant decrease in the levels of estradiol, testosterone, LH and significant increase in the levels of progesterone and FSH, reduced body weight and abdominal fat, decreased follicular sheath thickness, and increased granulosa cells due to the appearance of corpus luteum in the silymarin-treated ovaries. | None          | Silymarin exerts influence on PCOS. |
| Nabiuni et al, 2015 | Iran    | Doses of 20 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, and 300 mg/kg | 60 days + 144 adult female Wistar | Animal                          | Silymarin has anti-angiogenesis effects, reducing the proliferation and thickness of the follicular sheath layer, thereby reducing the production of testosterone. | None          | Silymarin exerts influence on PCOS |
| **Chamomile** |         |                      |                               |                                 |                      |               |                  |
| Rafraf et al, 2015 | Iran    | The intervention group received chamomile tea (3 g/150 mL water) three times per day | 60 days + 64 individuals with T2DM (males and females) | Patients with T2DM              | Chamomile tea significantly decreased HbA1C and serum insulin levels ($p < 0.001$), homeostatic no significant changes were reported in serum HDL. | None          | Chamomile exerts influence on PCOS |
| Zafari Zangeneh 2010 | Iran    | 25, 50, 75 mg/kg of Chamomile alcoholic extract | 10 days + 30 rats were divided into 4 groups: one group is control and other three groups consume doses (25, 50 and 75 mg/kg) of chamomile | Animal                          | Decrease the signs of PCOS in the ovarian tissue and help LH secretion. | None          | Chamomile exerts influence on PCOS |
### Author and year | Country | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS  
--- | --- | --- | --- | --- | --- | --- | ---  
**Chamomile**  
Heidary 2018<sup>13</sup>  
Iran  
4 tablets of chamomile containing 370 mg  
3 months + 80 women (40 patients in each group)  
Women with PCOS  
Testosterone level was decrease in the intervention group who received chamomile capsules. Changes in low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol, and triglycerides were not significant.  
None  
Chamomile exerts influence on PCOS  
**Heracleum persicum** (Persian Hogweed or Golpar)  
Alizadeh 2015<sup>15</sup>  
Iran  
200 mg, 400 mg/kg and 800 mg *Heracleum persicum* extract  
10 days + 30 rat  
Animal  
*Heracleum persicum* reduced LH, estradiol, and testosterone. The high dose of *Heracleum persicum* increase FSH levels.  
None  
*Heracleum persicum* exerts influence on PCOS  
Haj-Husein 2016<sup>16</sup>  
Iran  
The intervention group receive marjoram tea and placebo tea twice daily for 1 month  
4 weeks + 25 patients with PCOS participate in study (intervention group: n = 14; placebo group: n = 11)  
Patients with PCOS  
Furanocoumarin inhibit nitric oxide syntheses that lead to reduced releasing LH level and estradiol. The estradiol reduction helps to natural process of human reproduction.  
None  
*Heracleum persicum* exerts influence on PCOS  
**Mentha spicata** (Spearmint)  
Sadeghi Ataabadi 2017<sup>15</sup>  
Iran  
50 mg/kg spearmint oil or 300 mg/kg spearmint oil  
20 days + Group 1: control, Group 2: consume letrozole; Group 3: received letrozole; Group 4: received letrozole and spearmint oil (300 mg/kg); Group 5: consume letrozole and sesame oil; Group 6: consume 150 mg/kg spearmint oil; Group 7: spearmint oil; and Group 8: received sesame oil  
Animal  
Menta oil reduced body weight, testosterone concentration, ovarian cysts, and atretic follicles in PCOS rats.  
None  
Mentha exerts influence on PCOS  
Akdoan 2007<sup>15</sup>  
Turkey  
5 g of dried mentha leaves in 250 mL of boiling water  
5 days + 21 female hirsute patients, 12 with PCOS and 9 with idiopathic hirsutism  
Women with PCOS and idiopathic hirsutism  
Spearmint teas did not change testosterone and increase luteinizing hormone, follicle stimulating hormone, and estradiol.  
None  
Mentha exerts influence on PCOS
| Author and year | Country | Type of intervention | Time of experiment, and number | Study design and tested material | Significant outcomes | Adverse effect | Influence on PCOS |
|-----------------|---------|----------------------|--------------------------------|---------------------------------|----------------------|---------------|-------------------|
| **Foeniculum vulgare (fennel)**  |
| Fozalaee 2015   | Iran    | Capsule containing fennel (150 mg/kg) and metformin (100 mg/kg) | 63 days + 40 female rats were divided into five (group 1: control; Group 2: estradiol valerate; Group 3: PCOS + fennel received 150 mg/kg; Group 4: PCOS + fennel 2 group received fennel (100 mg/kg); Group 5: PCOS + metformin consumed metformin (100 mg/kg) | Animal | Rats treated with *Foeniculum vulgare* at doses of 150 mg/kg and 100 mg/kg had decreased in urea levels. | None | Fennel exerts influence on PCOS |
| Karampoor 2014  | Iran    | Capsule containing 250, 500, and 1000 mg/kg fennel extract | 10 days + 30 rats case and 6 rats were considered as control | Animal | Treatment groups have been increased serum concentrations of FSH, decrease LH and testosterone in treatment groups. The FSH hormone (dose of 500 and 1000 mg/kg levels) and testosterone (dose 1000 mg/kg) have reported statistically significant differences compared to control groups. | None | Fennel exerts influence on PCOS |
| Sadrefozalayi 2012 | Iran    | Intervention group received various doses of 100 mg/kg and 150 mg/kg | 4 weeks + 40 female rats (n = 8 in each group) Group 1: control, Group 2: *Foeniculum vulgare* (150 mg/kg), Group 3: received 4 mg in 0.2 mL of sesame oil Group 4: 150 mg/kg Group 5: 100 mg/kg | Animal | There was a significant decrease in serum progesterone level in the low dose of *Foeniculum vulgare* in the treatment group compared with a high dose of *Foeniculum vulgare*. The mean serum estrogen concentration in the treatment group with a high dose of *Foeniculum vulgare* and metformin shows a significant increase. | None | Fennel exerts influence on PCOS |
| Mokabrinejad et al 2019 | Iran    | Intervention group received fennel tea and control received metformin | 6 month + 61 patients with oligomenorrhea divided in two group (Group 1: fennel infusion plus dry cupping and Group 2: treatment with metformin) | Patients with oligomenorrhea | This study reported that the fennel tea plus dry cupping decreased the days between two menstrual cycles and pain of dysmenorrhea in PCOS patients. | None | Fennel exerts influence on PCOS |
that cinnamon acts as an insulin sensitizer [22]. Cinnamon includes different flavonoids and polyphenols that have free radical scavenging and antioxidant activities [23]. Some studies reported that Type-A polymers and procyanidine polyphenols in the cinnamon extract enhance insulin signaling at the post-receptor level, increase the activity of Phosphoinositide 3 (PI3) kinase, increase the glucose uptake via enhancing the GLUT4 glucose transporter, inhibit the glycogen synthesis, and enhance glycogen synthesis and hypoglycemic effects [22, 23]. A study by Wang et al. investigated the effect of cinnamon extract on insulin

![Table 1:](image-url)
resistance in patients with PCOS. In this study, the control group received 3 meals and 1 capsule of placebo for each meal and the intervention group received capsules containing 333 mg of cinnamon extract per serving 3 times a day. The intervention group had a significant decrease in fasting blood sugar (FBS) and insulin resistance. The cinnamon improved insulin sensitivity and reduced oral glucose tolerance test in this study [22].

In another study by Kort et al. the intervention group received the cinnamon supplement (1.5 g) for 6 months and the control group received a placebo. The regular menstrual cycle in the intervention group confirmed the progesterone secretion in the luteal phase of the menstrual cycle. But the androgen levels and the insulin resistance had no significant changes between the two groups [23].

Borzoei et al. reported that using 500 mg cinnamon 3 days for 8 weeks improved FBS, insulin, and total cholesterol in patients with PCOS [24]. Another study carried out on 66 women that were diagnosed as PCOS. Participants were randomly allocated to two groups. The intervention group was treated by cinnamon powder capsules 1.5 g/day in 3 divided doses for 3 months and the control group received a placebo. It was concluded that cinnamon significantly decreased insulin resistance and fasting insulin levels in women with PCOS [25]. Another study reported that the metformin group had a lower anti-Müllerian hormone level, which is related to PCOS and reduces follicle sensitivity to FSH, compared to the cinnamon group. [26]. However, more side effects were observed in the metformin group compared to the cinnamon group. The ginger and cinnamon supplementation increase catalase, glutathione peroxidase, and superoxide dismutase levels [27]. Dou et al. reported that Cinnamon supplementation decreased insulin resistance and improved the health status of patients with PCOS [28]. It is possible that cinnamon down-regulates serum testosterone and insulin level reduces insulin-like growth factor-1 and increases Insulin-like growth factor 1 (IGF) binding protein level in plasma as well as in the ovary in PCOS. Cinnamon is a potential therapeutic agent for the PCOS [28].

**Camellia sinensis**

The scientific name of green tea is *Camellia sinensis*. Green tea is one of the richest sources of flavonoids and is used as a medicinal plant. Studies have indicated that green tea consumption might decrease FBS levels in diabetic patients and reduces the risk of CVD, cancer, and metabolic syndrome. Catechin inhibits catechol-O-methyltransferase (COMT) which is responsible for reduction of norepinephrine. Norepinephrine has a long-term effect on lipid metabolism. In humans, green tea supplementation increases energy consumption, fat oxidation, and reduces weight up to 4.6% in obese subjects for 3 months. Green tea contains caffeine that increases metabolic rate even at small doses (such as 100 mg/day) [31–39]. The green tea extract enhanced lipolysis and reduced hypertrophy of the follicular theca layer and reduced the thickness of this layer in PCOS rats. Due to this reduction, the level of steroid hormones and androgens produced by the follicular theca layer will decrease. Green tea extract enhanced the follicles and corpus luteum, and reduced cystic follicles in the ovary [32]. A study by Chan et al. in 2006 in Hong Kong aimed to investigate the effects of Chinese green tea on weight and biochemical and hormonal profiles in obese patients with PCOS. In this study, 340 Chinese obese women with PCOS were randomly divided in the intervention and placebo groups. The intervention group received green tea capsules at a dose of 540 mg (6 capsules 3 a day times for 3 months) and the control group received a placebo. At the end of the study, it was concluded that there was no significant change in BMI, weight, waist-hip ratio, and skin folds between the intervention and placebo groups. However, the level of triglyceride in the intervention group increased significantly [29].

Dadian et al. investigated the effect of green tea consumption on weight loss and hormonal changes in obese patients with PCOS. Weight loss decreased fasting insulin levels and testosterone concentrations were significantly higher in the intervention group than the control group after 12 weeks of the intervention [30]. Green tea inhibited testosterone production and stimulation, reduced LH level, diastolic blood pressure, body and ovarian weight. However, some other studies indicated that green tea increases testosterone levels and it cannot be recommended to all women with PCOS, only those who do not have elevated levels [29–34].

**Fenugreek (Trigonella foenum-graecum L)**

Fenugreek (*Trigonella foenum-graecum L*) is an annual plant and a traditional spice crop which is cultivated in Asia. Its crust contains 10–20 yellow seeds with appetizing aroma. Fenugreek has anti-diabetic and cholesterol-lowering effects and decreases insulin resistance in women with PCOS [35]. Fenugreek extracts have soluble fibers which decrease blood sugar by reducing enzymatic digestion and absorption of carbohydrates,
thus decreasing post-prandial glucose levels [35, 36]. Fenugreek has hypoglycemic effects through stimulating insulin synthesis, insulin secretion from beta-pancreatic cells, and inhibiting alpha-amylase and sucrose [35, 36].

Hassanzadeh et al. investigated the effect of fenugreek seed extract on insulin resistance in women with PCOS. The intervention group received 3 tablets of 500 mg metformin and 2 tablets of 500 mg foenum, and the control group received 3 tablets of 500 mg metformin and 2 tablets of placebo for 2 months. A significant reduction was seen in ovarian cysts after 2 months. There was no change in fasting glucose, insulin sensitivity, and hormonal concentrations between the two groups [35]. Another study on premenopausal women with a similar methodology reported 46% reduction in cyst size and 71% of women reported the return of regular menstrual cycle after completion of the treatment [36]. However, fenugreek should be recommended to women with irregular periods and polycystic ovarian ultrasound, but not necessarily to those with impaired glucose tolerance [35, 36].

Silymarin

The flavonoid silymarin is extracted from the milk thistle (Silybum marianum L. Gaernt.). Silymarin has been reported to possess various pharmacological properties with hepatoprotective, anti-oxidant, anti-inflammatory, anti-cancer, and cardioprotective activities.

It is a strong inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb) activation. It helps to eliminate free radicals in the body and prevents peroxidation of lipids by increasing cellular glutathione [37, 38].

Silymarin has anti-angiogenesis effects which reduce proliferation of follicular cells, thereby reducing the production of testosterone, and increases in corpus luteum due to increasing progesterone hormone [37]. Silymarin lowers testosterone level but also acts as a hepatoprotective factor and can increase SHBG protein synthesis, and inhibit cyclooxygenase (COX) and inflammation by reducing cysts [37, 38]. Silymarin influences glucose 6-phosphatase and inhibits gluconeogenesis, reduces blood glucose level, and thereby decreases the symptoms of the PCOS. Reduction of oxidative stress is a beneficial effect in reducing blood glucose levels by silymarin, and silymarin reduces inflammation in the PCOS by inhibiting cyclooxygenase-2 (COX-2) and lipoxygenase [37, 38].

A study by Nebuni et al. in 2014 investigated the effect of silymarin on PCOS induced by estradiol valerate in rats. In this study, silymarin was administered to rats at doses of 20 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, and 300 mg/kg for 14 days [38]. It was reported that in the group treated with silymarin, body weight, abdominal size, number, and size of cysts were decreased. They reported no cyst at high doses (300 mg/kg), which could be due to anti-inflammatory properties of silymarin. Different doses of silymarin had positive effects such as a decrease in estradiol, testosterone, and LH and a significant increase in FSH and progesterone hormones due to the appearance of corpus luteum cysts in the ovary. Silymarin reduced inflammation and collagen in the follicular sheath and eventually reduced the layer thickness [37, 38].

Toch et al. in a meta-analysis reported the effects of a fixed combination of Berberis aristata and Silybum marianum on sugar and lipid profile. Silybum marianum decreased low-density lipoprotein, cholesterol, and plasma glucose levels [39]. Another study reported that expression levels of the insulin receptor in the Alzheimer’s group were significantly down-regulated compared with the healthy group, and silibinin (polyphenolic flavonoid extracted of Silybum marianum) supplementation decreased down-regulation the insulin receptor expression level. This result suggests that silibinin improves the brain’s insulin signaling pathways [40].

Chamomile

Chamomile is a medicinal herb which is native to Western Europe and North Africa. The main derivatives of chamomile are amino acids, polysaccharides, fatty acids, essential fatty acid, minerals, flavonoids, and phytoestrogens that have anti-inflammatory, antispasmodic, and antioxidant effects [41]. Antispasmodic effect of chamomile makes the menstrual cramps easier and reduce premature births [42, 43]. Apigenin is one of the major flavonoid chamomile components which inhibit the binding of flunitrazepam (benzodiazepine derivatives) [42]. Benzodiazepine joined to gamma aminobutyric acid (GABA) is a natural neurotransmitter amino acid in brain and reduces the secretion of LH [44]. Chamomile contains phytoestrogen which can decrease the menstrual disorder through changes in hormone positive estrogen feedback [45].

Rafraf et al. reported that chamomile significantly decreased hemoglobin A1C (HbA1C), the insulin levels, total cholesterol, TG, and LDL-C [41].

A study by Zanganeh et al. investigated the effects of chamomile extract on biochemical and clinical parameters in PCOS rats. The intervention group received chamomile extract in different doses of 25 mg/kg, 50 mg/kg, and 75
mg/kg. In rats treated with a dose of 50 mg/kg, cysts were disappeared, the number of follicles was increased, and the level of estradiol levels, gonadotropins, LH, and FSH was significantly decreased [43]. In another study, subjects received 370 mg of oral capsules of chamomile for 3 months; the level of testosterone decreased. In addition, phytoestrogens inhibit progesterone metabolizing enzyme, 20-alpha-hydroxysteroid dehydrogenase and increase progesterone hormone. Some phytoestrogen compounds that control this enzyme include 3- and 7-dihydroxyflavone and flavones. An increase in progesterone leads to an increase in basal metabolism rate and may be the cause of weight loss. Finally, the sterols found in chamomile can reduce cholesterol absorption. Phytoestrogens in chamomile extracts increase the dehydroepiandrosterone, which is produced in the liver. Hydroalcoholic extract of chamomile also contains ascorbic acid to prevent weight gain and reduce cholesterol levels [46].

**Heracleum persicum (Persian Hogweed or Golpar)**

*Heracleum persicum* is a perennial herb that commonly used in the preparation of food and medicine in Iran, Iraq, and Turkey [47]. *Heracleum persicum* contains alkaloids, terpenoids, terpene, and steroids. Hydroalcoholic extract of *Heracleum persicum* contain furocoumarins such as sphondin. Heracleum persicum inhibited cyclooxygenase-2 and decreased inflammation [48].

*Heracleum persicum* is used as an anti-inflammatory, antiseptic, anti-diabetic, and anti-bacterial in traditional medicine [47]. *Heracleum persicum* extract probably decrease plasma testosterone, body and testis weight, and thus can help to treat sexual dysfunction in males [49].

Moreover, the hydroalcoholic extract of *Heracleum persicum* changes plasma sex hormone levels, inhibits folliculogenesis, and affects sexuality in women [50]. Furanocoumarins such as sphondin, xanthotoxin, and pimpinellin in the *Heracleum persicum* inhibits nitric oxide (NO) syntheses that reduced LH levels and estradiol release. The estradiol reduction helps the natural process of human reproduction [49, 50]. Haj Hosseini et al. investigated the effect of *Heracleum persicum* tea on hormone profile in PCOS women. The intervention group received 2 cups daily (containing 250 ml of herbal tea for 4 week) and the control group received a placebo. *Heracleum persicum* caused a significant decrease in fasting insulin, DHEA-S (dehydroepiandrosterone sulfate) levels, and a significant improvement in HOMA-IR index. Also, *Heracleum persicum* reduces androgens, especially adrenal androgens. Another study reported that *Heracleum persicum* reduced LH, estradiol, and testosterone, while increased FSH in PCOS rats [51]. Alkan et al, found that *Heracleum persicum* extract decreased plasma glucose and HbA1c in diabetic groups and increased insulin and c-peptide levels [52].

**Mentha**

Mentha (peppermint) is a medicinal plant of the Lamiaceae family. The mentha is native to East India and Asia. Essential oils of mentha are used in the food and beverage industries. Mentha has strong inhibitory effects which induce cytochrome P450 3A4 (CYP3A4) that leads to a change in the concentration of steroid hormones and androgen and reduce free testosterone levels due to increased SHBG. Peppermint tea can increase the level of LH, FSH, and estradiol due to physiological changes in the menstrual cycle. Peppermint tea can replace anti-androgenic treatments for hirsutism [53–55].

One study by Mehmet Akdogan et al. in Turkey investigated the effect of peppermint tea on the level of androgen in women with hirsutism. In this study, the intervention group received a cup of peppermint tea, containing 5 grams of dried mentha leaves in 250 ml of boiling water (5 days, twice a day) during the follicular phase of menstrual period. The intervention group had a significant decrease in the level of free testosterone, triglyceride, and significant increase in the levels of LH, FSH, and Prostaglandin E2 (PGE2). However, the level of DHEA and total testosterone did not decrease substantially [54]. In another clinical trial, the intervention group received peppermint tea or chamomile tea twice a day for 30 days and covered one complete menstrual cycle. The results of the studies showed that peppermint tea caused a significant decrease in testosterone levels and an increase in LH and FSH levels. Similarly, the degree of hirsutism is reduced [55]. Another study investigated the effect of herbal mixture supplements including menthe, zingiber, and *Cinnamomum* with and without CC in PCOS women. They found that these supplements have important effects on the antioxidants levels, glycemic control, menstrual regulation, and pregnancy rate [27].

**Foeniculum vulgare (fennel)**

*Foeniculum vulgare* (fennel) is used in traditional medicine to treat hormonal and metabolic disorders in women with PCOS. Fennel is regarded as phytoestrogen and have
protective effects against oxidative stress and kidney disease. The essential oil of *Foeniculum vulgare* has antimicrobial and antioxidant effects [57, 58].

The chemical analysis of the extract of fennel showed that linoleic acid (54.9 %), palmitic acid (5.4 %) and oleic acid (5.4 %) were major components of fennel. The palmitic acid β-oxidation has anti-androgenic effects. This compound also exerts an anti-androgenic effect by inhibiting the formation of the dihydrotestosterone receptor complex and reducing testosterone levels. *Foeniculum vulgare* may increase the aromatase enzyme activity and reduce testosterone levels [57]. Long-term use of the *Foeniculum vulgare* has a negative feedback effect on LH and testosterone levels. Reducing the androgen levels lead to reducing LH which can be a natural menstrual cycle in women with PCOS. *Foeniculum vulgare* extract does not change creatinine level but decreases urea. Kerempour et al. in Iran investigated the effect of hydro-alcoholic extract of *Foeniculum vulgare* seeds on the serum levels of sex hormones in rats with PCOS. In this study, *Foeniculum vulgare* was injected intraperitoneally in different doses of 250 mg/kg, 500 mg/kg, and 1000 mg/kg for 10 days. The intervention group received 500 mg/kg and 1000 mg/kg FSH significantly increased, and testosterone and LH levels were decreased in the group treated with 1000 mg/kg dose [58]. In line with this study, Fozalaee reported that the rats received a low dose of *Foeniculum vulgare* had a lower progesterone level than the control group [59].

Another study indicated that *Foeniculum vulgare*, as well as metformin, decreased the days between two menstrual cycles and pain of dysmenorrhea in PCOS patients [60].

**Potentilla**

*Potentilla* is used to treat menstrual irregularities, regulate sex hormones and improve fertility. Recent studies reported the non-estrogenic effects of *Potentilla* [61]. Different phytochemicals derivatives including tannins, phenolic acid, and triterpenoids have hypoglycemic, hypolipidemic, and anti-inflammatory activities. These compounds can decrease fasting blood glucose level, glycated serum protein, malondialdehyde, and NO through inhibition of glycogen phosphorylase activity [62, 63].

*Potentilla* increases the number of follicles and reduces the number of ovarian cysts. Phytoestrogens that have anti estrogenic effects are found in this plant. Vitex and lactone in *Potentilla* extract bind to the Dopamine receptor D2 (D2 R) of dopamine in the hypothalamus and glandular pituitary, thereby inhibiting prolactin secretion and reducing fibrocystic mastopathy [61, 64].

Jaldar et al. investigated the effects of the ethanolic root extract of *Potentilla* on ovarian tissue changes in rats with PCOS. The intervention group received 365 mg/kg dose for 30 days. *Potentilla* treatment did not significantly change the number of offspring [64].

Wang et al. investigated network pharmacology-based analysis on *Potentilla* derivates and found that *Potentilla* compounds may have important effects on glucose uptake [65].

**Licorice**

Licorice is a member of the Leguminosae family, a native plant that is growing in Spain, Italy, Turkey, Iran, Iraq, Central Asia, and Northeast China. Licorice may have estrogen-like activity and mild inhibitory effects on the metabolism of endogenous hormones [66]. Licorice inhibits the activity of 17-hydroxyl esterase dehydrogenase and 17,20-lyase activity, stimulates aromatase activity, affects α5 and β5 reductase, and is used for the treatment of menopause due to estrogen-like effects. Licorice reduces excess hair growth due to enzymatic effects on the melatonin production cycle and possibly inhibits tyrosinase activity [66, 67]. Also, licorice reduces serum hormones level by damaging the activity of 11β- hydroxysteroids dehydrogenase and increasing the aromatase activity or by progesterone-like activity [66–68]. Faghihi et al. reported that combination therapy of licorice gel and laser are much more effective than laser alone [67]. Another study concluded that treatment with licorice and spironolactone reduced the activity of the renin-angiotensin system but did not affect the blood pressure in the treatment group [68]. Yang et al. found that licorice extract inhibits the symptoms of PCOS by regulating controlling levels of serum FSH, LH/FSH ratio, and irregular ovarian follicles [69].

**Marrubium vulgare (White Horehound)**

*Marrubium vulgare* is a flowering plant in the mint family, a native plant that is growing in Europe, northern Africa, and Asia [44]. *Marrubium vulgare* contains polyphenols and flavonoids that produced hypoglycemic effects, reduced cholesterol, triglyceride, and oxidative stress. Some flavonoids, such as apigenin, competitively inhibit the binding of flunitrazepam, thereby reduce the secretion of LH [44, 70, 71]. Also, the β-testosterone in the extract
of Marrubium vulgare reduces LH. β-sitosterol reduces testosterone synthesis by lowering cholesterol. β-sitosterol reduces estradiol levels by decreasing aromatase enzyme activity, thereby preventing conversion testosterone to estrogen. Also, apigenin and ursolic acid of white horehound extract, inhibit cytochrome P450 and inhibit the conversion of cholesterol to pregnenolone, and thus reduce the synthesis of steroid hormones such as progesterone [70, 71].

A study by Mokhtari et al. was conducted to investigate the effect of bleach extract on hormonal parameters in rats with PCOS. In this study, the experimental group orally received doses of 500 mg/kg and 1000 mg/kg for 21 days. LH hormone was significantly decreased in 1000 mg/kg dose [70].

### Conclusion

This study reported that herbal medicines may have beneficial effects on PCOS. The compounds of herbal medicine can affect lipid profiles, insulin resistance, blood glucose, the serum levels of hormones, and the ovarian tissue. Therefore, these plants can be considered as a new approach to treatment or controlling PCOS. Nonetheless, due to the inadequacy of studies and contradictory results, further investigations are needed in this regard in the future.

### Conflict of interest

Authors state no conflict of interest

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