

Research Article

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Fatemeh Ashkar, Shahla Rezaei, Sara Salahshornezhad, Farhad Vahid, Maryam Gholamalizadeh, Samaneh Mirzaei Dahka, Saeid Doaei*

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 role 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 androgen synthesis and increases LH function. The ovaries produce too much testosterone androstenedione and dehydroepiandrosterone in PCOS patients [3, 4].

*Corresponding author: Saeid Doaei, Research Center of Health and Environment, Guilan University of Medical Sciences, Rasht, Iran, E-mail: sdoaei@yahoo.com

Fatemeh Ashkar, Sara Salahshornezhad, Department of clinical nutrition, school of nutrition and food science, Shiraz University of medical science, Shiraz, Iran

Shahla Rezaei, Student Research Committee, PhD student in Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

Farhad Vahid, Assistant professor in nutrition, Department of Nutritional Sciences, School of Health, Arak University of Medical Sciences, Arak, Iran

Maryam Gholamalizadeh, Students Research Committee, Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Samaneh Mirzaei Dahka, Student Research Committee, School of Nursing and Midwifery, Guilan; University of Medical Sciences, Rasht, Iran

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 glucose uptake and improve the conditions in PCOS patient [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

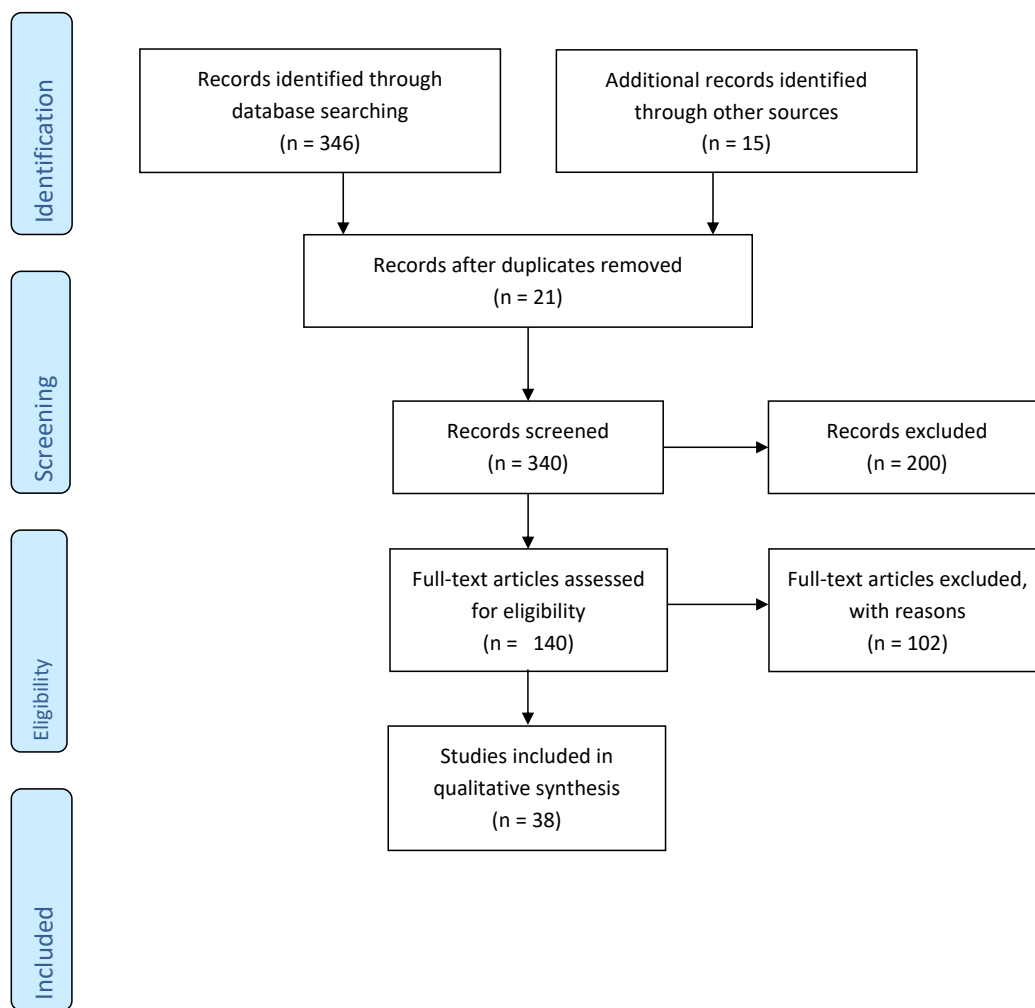


Figure 1: The number of records identified, included and excluded through the different phases of the review.

(3β -Hydroxysteroid dehydrogenase) 3β HSD 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 3β HSD and 17β -Hydroxysteroid dehydrogenase (17β HSD) activities. 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 3β HSD and 17β HSD 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
<i>Aloe barbadensis</i> Mill. or <i>Aloe vera</i>							
Desai BN et al, 2011 ¹⁴	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	<i>Aloe vera</i> reduced TG and LDL-C levels, increase HDL-C, improved glucose intolerance and lipid metabolizing enzyme activities. The <i>Aloe vera</i> derivatives have anti-hyperlipidemic effects.	None	<i>Aloe vera</i> exert influence on PCOS. It can manage PCOS and dyslipidemia.
Maharjan et al, 2014 ¹⁶	India	<i>Aloe vera</i> gel (1 ml dose daily for 45 days)	45 days + 8 control and 8 PCOS group that received <i>Aloe vera</i> gel	Animal	<i>Aloe vera</i> gel formulation exerts have a protective effect in PCOS and high dose <i>Aloe</i> treatment decrease atretic follicles and reverting ovary to normalcy. Restoring the ovarian steroid status, by modulation of key steroidogenic enzymes activities.	None	<i>Aloe vera</i> had exerted influence on PCOS.
Radha et al, 2014 ¹⁷	India	<i>Aloe vera</i> 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	<i>Aloe vera</i> had exerted influence on PCOS.
Moniruzaman 2012 ¹⁸	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 <i>Aloe vera</i> (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 <i>Aloe vera</i>	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	<i>Aloe vera</i> had exerted influence on PCOS.

Continued **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
<i>Aloe barbadensis</i> Mill. or <i>Aloe vera</i>							
Ho-Chun Choi 2012 ¹⁹	South Korea	700 mg capsule containing processed aloe vera gel(147 mg/cap), aloesin powder (3 mg/cap), yeast chromone (125 mg/cap), and excipients (soy bean oil, yellow beeswax, and lecithin) (425 mg/cap) The control group received 700 mg soft capsule containing natural pigment (4.2 mg/cap) and excipients (soybean oil, yellow beeswax, and lecithin) (695.8 mg/cap).	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	<i>Aloe vera</i> had exerted influence on PCOS.
Kim et al, 2018 ²¹	Republic of Korea	<i>Aloe Vera</i> (100 mg/g) or metformin (100 mg/g) for 3 weeks	3 weeks + rats divided in to 2 group (group1 received (100 mg/g <i>Aloe vera</i> and group 2 received metformin	Animal	After oral supplementation with <i>Aloe vera</i> fasting blood glucose decrease in mice. <i>Aloe vera</i> is insulin sensitizer that influence on pancreatic β -cells.	None	<i>Aloe vera</i> had exerted influence on PCOS.
Cinnamon							
Wang et al, 2007 ²²	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 ²³	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.

Continued **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
Cinnamon							
Hajimonfared-nejad 2017 ²⁵	Iran	cinnamon powder capsules 1.5 g/day in 3 divided doses for 12 weeks	12 weeks + 66 women participated in the clinical trial 33 women receive cinnamon and 33 women received placebo	Women with PCOS	Fasting insulin, LDL-C, and insulin resistance were reduced after 12 weeks in intervention group compared with control group.	There was Observed of rash and itchiness in one patient.	Cinnamon had exerted influence on PCOS.
Borzoei 2017 ²⁴	Iran	3 cinnamon capsules (each one contained 500 mg cinnamon) or placebo daily	8 weeks + 84 overweight or obese PCOS patients (42 subjects in cinnamon and 42 subjects in placebo groups)	Overweight or obese PCOS patients	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.	None	Cinnamon had exerted influence on PCOS.
Wiweko 2017 ²⁶	Indonesia	1500 mg metformin divided into two doses or 100 mg DLBS3233 (including cinnamon) for 6 months	6 months + 20 received metformin, and 18 patients received	Women with PCOS	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.	More side effects were observed in the metformin group compare with cinnamon group.	Cinnamon had exerted influence on PCOS.
Dou et al, 2018 ²⁸		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	20 days + the animal randomly divided into 3 groups (control group (n=10), DHEA group (n=25), DHEA + cinnamon group (n=25))	Animal	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.	None	Cinnamon had exerted influence on PCOS.

Continued **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
<i>Camellia sinensis</i> (Green Tea)							
Chan et al, 2006 ²⁹	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 ³⁰	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 ³¹	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.

Continued **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
<i>Camellia sinensis</i> (Green Tea)							
Ghafurniyan 2014 ³²	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 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 ³³	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 ³⁴	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.
<i>Fenugreek</i> (<i>Trigonella foenum-graecum</i> L)							
Bashtian et al, 2012 ³⁵	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 ³⁶	USA	<i>Trigonella foenum-graecum</i> 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.

Continued **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 ³⁷	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 ³⁸	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 ⁴¹	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 ⁴³	Iran	25, 50, 75 mg/kg of <i>Chamomile alcoholic</i> 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 <i>chamomile</i>	Animal	Decrease the signs of PCOS in the ovarian tissue and help LH secretion.	None	Chamomile exerts influence on PCOS

Continued **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
Chamomile							
Heidary 2018 ⁴²	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
<i>Heracleum persicum</i> (Persian Hogweed or Golpar)							
Alizadeh 2015 ⁵¹	Iran	200 mg, 400 mg/kg and 800 mg <i>Heracleum persicum</i> extract	10 days + 30 rat	Animal	<i>Heracleum persicum</i> reduced LH, estradiol, and testosterone. The high dose of <i>Heracleum persicum</i> increase FSH levels.	None	<i>Heracleum persicum</i> exerts influence on PCOS
Haj-Husein 2016 ⁵⁰	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	<i>Heracleum persicum</i> exerts influence on PCOS
<i>Mentha spicata</i> (Spearmint)							
Sadeghi Ataabadi 2017 ⁵⁵	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	Mentha oil reduced body weight, testosterone concentration, ovarian cysts, and atretic follicles in PCOS rats.	None	Mentha exerts influence on PCOS
Akdoan 2007 ⁵³	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

Continued **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
Foeniculum vulgare (fennel)							
Fozalae 2015 ⁵⁹	Iran	Capsule containing fennel (150 mg/kg) (100 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 <i>Foeniculum vulgare</i> at doses of 150 mg/kg and 100 mg/kg had decreased in urea levels.	None	Fennel exerts influence on PCOS
Karampoor 2014 ⁵⁸	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 ⁵⁷	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: <i>Foeniculum vulgare</i> (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 <i>Foeniculum vulgare</i> in the treatment group compared with a high dose of <i>Foeniculum vulgare</i> . The mean serum estrogen concentration in the treatment group with a high dose of <i>Foeniculum vulgare</i> and metformin shows a significant increase.	None	Fennel exerts influence on PCOS
Mokaberinejad et al 2019 ⁶⁰	Iran	Intervention group received fennel tea and control received metformin	6 month + 61 patients with oligomenorrhoea divided in two group (Group 1: fennel infusion plus dry cupping and Group 2: treatment with metformin)	Patients with oligomenorrhoea	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

Continued **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
<i>Potentilla</i>							
Jelodar 2017 ⁴¹	Iran	Capsule containing 365 mg/kg <i>Vitex</i> extract	30 days + 28 mice	Animal	<i>Potentilla</i> treatment did not significantly change the number of offspring.	None	<i>Potentilla</i> exerts influence on PCOS
Licorice or <i>Glycyrrhiza glabra</i>							
Faghihi 2015 ⁶⁷	Iran	Licorice gel plus alexandrite laser	24 weeks + 90 female subjects with hirsutism (Subjects were divided into two groups: Group 1: alexandrite laser plus 15% licorice gel and Group 2: control)	Women with hirsutism	A treatment of idiopathic hirsutism with licorice gel plus laser is more effective than laser only.	Nno serious adverse reactions	Licorice with laser exerts influence on hirsutism
Armanini 2006 ⁶⁸	Italy	Group (1) received 100 mg spironolactone and (group 2) spironolactone plus 3.5 g of licorice a day	60 days +32 woman(16 woman consume 100 mg spironolactone and 16 subjects received spironolactone plus 3.5 g of licorice)	Woman with PCOS	The blood pressure was significantly reduced in spironolactone treatment group, while it was not significant change in women receiving spironolactone plus licorice.	None	Licorice does not exert influence on PCOS
Yang et al, 2018 ⁶⁹	South Korea	Licorice (300 mg/kg)	2 weeks + 18 rats (3 groups n = 6 rats in each group)	Animal	licorice extract inhibits the symptoms of PCOS by regulating controlling levels of serum FSH, LH/FSH ratio, and irregular ovarian follicles.	None	Licorice exerts influence on PCOS
<i>Marrubium vulgare</i> (White Horehound)							
Mokhtae ⁷⁰	Iran	Experimental group orally received doses of 500 mg/kg and 1000 mg/kg for 21 days.	21 days + 48 adult female rats	Animal	LH hormone significantly decreased in dose 1000 mg/kg and estradiol and progesterone decreased in doses 500 mg/kg and 1000 mg/kg and testosterone decreased in dose 1000 mg/kg.	none	White Horehound 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

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 into 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. Gaertn.). 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. Phytosterols 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 spondin. *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 spondin, 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, Fozalae 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].

Potentillas 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* derivatives 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 $\alpha 5$ and $\beta 5$ 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 11 β -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/and 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

References

- Howe E. Polycystic ovarian syndrome. PCOS; 2015.
- Tehrani FR, Simbar M, Tohid M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: iranian PCOS prevalence study. *Reprod Biol Endocrinol*. 2011 Mar;9(1):39.
- Mohseni Kouchesfahani H, Nabyooni M, Adham H. Investigating the therapeutic effect of eee venom on polycystic ovarian syndrome in rats. *Shahid Beheshti University of Medical Sciences*. 2010;15(1):1–6.
- Marx TL, Mehta AE. Polycystic ovary syndrome: pathogenesis and treatment over the short and long term. *Cleve Clin J Med*. 2003 Jan;70(1):31–3.
- Goodarzi MO, Carmina E, Azziz R. DHEA, DHEAS and PCOS. *J Steroid Biochem Mol Biol*. 2015 Jan;145:213–25.
- Deswal R, Yadav A, Dang AS. Sex hormone binding globulin - an important biomarker for predicting PCOS risk: A systematic review and meta-analysis. *Syst Biol Reprod Med*. 2018 Feb;64(1):12–24.
- Hopkinson ZE, Sattar N, Fleming R, Greer IA. Polycystic ovarian syndrome: the metabolic syndrome comes to gynaecology. *BMJ*. 1998 Aug;317(7154):329–32.
- Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril*. 2016 Jul;106(1):6–15.
- Lua AC, How CH, King TF. Managing polycystic ovary syndrome in primary care. *Singapore Med J*. 2018 Nov;59(11):567–71.
- Jin P, Xie Y. Treatment strategies for women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2018 Apr;34(4):272–7.
- Regidor PA, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. *New clinical data and review of the literature. Horm Mol Biol Clin Investig*. 2018 Mar;34(2):/j/hmbci.2018.34.issue-2/hmbci-2017-0067/hmbci-2017-0067.xml.
- Xu Y, Wu Y, Huang Q. Comparison of the effect between pioglitazone and metformin in treating patients with PCOS: a meta-analysis. *Arch Gynecol Obstet*. 2017 Oct;296(4):661–77.
- Ma QW, Tan Y. Effectiveness of co-treatment with traditional Chinese medicine and letrozole for polycystic ovary syndrome: a meta-analysis. *J Integr Med*. 2017 Mar;15(2):95–101.
- Desai BN, Maharjan RH, Nampoothiri LP. Aloe barbadensis Mill. formulation restores lipid profile to normal in a letrozole-induced polycystic ovarian syndrome rat model. *Pharmacognosy Res*. 2012 Apr;4(2):109–15.
- Doaei S, Hajiesmaeil M, Aminifard A, Mosavi-Jarrahi SA, Akbari ME, Gholamalizadeh M. Effects of gene polymorphisms of metabolic enzymes on the association between red and processed meat consumption and the development of colon cancer; a literature review. *J Nutr Sci*. 2018 Oct;7:e26.
- Gholamalizadeh M, Doaei S, Akbari ME, Rezaei S, Jarrahi AM. Influence of fat mass-and obesity-associated genotype, body mass index, and dietary intake on effects of iroquois-related homeobox 3 gene on body weight. *Chin Med J (Engl)*. 2018 Sep;131(17):2112–3.
- Radha M, Padamnabhi N, Laxmipriya N. Evaluation of Aloe barbadensis mill. Gel on letrozole induced polycystic ovarian syndrome (pcos) rat model-a dose dependent study. *Int J Pharm Sci Res*. 2014;5(12):5293.
- Moniruzzaman M, Rokeya B, Ahmed S, Bhowmik A, Khalil MI, Gan SH. In vitro antioxidant effects of Aloe barbadensis Miller extracts and the potential role of these extracts as antidiabetic and antilipidemic agents on streptozotocin-induced type 2 diabetic model rats. *Molecules*. 2012 Nov;17(11):12851–67.
- Choi HC, Kim SJ, Son KY, Oh BJ, Cho BL. Metabolic effects of aloe vera gel complex in obese prediabetes and early non-treated diabetic patients: randomized controlled trial. *Nutrition*. 2013 Sep;29(9):1110–4.
- Rizwan Faisal, Effect of Aloe vera Whole Leaf Extract on Blood Glucose, yperinsulinemia, and Insulin Resistance in Streptozotocin Induced Type 2 Diabetic Rats. December 2015, *Medical Forum Monthly* 26(12).
- Kim K, Chung MH, Park S, Cha J, Baek JH, Lee SY, et al. ER stress attenuation by Aloe-derived polysaccharides in the protection of pancreatic β -cells from free fatty acid-induced lipotoxicity. *Biochem Biophys Res Commun*. 2018 Jun;500(3):797–803.
- Wang JG, Anderson RA, Graham GM 3rd, Chu MC, Sauer MV, Guarnaccia MM, et al. The effect of cinnamon extract on insulin resistance parameters in polycystic ovary syndrome: a pilot study. *Fertil Steril*. 2007 Jul;88(1):240–3.

23. 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- e6. <https://doi.org/10.1016/j.ajog.2014.05.009>.
24. Borzoei A, Rafrat M, Asghari-Jafarabadi M. Cinnamon improves metabolic factors without detectable effects on adiponectin in women with polycystic ovary syndrome. *Asia Pac J Clin Nutr*. 2018;27(3):556–63.
25. Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raei MJ, Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: A randomized double-blind placebo controlled clinical trial. *Phytother Res*. 2018 Feb;32(2):276–83.
26. Wiweko B, Susanto CA. The effect of metformin and cinnamon on serum anti-mullerian hormone in women having PCOS: A Double-blind, randomized, controlled trial. *J Hum Reprod Sci*. 2017 Jan-Mar;10(1):31–6.
27. Ainehchi N, Khaki A, Farshbaf-Khalili A, Hammadeh M, Ouladsahebmadarek E. The Effectiveness of Herbal Mixture Supplements with and without Clomiphene Citrate in Comparison to Clomiphene Citrate on Serum Antioxidants and Glycemic Biomarkers in Women with Polycystic Ovary Syndrome Willing to be Pregnant: A Randomized Clinical Trial. *Biomolecules*. 2019 Jun;9(6):215.
28. Dou L, Zheng Y, Li L, Gui X, Chen Y, Yu M, et al. The effect of cinnamon on polycystic ovary syndrome in a mouse model. *Reprod Biol Endocrinol*. 2018 Oct;16(1):99.
29. Chan CC, Koo MW, Ng EH, Tang OS, Yeung WS, Ho PC. Effects of Chinese green tea on weight, and hormonal and biochemical profiles in obese patients with polycystic ovary syndrome—a randomized placebo-controlled trial. *J Soc Gynecol Investig*. 2006 Jan;13(1):63–8.
30. Allahdadian M, Ranjbar H, Ghasemi H, Janighorban M, Dadkhah A, Allahdadian F, et al. Exploring the effect of green tea on weight loss and serum hormone levels in overweight and obese patients with polycystic ovary syndrome. *Avicenna Journal of Clinical Medicine*. 2015 Jun;22(1):16–22.
31. Tomatis V, Wassell S, Venables M, Walker C, Ray S, Siervo M, Griffin J, Bluck L. Effects of Green Tea and Coffee Polyphenols on Cardiometabolic Function in Women with Polycystic Ovary Syndrome. *The FASEB Journal*. 2015 Apr;29(1 supplement):LB271.
32. Ghafurniyan H, Azarnia M, Nabiuni M, Karimzadeh L. The effect of green tea extract on reproductive improvement in estradiol valerate-induced polycystic ovarian syndrome in rat. *Iranian journal of pharmaceutical research*. *Iran J Pharm Res*. 2015;14(4):1215–33.
33. Tehrani HG, Allahdadian M, Zarre F, Ranjbar H, Allahdadian F. Effect of green tea on metabolic and hormonal aspect of polycystic ovarian syndrome in overweight and obese women suffering from polycystic ovarian syndrome: A clinical trial. *J Educ Health Promot*. 2017 May;6(1):36.
34. Mombaini E, Jafarirad S, Husain D, Haghhighizadeh MH, Padfar P. The impact of green tea supplementation on anthropometric indices and inflammatory cytokines in women with Polycystic Ovary Syndrome. *Phytother Res*. 2017 May;31(5):747–54.
35. 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.
36. 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). *Int J Med Sci*. 2015 Oct;12(10):825–31.
37. Kayedpoor P, Mohamadi S, Karimzadeh-Bardei L, Nabiuni M. Anti-inflammatory Effect of Silymarin on Ovarian Immunohistochemical Localization of TNF- α Associated with Systemic Inflammation in Polycystic Ovarian Syndrome. *Int J Morphol*. 2017 Jun;35(2). <https://doi.org/10.4067/S0717-95022017000200054>.
38. Nabiuni M, Kayedpoor P, Mohammadi S, Karimzadeh L. Effect of silymarin on estradiol valerate- induced polycystic ovary syndrome. *MEDICAL SCIENCES*. 2015;25(1):16-26 URL: <http://tmuj.iautmu.ac.ir/article-1-900-fa.html>
39. Tóth B, Németh D, Soós A, Hegyi P, Pham-Dobor G, Varga O, et al. The Effects of a Fixed Combination of *Berberis aristata* and *Silybum marianum* on Dyslipidaemia—A Meta-analysis and Systematic Review. *Planta Med*. 2019 Nov.
40. Liu P, Cui L, Liu W, Hayashi T, Mizuno K, et al. Silibinin ameliorates STZ-induced impairment of memory and learning by up-regulating insulin signaling pathway and attenuating apoptosis. *Physiol Behav*. 2020 Jan;213:112689.
41. Rafrat M, Zemestani M, Asghari-Jafarabadi M. Effectiveness of chamomile tea on glycemic control and serum lipid profile in patients with type 2 diabetes. *J Endocrinol Invest*. 2015 Feb;38(2):163–70.
42. Adib-Hajbaghery M, Mousavi SN. The effects of chamomile extract on sleep quality among elderly people: A clinical trial. *Complement Ther Med*. 2017 Dec;35:109–14.
43. Farideh ZZ, Bagher M, Ashraf A, Akram A, Kazem M. Effects of chamomile extract on biochemical and clinical parameters in a rat model of polycystic ovary syndrome. *J Reprod Infertil*. 2010 Oct;11(3):169–74.
44. Bouterfas K, Mehdadi Z, Elaoufi M, Latreche A, Benchiha W, editors. Antioxidant activity and total phenolic and flavonoids content variations of leaves extracts of white Horehound (*Marrubium vulgare* Linné) from three geographical origins. *Annales pharmaceutiques francaises*. Elsevier; 2016. <https://doi.org/10.1016/j.pharma.2016.07.002>.
45. Johari HA, Sharifi ES, Mardan MA, Kafilzadeh FA, Hemayatkhah VA, Kargar HO, et al. The effects of a hydroalcoholic extract of *Matricaria chamomilla* flower on the pituitary-gonadal axis and ovaries of rats. *Int J Endocrinol Metab* 2011;9:330-46. Heidary M, Yazdanpanahi Z, Dabbaghmanesh MH, Parsanezhad ME, Emamghoreishi M, Akbarzadeh M. Effect of chamomile capsule on lipid-and hormonal-related parameters among women of reproductive age with polycystic ovary syndrome. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2018;23.
47. Yang LL, Liang YC, Chang CW, Lee WS, Kuo CT, Wang CC, et al. Effects of sphondin, isolated from *Heracleum laciniatum*, on IL-1 β -induced cyclooxygenase-2 expression in human pulmonary epithelial cells. *Life Sci*. 2002 Nov;72(2):199–213.
48. Barzegari Firouzabadi F, Mirhosseini M. Effect of Persian hogweed (*Heracleum persicum*) on the morphological changes in mice testes and the level of hormone testosterone. *RJMS*. 2012;19(99):18–24.

49. Hajhashemi V, Sajjadi SE, Heshmati M. Anti-inflammatory and analgesic properties of *Heracleum persicum* essential oil and hydroalcoholic extract in animal models. *J Ethnopharmacol.* 2009 Jul;124(3):475–80.
50. Haj-Husein I, Tukan S, Alkazaleh F. The effect of marjoram (*Origanum majorana*) tea on the hormonal profile of women with polycystic ovary syndrome: a randomised controlled pilot study. *J Hum Nutr Diet.* 2015.
51. Alizadeh F, Azarnia M, Mirabolghasemi G, Karampoor P. Effect of Fruit *Heracleum Persicum* Extract on Changes in Serum Levels of Sex Hormones in Rats with Polycystic Ovary Syndrome (PCOS). *Armaghane danesh.* 2015;20(1):31-42
52. Alkan EE, Celik I. The therapeutics effects and toxic risk of *Heracleum persicum* Desf. extract on streptozotocin-induced diabetic rats. *Toxicol Rep.* 2018 Aug;5:919–26.
53. Akdoğan M, Tamer MN, Cüre E, Cüre MC, Köroğlu BK, Delibaş N. Effect of spearmint (*Mentha spicata* Labiatae) teas on androgen levels in women with hirsutism. *Phytother Res.* 2007 May;21(5):444–7.
54. Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytother Res.* 2010 Feb;24(2):186–8.
55. Sadeghi Ataabadi M, Alaei S, Bagheri MJ, Bahmanpoor S. Role of Essential Oil of *Mentha Spicata* (Spearmint) in Addressing Reverse Hormonal and Folliculogenesis Disturbances in a Polycystic Ovarian Syndrome in a Rat Model. *Adv Pharm Bull.* 2017 Dec;7(4):651–4.
56. Ainehchi N, Khaki A, Farshbaf-Khalili A, Hammadeh M, Ouladsahebmadarek E. The Effectiveness of Herbal Mixture Supplements with and without Clomiphene Citrate in Comparison to Clomiphene Citrate on Serum Antioxidants and Glycemic Biomarkers in Women with Polycystic Ovary Syndrome Willing to be Pregnant: A Randomized Clinical Trial. *Biomolecules.* 2019 Jun;9(6):215.
57. Sadrefozalayi S, Farokhi F. Effect of the aqueous extract of *Foeniculum vulgare* (fennel) on the kidney in experimental PCOS female rats. *Avicenna J Phytomed.* 2014 Mar;4(2):110–7.
58. Karampoor P, Azarnia M, Mirabolghasemi G, Alizadeh F. The effect of hydroalcoholic extract of fennel (*foeniculum vulgare*) seed on serum levels of sexual hormones in female wistar rats with polycystic ovarian syndrome (PCOS). *J Arak Univ Med Sci.* 2014 Aug;17(5):70–8.
59. Fozalae SS, Farokhi F. The Effect of Metformin and Aqueous Extract *Foeniculum vulgare* (Fennel) on Endometrial Histomorphometry and the Level of Steroid Hormones in Rats with Polycystic Ovary Syndrome. *Qom University of Medical Sciences Journal.* 2015;8(5).
60. Mokaberinejad R, Rampisheh Z, Aliasl J, Akhtari E. The comparison of fennel infusion plus dry cupping versus metformin in management of oligomenorrhoea in patients with polycystic ovary syndrome: a randomised clinical trial. *J Obstet Gynaecol.* 2019 Jul;39(5):652–8.
61. Mazurek S, Fecka I, Węglińska M, Szostak R. Quantification of active ingredients in *Potentilla tormentilla* by Raman and infrared spectroscopy. *Talanta.* 2018 Nov;189:308–14.
62. Vickers NJ. Animal Communication: When I'm Calling You, Will You Answer Too? *Curr Biol.* 2017 Jul;27(14):R713–5.
63. Syiem D, Syngai G, Khup PZ, Khongwir BS, Kharbuli B, Kayang H. Hypoglycemic effects of *Potentilla fulgens* L in normal and alloxan-induced diabetic mice. *J Ethnopharmacol.* 2002 Nov;83(1-2):55–61.
64. Jelodar G, Askari K. Effect of hydroalcoholic extract of *Vitex agnus-castus* fruit on fertility and estrous cycle in letrozole-induced polycystic ovary (PCOS) in rat. *RJMS.* 2017;24(156):42–8.
65. Wang N, Zhu F, Shen M, Qiu L, Tang M, Xia H, et al. Network pharmacology-based analysis on bioactive anti-diabetic compounds in *Potentilla discolor bunge*. *J Ethnopharmacol.* 2019 Sep;241:111905.
66. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological effects of *Glycyrrhiza glabra* (licorice): a review. *Phytother Res.* 2017 Nov;31(11):1635–50.
67. Faghihi G, Irajli F, Abtahi-Naeini B, Saffar B, Saffaei A, Pourazizi M, et al. Complementary Therapies for Idiopathic Hirsutism: Topical Licorice as Promising Option. *Evidence-Based Complementary and Alternative Medicine.* 2015;2015.
68. Armanini D, Castello R, Scaroni C, Bonanni G, Faccini G, Pellati D, et al. Treatment of polycystic ovary syndrome with spironolactone plus licorice. *Eur J Obstet Gynecol Reprod Biol.* 2007 Mar;131(1):61–7.
69. Yang H, Kim HJ, Pyun BJ, Lee HW. Licorice ethanol extract improves symptoms of polycystic ovary syndrome in Letrozole-induced female rats. *Integr Med Res.* 2018 Sep;7(3):264–70.
70. Mokhtari M, Ebrahimpoor MR, Harfsheno S. The effects of alcoholic extract of *Marrubium vulgare* on hormonal parameters in female rat model of polycystic ovarian syndrome. *MEDICAL SCIENCES.* 2014;24(2):74–80.
71. Gavarić A, Vladić J, Ambrus R, Jokić S, Szabó-Révész P, Tomić M, et al. Spray Drying of a Subcritical Extract Using *Marrubium vulgare* as a Method of Choice for Obtaining High Quality Powder. *Pharmaceutics.* 2019 Oct;11(10):523.