



A comprehensive review of clinical studies with herbal medicine on polycystic ovary syndrome (PCOS)

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Abstract

Background Polycystic ovary syndrome (PCOS) is a frequent medical condition characterized by both metabolic and reproductive disorders. Different pharmaceutical treatments have been proposed for PCOS. However, side effects of long-term treatments and their probable low efficacy have made complementary and alternative treatments a valuable option. Recent reports have indicated the increased use of complementary treatments. Herbal medicine, as part of complementary medicine, was first introduced in traditional Persian and Chinese medicine. Medicinal herbs have been used for a long time in the treatment of gynecological and infertility problems of PCOS patients. In this study, we aimed to review herbal medicines used for PCOS worldwide.

Methods PubMed, Embase, Cochrane, and Scopus databases were searched for clinical trials and Randomized Controlled Trials based on related keywords. Data were collected from 1990 to 2019.

Results According to a multitude of studies, a wide spectrum of herbs can be used to improve various aspects of PCOS. Herbs such as *Cinnamomum verum*, *Trigonella foenum-graecum* L., and *Vitex agnus-castus* can impact on menstrual and ovulatory dysfunctions, obesity, insulin resistance, lipid-metabolism dysfunction, and androgen excess-related conditions.

Conclusion Some plants as natural remedies may have beneficial effects on improving different aspects of PCOS; but further studies are needed to investigate their mechanisms and safety.

Keywords Polycystic ovary syndrome · PCOS · Herbal medicine · Complementary medicine

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most frequent conditions, which affects both metabolic and reproductive systems. PCOS is best known for irregular menstrual cycles, chronic anovulation, and hyper-androgenism [1, 2]. According to the Rotterdam criteria, the prevalence of PCOS is 10%, while the prevalence of polycystic ovaries is 28% [3]. The pathogenesis of this disorder is not clear yet although it probably has epigenetic origins; therefore, there is no single effective treatment available for this disease [4, 5].

Different pharmaceutical treatments have been proposed for PCOS. However, they have disadvantages, such as adverse effects, low compliance of patients with long-term pharmaceutical treatments, low efficacy, and contraindications in some cases; therefore, complementary treatments can be proper alternatives [6–9]. Today, oral contraceptives are the most common options for the treatment of PCOS. They act by decreasing free androgens in the blood and suppressing the secretion of gonadotropins [10]. Clomiphene citrate is a non-steroidal selective estrogen receptor modulator (SERM), and Letrozole is an aromatase inhibitor, widely used for ovulation induction. Clomiphene citrate is the first-line therapy although there is growing evidence that Letrozole has higher efficacy and safety for the mother and fetus [11, 12]. Metformin is used to treat insulin resistance, which is an important factor in the Rotterdam criteria, in patients with PCOS. Overall, treatment of insulin resistance along with hyper-androgenism improves hormonal, metabolic, and reproductive functions [13].

Recently use of complementary treatments has increased, and today, approximately 40% of adults benefit from

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complementary treatments [14, 15]. Women use complementary medicine more than men, especially for self-treatment purposes [16]. Evidence suggests that 40% of non-pregnant/non-postpartum women use complementary medicine, while the corresponding figure in pregnant and postpartum women is 37% and 28%, respectively [17].

Herbal medicine, as part of complementary medicine, was first introduced in traditional Persian and Chinese medicine [18]. Chinese herbs have a long history in the management of gynecological problems and infertility of PCOS patients [19]. In traditional Persian medicine, PCOS was referred to as oligo-amenorrhea, a prominent manifestation of the disease [20]. Various medicinal plants have been proposed as treatment for oligo-amenorrhea in traditional Persian medicine [21].

In this study, we reviewed different approaches of herbal medicine in the treatment of PCOS and examined their mechanisms, and efficacy. We also investigated the direct effects of herbal extracts on reproduction, irregular menstruation, hyper-androgenism, and metabolic disorders in PCOS patients.

Methods

We conducted this comprehensive literature search of English-language studies in electronic databases, including PubMed, Science Direct, Scopus, and Cochrane Library from 1990 to March 2019 in order to retrieve clinical studies on herbal treatments for PCOS. The keywords included “polycystic ovary syndrome”, “PCOS” in title/abstract AND “plant”, “herb”, “phyto”, “extract or root”, “fruit”, “water”, “alcoholic”, “powder”, “traditional medicine”, “complementary” or “alternative” in all fields. We reviewed articles based on their titles and abstracts according to the inclusion and exclusion criteria. The inclusion criteria in this study were English articles, clinical trials, and randomized controlled trials (RCTs). On the other hand, reviews, case reports, short communications, and letters to editors were excluded from the study. The full texts of some studies were not available, thus their data may not be fully completed. In some studies, the components of plant compounds were not clearly determined. Finally, a total of 42 articles were selected. Data were collected from the full text manuscripts and included different types of herbs, different parts of herbs, year of publication, type of study, sample size, and reproductive, metabolic, and other effects of plants on PCOS. Figure 1 presents a diagram of the study selection process.

Results

The etiology of PCOS remains unclear. This syndrome presents with a variety of symptoms, such as hormonal

imbalance, reproductive dysfunction, and metabolic disorders. Ovarian dysfunction is the main finding of PCOS [22]. According to the findings many herbal medicines exerted therapeutic effects on various aspects of PCOS.

These herbs could affect menstrual and ovulatory dysfunctions, obesity, insulin resistance, hyperinsulinemia, lipid-metabolism dysfunction, hirsutism, and other excess-androgen-related conditions [23, 24].

Table 1A presents a brief summary of the results.

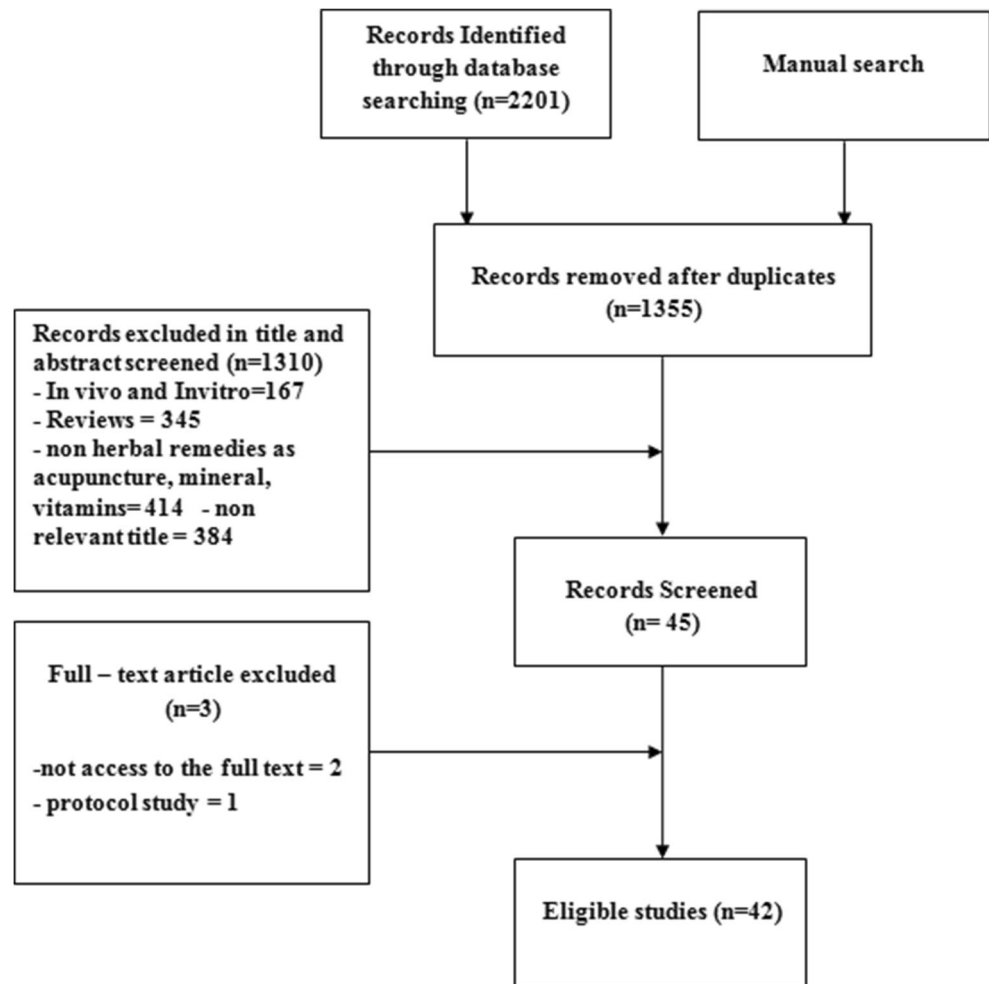
Infertility/ovulatory dysfunction

Few studies were found concerning infertility in spite of its importance. *Trigonella foenum-graecum* L., which improved the ovarian function and menstrual cycle regularity, could increase the fertility rate [29, 41]. Likewise, *Danzhi xiaoyao* and *Linum usitatissimum* L. powder had similar effects on fertility [47, 58]. In addition, *Grifola frondosa* ameliorated ovulation [34] and augmented fertility. Also, other herbs might influence impact infertility only in combination with other medications. Administration of *Cimicifuga racemosa* along with Clomiphene, could increase the fertility potential of PCOS patients [36]. Another survey revealed that long-term treatment with *Cimicifuga racemosa* as a phytoestrogen could be used as an alternative to Clomiphene [46]. On the other hand, the combination of Berberine (Coptidis rhizome) and with Letrozole had no significant positive effects on the fertility rate [39] while, administration of Berberine along with Metformin showed promising results in in vitro fertilization (IVF) of PCOS patients [53].

Hormonal status/menstruation cycle

Herbal medicines not only improve reproductive dysfunctions, but also play a remarkable role in balancing the hormonal status and menstrual cycles. Use of *Cinnamomum cassia* supplement for at least six months could normalize the menstrual cycles [44]. Cinnamon, as a bioactive medication, resulted in the reduction of anti-mullerian hormone and had fewer side effects in comparison with Metformin [49]. In addition cinnamon in conjunction with *Glycyrrhiza spp.*, *Paeonia lactiflora* Pall., and *Hypericum perforatum* L. decreased the level of luteinizing hormone (LH). However, it exerted no significant effects on the level of follicle-stimulating hormone (FSH) or testosterone levels [27]. It seems that cinnamon in all forms (extract, powder, and supplement) influenced the hormonal status and menstrual cycles [31, 45]. *Trigonella foenum-graecum* L. was effective in the regulation of menstrual cycle and had promising effects on fertility [29]. In addition, Tian gui, a Chinese herb could decrease the testosterone level and modify hyper-androgenism [35]. On the other hand, Unkei-to, a Japanese herb could cause a significant reduction in LH level and increase the level of

Fig. 1 Flow diagram of the study selection process



estradiol, leading to the improvement of menstrual cycles [40]. Based on previous studies, regular consumption of Chinese multi-herbs controlled the menstrual cycles substantially, and created a sense of well-being in patients [47]. A survey of *Linum usitatissimum* L. demonstrated its efficacy in the regulation of menstrual cycles without causing considerable alterations in hormone levels or hirsutism [52]. On the other hand, drinking marjoram tea improved the hormonal status [56]. It was revealed *Vitex agnus-castus* had similar advantages to oral contraceptives in the regulation of menstrual cycles with notably fewer side effects. *Vitex agnus-castus* did not change the testosterone or prolactin levels [33]. Nevertheless *Nigella sativa* L. [59] and *Apium graveolens* L. along with *Pimpinella anisum* L. [62] regulated the menstrual cycles and decreased LH level in PCOS patients with oligomenorrhea.

Only few surveys are available regarding the anti-androgenic effects of herbs and their impact on hirsutism. It was found that spearmint tea [32], *Anethum graveolens* L., *Asparagus racemosus* Willd. [42], and *Matricaria chamomilla* L. [63] could reduce the testosterone level and severity of hirsutism. Although *Camellia sinensis* L. [28] and Tian gui

[35] were reported to decrease the testosterone level, their impact on hirsutism has not been reported. It seems that more studies are needed to clarify the potential effects of herbs on hirsutism. Moreover, the effect of Soy has been investigated in several studies with controversial findings. In one study, eight-week administration of Soy showed no considerable effects on LH, FSH, or estradiol levels [26]. On the other hand, another survey reported the advantageous impact of Soy on improving the hormonal status when used for 12 weeks [43]. Also, wood betony (as a phytoestrogen) could be used in the treatment of abnormal uterine bleeding (AUB) secondary to PCOS as an alternative to medroxyprogesterone [54].

Metabolic dysfunction

There are studies regarding the impact of herbs on metabolic dysfunction with promising results reported in PCOS patients. Cinnamon along with *Glycyrrhiza spp.*, *Paeonia lactiflora* Pall., and *Hypericum perforatum* L. reduced the body mass index (BMI) and insulin level with no significant impact on fasting blood sugar (FBS) [27]. Administration of *Cinnamomum zeylanicum* Blume and *Nigella sativa* L. led to

Table 1 Clinical trial studies on medicinal plants used for treatment of PCOS patients

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
1	Borzoei A, et al., Iran 2017 [25]	<i>Cinnamomum zeylanicum</i> Blume	Cinnamon bark powder prepared as capsule	84	8 weeks	Significant differences of serum TAC ($P = 0.005$) and MDA ($P = 0.014$) between cinnamon & placebo groups after the intervention. \uparrow TAC ($P = 0.001$) without statistical decrease in serum MDA level ($P = 0.102$) in cinnamon group at the end of study compared to the baseline. \downarrow total cholesterol and LDL and \uparrow HDL serum levels in cinnamon group at the end of the study compared to the baseline ($P < 0.05$). No significant change on serum TG level in cinnamon group.
2	Forouhari S, et al., Iran 2013 [26]	<i>Glycine max</i> (L.) Merr.	Soy flour as a loaf of soy bread	42	2 months	No significant effects on serum FSH, Estradiol, and testosterone level following soy bread consumption after the intervention ($P > 0.05$).
3	Arentz S, et al., Australia 2017 [27]	<i>Cinnamomum verum</i> j. Presl, <i>Glycyrrhiza glabra</i> L., <i>Hypericum perforatum</i> L., <i>Paeonia lactiflora</i> Pall. and <i>Tribulus terrestris</i> L.	Herbal extracts as tablets	122	3 months	\downarrow Oligomenorrhoea of 32.9% in herbal medicine plus lifestyle group compared with lifestyle alone ($P < 0.01$). \downarrow BMI ($P < 0.01$); \downarrow Waist circumference ($P < 0.01$); \downarrow insulin ($P = 0.02$), and \downarrow LH ($P = 0.04$); \downarrow blood pressure ($P = 0.01$); improvement in the quality of life ($P < 0.01$), depression, anxiety, and stress ($P < 0.01$); and pregnancy rates ($P = 0.01$) in combination group compared with lifestyle intervention alone.
4	Tehrani HG, et al., Iran 2017 [28]	<i>Camellia sinensis</i> L.	<i>Camellia sinensis</i> L. as tablets (Green Teadin pills)	60	12 weeks	\downarrow Weight ($P = 0.031$), \downarrow fasting insulin ($P < 0.0001$), and \downarrow free testosterone ($P < 0.0001$) after treatment between groups (green tea & control).
5	Swaroop A, et al., India 2015 [29]	<i>Trigonella foenum-graecum</i> L.	Hydro-alcoholic extract of seeds as capsules	50	3 months	\uparrow LH ($p = 0.045$) and \uparrow FSH ($P = 0.010$), \downarrow LH/FSH ratio (not statistically significant), \downarrow ovarian volume, \downarrow cyst size in 47 subjects, complete resolving of cysts in 36 patients, regular menstrual cycles in 71% of subjects, \uparrow Hb levels, \downarrow ALP, no significant change in WBC, AST, ALT, BUN, and creatinine and 12% pregnancy after intervention compared to the baseline. No serious side effect in Agnugol group.
6	Shayan A, et al., Iran 2016 [30]	<i>Vitex agnus-castus</i> L.	Dry extract as Agnugol tablet	120	3 months	No difference in the length of menstruation, intervals of menstrual cycles, and the number of pads in two groups (Agnugol

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
7	Hajimonfarednejad M, et al., Iran 2017 [31]	<i>Cinnamomum cassia</i> (L.) J.Presl.	Barks powder	66	12 weeks	& Metformin) after the intervention. No serious side effect in Agnugol group. ↓ Weight, ↓ BMI, ↓ waist circumference (not statistically significant), ↓ fasting insulin ($P = 0.024$), HOMA-IR ($P = 0.014$), ↓ LDL ($P = 0.049$) and HDL ($P = 0.033$) after the intervention in cinnamon group in comparison with the placebo group. Both groups received medroxy progesterone acetate at the beginning of the study. No serious side effect in cinnamon group
8	Paul Grant, UK 2009 [32]	<i>Mentha spicata</i> L.	tea	42	30 days	↓ Free and total testosterone, ↑ LH, ↑ FSH, ↓ degree of hirsutism scored by the modified DQLI in spearmint tea group ($P < 0.05$), ↓ Ferriman-Galwey score of hirsutism (not statistically significant) between two groups (spearmint & placebo) at the end of the study ($P = 0.12$). No side effect was reported.
9	Shahnazi M, et al., Iran 2016 [33]	<i>Vitex agnus-castus</i> L.	Fruit extract	70	3 months	Normalization the menstrual cycle duration in 68.6% of the LD group and 60% of the extract participants (no statistically significant difference between the two groups ($P = 0.45$). ↓ Free testosterone, prolactin, and DHEAS level in the LD and the extract groups at the end of study (no statistically significant difference between the two groups). Mood changes and Spotting were reported in Vitex group (no statistically significant difference between groups).
10	Chen J, et al. Japan 2010 [34]	<i>Grifola frondosa</i>	MSX tablets, containing <i>Grifola frondosa</i> extract and its dried powder	72	12–16 weeks	Ovulation in 76.9% MSX and in 93.5% CC groups but not significant ($P = 0.124$). Epigastralgia in two MSX group patients.
11	Kuek S et al.,China 2011 [35]	–	A capsule containing 11 herbs	47	3 months	↓ Testosterone, ↓ SHBG, ↓ FAI, ↓ FINS, ↓ ovarian volume, ↑ DHEAS ($P < 0.05$), without change in FPG in Tian Gui group after treatment compared before. ↓ Testosterone in the three groups (Tian Gui, metformin and Dian), but no statistically significant difference between the groups. Significant changes in DHEA-S and SHBG between the three groups. No side effect was reported.

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
12	Shahin A.Y and Mohammed S.A., Egypt 2014 [36]	<i>Cimicifuga racemosae</i> (L.) Nutt.(CR)	Dry extract of CR rhizome in the form of film-coated tablets	206	2 months	↓ Mid-cycle LH ($P = 0.001$), ↑ progesterone ($P = 0.001$) and ↑ estradiol in the second half ($P = 0.01$), ↑ endometrial thickness ($P = 0.001$), ↑ pregnancy rate ($P < 0.01$) in CC + CR group compared to the CC group alone.
13	Chan C. et al., Hong Kong 2006 [37]	–	Lung Chen tea leaves as capsule	34	3 months	↓ Body weight (2.4%) after treatment in green tea group but not statistically significant. No remarkable change in hormone levels and biochemical profiles except TG between two groups after treatment. ↑ TG in green tea group compared to the placebo at the end of the study. No side effect was reported.
14	Ebrahimi-Mamaghani M, et al., Iran 2014 [38]	<i>Allium cepa</i> L.	Raw red onions	54	8 weeks	↓ Total cholesterol, ↓ LDL in two groups (high onion & low onion), but further in the high-onion group after treatment. No significant change in FBS, TG, and LDH by onion treatment.
15	Ke Wu X, et al., Chinese 2016 [39]	–	Berberine in the form of capsule	644	6 months	↑ Accumulative live births, ↑ conception, ↑ pregnancy, and ↑ ovulation rates in the letrozole and combination groups (letrozole + berberine) after treatment compared to berberine group. No serious side effect among the three groups (letrozole, berberine, and combination groups).
16	Ushiroyama T, et al., Osaka 2001 [40]	<i>Paeonia lactiflora</i> Pall. with <i>Cinnamomum cassia</i> (L.) J. Presll.	Unkei-to	100	8 weeks	↓ LH and ↑ estradiol and making dominant follicle in Unkei-to group. Improvement of menstrual cyclicity of 50% PCOS subjects in Ukei-to group, but no statistically significant difference between the two groups (Unkei-to & control).
17	Hassanzadeh Bashtian M, et al., Iran 2013 [41]	<i>Trigonella foenum-graecum</i> L.	Hydroalcoholic extract of seeds	58	8 weeks	↓ Significant in polycystic-appearing ovaries in ultrasound scans in extract group at the end of the study ($P = 0.01$). No significant changes in BMI, HOMA-IR, QUICKI, testosterone, 17- α hydroxy progesterone levels, and Ferriman–Gallwey score in both groups (herbal extract & placebo) Normalizing menstrual cycle in 12 women with oligo-amenorrhea in extract group. Both groups received metformin during the study.
18	Kumarapeli M, et al. Sri Lanka 2018 [42]	–	Satapushpa Shatavari Powder (SSP) 5 g	60	2 weeks	↓ Ovarian volume, and normalized menstrual cycle at the end of the

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
		<i>Anethum graveolens</i> L. <i>Asparagus racemosus</i> Willd.	TDS/.oral Satapushpa ShatavariGrita (SSG), 60 ml / daily /enema			study compared to the baseline in three groups (oral, rectal and oral + rectal). Significant ↑ endometrial thickness, and ↓ hirsutism rate in oral+rectal group after intervention compared to other groups.
19	Jamilian M and Asemi Z., Iran 2016 [43]	<i>Glycine max</i> (L.) Merr	Soy isoflavone supplements as capsule	70	12 weeks	↓ Insulin ($P < 0.001$), ↓ HOMA-IR and HOMA-B ($P < 0.001$), ↑ QUICKI ($P = 0.01$), ↓ free androgen index ($P < 0.001$), ↓ TG ($P = 0.04$), ↑ plasma total glutathione ($P = 0.04$), ↓ MDA ($P = 0.001$) after treatment compared to the placebo group.
20	Kort DH, Lobo RA Columbia 2014 [44]	<i>Cinnamomum Verum</i> J. Presl.	Cinnamon as supplement	45	6 months	Significant improvement in menstrual cyclicity and ovulatory cycle in cinnamon group compared with baseline and placebo. No considerable change in markers of insulin resistance, serum androgen, SHBG levels, weight, and ovarian volume in both groups. No serious adverse effect.
21	Wang J G et al., USA 2007 [45]	<i>Cinnamomum verum</i> J. Presl.	Extract	15	8 weeks	↓ FBS ($P > 0.03$), ↑ QUICKI ($P > 0.03$), ↓ HOMA-IR ($P > 0.03$), ↓ in mean 2hppbs and improved insulin sensitivity in the extract group but not statistically different from the control (placebo).
22	Kamel Hany H. Egypt 2012 [46]	<i>Cimicifuga racimosa</i> (L.) Nutt. (CR)	Extract	100	3 months	↓ LH ($P = 0.007$), ↓ FSH/LH ratio ($P = 0.06$), ↑ progesterone ($P = 0.0001$), ↑ endometrial thickness ($P = 0.0004$), ↑ ovulation ($P = 0.0001$) and fewer side-effects in CR compared to the CC group after intervention. ↑ Pregnancy rate in CR compared to CC group but not statistically significant.
23	Lai L, et al., Chinese 2017 [47]	–	Granulated extracts as a tea from 14 to 20 herbs	40	6 months	Significant improvement in menstrual rates in two groups (standardized Chinese hebal medicine & individualized chinese herbal medicine) but no statistically significant difference between groups ($P = 0.26$), ↓ hirsutism scores but not significant ($P = 0.09$) in two groups. No significant change in BMI or weight in two groups at the end of the study.
24	Kalgaonkar S et al., USA 2011 [48]	<i>Prunus dulcis</i> (Mill.) <i>Juglans regia</i> L.	Walnuts, Almonds	36	6 weeks	↓ LDL ($P = 0.05$), ↓ Apo protein B ($P < 0.03$), ↑ insulin response ($P < 0.02$), ↑ PUFA, ↓ HgBA1c ($P = 0.0006$) and ↑ SHBG

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
						($P = 0.0038$) in walnut group. ↓ LDL (not statistically significant) and ↓ FAI ($P = 0.0470$) in almond group. ↑ Adiponectin in two groups (walnuts or almonds).
25	Wiweko B and Susanto C. A. Indonesia 2017 [49]	<i>Lagerstroemia spesiosa</i> (L.) and <i>Cinnamomum burmanni</i> Blume	Extract as tablet	38	6 months	↓ AMH level in 2 groups after treatment but further reduction in metformin group with more side effects. Significant ↓ BMI in herbal group after treatment. All subjects received metformin during the study.
26	Mombaini E, et al., Iran 2017 [50]	<i>Camellia sinensis</i> L.	<i>Camellia sinensis</i> L. leaf powder as tablets	50	45 days	Significant ↓ in weight, BMI, waist circumference, and body fat percentage after the intervention in the green tea group, but no significant difference between the two groups (green tea & placebo) was observed. No significant difference in the inflammatory factors in comparison with between- and within- groups at the end of the study. No serious side effect.
27	Khani B, et al. Iran 2011 [51]	<i>Glycine max</i> (L.) Merr.	Soy supplement as Genistein capsules	146	3 months	Significant ↓ LH, ↓ TG, ↓ LDL, ↓ DHEAS and ↓ testosterone after treatment in the Genistein group. No significant difference in HDL and FSH serum levels in two groups (Genistein and placebo) before and after intervention.
28	Farzana F, et al., India 2015 [52]	<i>Linum usitatissimum</i> L.	Flaxseed powder	32	3 months	↓ Ovarian volume, number of follicles ($P < 0.01$), improvement in menstrual cyclicality and pregnancy (40% and 10% respectively), Ns change in hirsutism, BW, and BS after intervention compared to before.
29	An Y, et al., China 2014 [53]	–	Berberine hydrochloride as tablets	150	3 months	↓ Testosterone, ↓ free androgen, ↓ FBS, ↓ fasting insulin, ↓ HOMA-IR, ↑ SHBG, ↑ pregnancy rate, and ↓ severe ovarian hyperstimulation syndrome in berberine and metformin group compared to placebo after treatment. ↓ BMI, ↓ lipid parameters and ↓ FSH, ↑ live birth rate ($P = 0.047$) and less frequent unwanted events in berberine compared to metformin group after treatment.
30	Jalilian N, et al., Iran 2013 [54]	<i>Stachys lavandulifolia</i> Vahl	Dried aerial parts of wood betony (AWB)	66	3 months	↓ Prevalence rate of AUB symptoms in two groups (AWB & MPA). Adverse events in 24.2% cases of MPA compared to 45.5% in AWB but less serious side effects for AWB compared to MPA. The odds for adverse

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
						reaction of MPA = 0.40 (95% CIs: 0.14–1.19, P value = 0.099) time odds of AWB. Remarkable changes of sonographic findings in AWB after treatment compared to MPA ($P = 0.036$).
31	Mirmasoumi G, et al., Iran 2017 [55]	<i>Linum usitatissimum</i> L.	Flaxseed oil in form of capsule	60	12 weeks	↓ Insulin values, ↓ HOMA-IR ($P = 0.01$), ↓ Ferriman–Gallwey score ($P = 0.001$), ↑ QUICKI ($P = 0.01$), ↓ TG ($P = 0.01$), ↓ VLDL ($P = 0.01$), ↓ CRP ($P = 0.004$) in treatment group compared to placebo after intervention. Ns change in hormonal profile and plasma nitric oxide at the end of the study in treatment group. No adverse event in treatment group.
32	Haj-Husein Iet al., Jordan 2015 [56]	<i>Origanum majorana</i> L.	Marjoram tea	25	1 month	↓ DHEAS, ↓ fasting insulin ($P < 0.05$), in marjoram groups after treatment. ↓ HOMA-IR in intervention group compared to placebo ($P < 0.05$).
33	Liang, Y et al., China 2016 [57]	–	Chinese medical decoction (CCD)	40	2 months	↑ Oocyte retrieval number, ↑ 2pronuclear fertilization rate, ↑ embryo rate and ↓ ROS in treatment group compared to control.
34	Liu Y, Mao LH., China 2013 [58]	–	Dan-zhi Xiao-yao (Chinese medicine formulation) as pills	60	3 menstrual cycles	Significant ↓ Insulin, ↓ LH, ↓ testosterone after treatment compared to before in two groups ($P < 0.05$) but no significant difference between the groups. No remarkable change in BMI between two groups after treatment. Significant improvement in PMS and menstrual symptoms in integrative group. Higher ovulation and pregnancy rate in integrative versus western group (86.01% vs 65.5% and 60% vs 36.7%, respectively).
35	Naeimi S A et al., Iran 2018 [59]	<i>Nigella sativa</i> L.	powdered seed in form of capsule	10	4 menstrual cycles	Significant ↓ cholesterol, ↓ TG, ↓ FBS, ↓ Insulin, ↓ AST, ↓ LH, and ↓ HOMA-IR, ↑ menstrual cycle/month and ↓ menstrual cycle interval after intervention.
36	Borzoei A, et al., Iran 2017 [60]	<i>Cinnamomum zeylanicum</i> Blume	Cinnamon bark powder prepared as capsule	84	8 weeks	Significant FBS, ↓ Insulin, ↓ HOMA-IR, ↓ cholesterol, ↓ LDL, ↓ weight and ↑ HDL in cinnamon group compared to placebo. Significant ↓ TG, ↓ BMI in cinnamon group compared to its base line. No remarkable change in adiponectin in both groups.
37	Esmaeilnezhad Z, et al., Iran 2019 [61]	<i>Punicagranatum</i> L.	juice	92	8 weeks	Significant ↓ HOMA-IR, ↓ BMI, weight and waist circumferences in synbiotic pomegranate juice

Table 1 (continued)

No	Authors /country/ year	Scientific name	Part/ compound	Sample size	Duration of study	Results
38	Moini A, et al., Iran 2018 [62]	<i>Apium graveolens</i> L. and <i>Pimpinella anisum</i> L.	powdered seeds in form of capsule	72	4 menstrual cycles	and synbiotic beverage compared to baseline and control group. Significant ↓ testosterone in synbiotic pomegranate juice and synbiotic beverage compared with baseline ↑ menstrual cyclicity, ↓ testosterone and ↓ LH/FSH in intervention group compared to the metformin group
39	Heidary M, et al., Iran 2018 [63]	<i>Matricaria chamomilla</i> L.	Chamomilpowder as capsule	80	3 months	Significant ↓ testosterone after treatment in chamomile group. No remarkable change in LDL, HDL, TG, DHEA, and LH/FSH in treatment and control group.
40	Armanini D, et al., Italy 2006 [64]	<i>Glycyrrhiza glabra</i> L.	licorice powder	32	–	No remarkable change in blood pressure and no complain of symptoms related to volume depletion in spironolactone plus licorice group compared to spironolactone treatment.
41	Mokaberinejad R, et al., Iran, 2019 [65]	<i>Foeniculum vulgare</i> Mill.	Fennel seed infusion	61	6 months	↓ Menstrual cycle interval and ↓ dysmenorrhea severity in treatment group compared to metformin group after 3 and 6 months. No adverse event in treatment group.
42	Ding CF. et al., China 2014 [66]	–	Chinese medicine formulation as decoction	355	3menstrual cycles	Significant ↓ spiral artery pulsatility index, ↓ resistance index, ↑ endometrial thickness, in group 2 (clomiphene + human menopause gonadotropin + human chorionic gonadotropin + Cangfu daotan) compared to group 1 (clomiphene + human menopause gonadotropin + human chorionic gonadotropin). ↓ HOMA-IR in group 2 after treatment compared to before.

N.S; not significant, ↑; increased, ↓; decreased TAC; total antioxidant capacity, MDA; malondialdehyde, LDL; low-density lipoprotein, HDL; high-density lipoprotein, VLDL; very low-density lipoprotein cholesterol, TG; triglycerid, FSH; follicle-stimulating hormone, LH; luteinizing hormone, Hb; hemoglobin, HgBA1c; hemoglobin A1c or glycosylated hemoglobin, BMI; body mass index, CC; clomifene citrate, HOMA-IR; homeostatic model assessment insulin resistance, HOMA-B; homeostasis model of assessment β-cell function DQLI; dermatology quality of life index, LD; combined low-dose oral contraceptives, DHEAS; dehydroepiandrosterone sulfate, CC; clomiphene citrate, AST; aspartate transaminase, ALT; alanine transaminase, ALP; alkaline phosphatase, BUN; blood urea nitrogen, WBC; white blood cell, SHBG; sex hormone-binding globulin, T; testosterone, LDH; lactate dehydrogenase, FBS; fasting blood sugar, FAI; free androgen index, FINS; fasting insulin, FPG; fasting plasma glucose, QUICKI; quantitative insulin sensitivity check index, PMS; premenstrual syndrome, AMH; anti-müllerian hormone, BS; blood suger, BW; body weight, AUB; abnormal uterine bleeding, ROS; reactive oxygen species, CRP; C-reactive protein, LDH; lactate dehydrogenase, PUFA; polyunsaturated fatty acids, MPA; medroxyprogesterone acetate, Met; metformin, 2hppbs; 2 h postprandial blood suger

a substantial decrease in the serum level of FBS, insulin, and insulin resistance, as well as cholesterol, triglyceride, and low-density lipoprotein (LDL) levels [25, 31, 44]. It should be noted that this reduction occurred by all forms of *Cinnamomum cassia* including supplements [25, 44], powder [31], and extract [45]. The supplement form seems to have

greater efficacy when used for more than 12 weeks. In addition, use of *Lagerstroemia spesiosa* L. and *Cinnamomum burmanii* for six months considerably reduced the patients' BMI [49].

Different findings have been reported regarding the effectiveness of different species of green tea in metabolic

dysfunction of PCOS patients [28]. It was found that consumption of *Camellia sinensis* L. and *Punica granatum* L. juice could reduce body weight, BMI, waist circumference, serum insulin, and insulin resistance [50]. However, Chinese green tea showed no effects on BMI, lipid profile, or serum insulin level [37]. In addition *Nigella sativa* L. could reduce insulin, insulin resistance indices, cholesterol, and triglyceride level after four months [59].

Vitex agnus-castus [30], Tian-gui [35], and Berberine [53] were found to have similar therapeutic effects to Metformin on metabolic dysfunction in PCOS patients. Administration of Soy supplements (isoflavon and Soy-phytoestrogen) for at least 12 weeks decreased insulin resistance and serum level of triglyceride, there by modifying metabolic dysfunction [43, 51]. In addition to herbs, consumption of foods such as red onion (*Allium cepa* L.) [38], flaxseed oil [55], walnut, and almond [48] was showed to ameliorate the lipid-profile and metabolic dysfunctions in PCOS patients. In addition, Danzhixia-oyae and Marjoram tea induced favorable effects on decreasing fasting serum insulin level [53, 56].

Oxidative stress

Reduction of oxidative stress is one of the possible mechanisms contributing to the therapeutic effects of herbs in PCOS. Although the majority of previous studies have described the anti-oxidative effects of herbs as the main therapeutic mechanism, only few papers have surveyed this phenomenon in details. In one study, Cinnamon supplement considerably reduced Malondialdehyde level and increased the total serum antioxidant capacity [25]. Cangfu Congxian decoction decreased the production of oxygen radicals and oxidative stress in granulosa cells of the ovaries [57]. Overall Soy supplements could alter oxidative stress through two different mechanisms: (i) reducing Malondialdehyde level, and (ii) increasing total glutathione [43].

Sonographic findings

Since sonographic criteria are of paramount importance in the diagnosis of PCOS, effects of herbs on sonographic findings are worth being evaluated. A remarkable decrease in the ovarian volume as well as cyst number was reported in two separate studies evaluating the therapeutic effects of *Trigonella foenum-graecum* L. on PCOS [29, 41]. Likewise, *Linum usitatissimum* L. exhibited the same reducing effects on the ovarian volume and cyst numbers [52]. In line with these findings, Tian-gui was shown to decrease the ovarian volume when administered for three months [35]. Furthermore, treatment with Unkei-toled to a considerable improvements in dominant follicle formation on sonography [40]. Eight-week treatment with wood betony (*Stachys lavandulifolia*) resulted in the considerable reduction of polycystic-appearing ovaries

[54]. Administration on *Anethum graveolens* L. and *Asparagus racemosus* Willd. not only decreased the ovarian volume but also increased the endometrial thickness [42]. In addition, the impact of *Cinnamomum verum* J. Presl on PCOS patients was investigated in a previous study. Although improvements were observed in the menstrual cycles, hormonal status, and metabolic dysfunction, no considerable sonographic findings were reported [44].

Adverse effects

The adverse effects of herbs have not been precisely addressed in the majority of studies, and limited information is available in this area. However, previous studies reported minimum side effects. Three independent studies comparing *Vitex agnus-castus* [30], *Lagerstroemia spesiosa* L., *Cinnamomum burmanii* [49], and berberine [53] with metformin as an established treatment concluded that herbs had considerably fewer adverse effects. In addition, wood betony (*Stachys lavandulifolia*) was reported to have fewer adverse effects in comparison with medroxyprogesterone acetate [54]. Regarding the adverse effects, administration *Cimicifuga racimosa* was as safe as clomiphene citrate in 100 PCOS patients [46]. Also, in another study, on 664 patients, administration of berberine and letrozole for six months caused no remarkable difference in the presentation of adverse effects [39]. Also, no complication was reported following treatment with *Cinnamomum cassia* for three months and spearmint tea for eight weeks [31, 32]. A limited number of PCOS patients receiving *Grifola frondosa* exhibited mild epigastric pain and discomfort [34]. In addition, mild adverse gastrointestinal events, constipation, and nausea were reported after the administration of berberine [39]. In a survey evaluating the impact of Cinnamomum in combination with *Glycyrrhiza spp.*, *Paeonia lactiflora*, and *Hypericum perforatum* L. only two out of 122 patients experienced complications; one patient presented with a flu-like syndrome, and one with abnormal uterine bleeding [27]. It is worth mentioning that the adverse effects attributed to *Grifola frondosa*, Cinnamon, and berberine resolved after a short period of withdrawal [27, 34, 39].

Discussion

PCOS is a multi-organ disorder with an unclear pathophysiology, multiple clinical manifestations, and serious complications. Management of PCOS requires a multidisciplinary approach. Since common treatments for PCOS are not fully effective and have some unwanted side-effects, attempts must be made to find more advantageous therapeutic options with minimal adverse effects. Accordingly, medicinal plants, which contain multiple active components without major adverse effects, have become popular.

A multitude of studies have revealed that a wide spectrum of herbs could be used in the treatment of clinical and laboratory symptoms of PCOS, including menstrual irregularities, infertility, hormonal status, insulin resistance, lipid profile, and anthropometric indices. These herbs have been used together or in combination with conventional treatments; however, review of previous studies showed that most of these herbs were used alone.

According to the present study, some researchers investigated various therapeutic effects of plants on PCOS. Overall, herbs, including Cinnamon species, *Vitex agnus-castus*, *Foeniculum vulgare* Mill, and *Linum usitatissimum* L. seem to be helpful in regulating the menstrual cycles and improving hormonal and metabolic indices [31, 45, 52].

The main mechanisms of the effectiveness of medicinal plants in PCOS are not yet fully understood. Nevertheless, these mechanisms seem to improve the hormonal balance of LH, FSH, and testosterone, and enhance oxidative stress and metabolic disorders.

Evidence suggests that *Vitex agnus-castus* can regulate the menstrual cycles and improve fertility by inducing an increase in the level of midluteal progesterone, mild inhibition of FSH release, stimulation of LH release [67, 68], inhibition of type II dopamine receptors, increase of CAMP level, and prolactin depletion [68]. In addition, the presence of flavonoid compounds in the vitex extract converts testosterone to estradiol and decreases the serum testosterone level by increasing the activity of aromatase [69]; this herb can reduce oxidative stress in PCOS due to its flavonoid and phenolic content [70].

Furthermore, cinnamon species have been frequently used in various studies. They have been administered as powder, extract, or supplement for PCOS patients to (i) improve the menstrual cycle and serum antioxidant level, (ii) reduce FBS/insulin, (iii) modify insulin resistance indices, and (iv) decrease weight/BMI [25, 31, 44, 45]. In fact, cinnamon-extracted bioactive agents can stimulate glycogen synthesis, increase glucose uptake, and increase insulin sensitivity by activating insulin receptors and inhibiting dephosphorylation of these receptors [71, 72]. Antioxidant compounds in plants, such as celery and cinnamon, protect the ovarian tissue against oxidative stress in PCOS by decreasing lipid peroxidation, superoxide dismutase, glutathione peroxidase, and reactive oxygen species in the ovarian tissue [73].

Trigonella foenum-graecum L. can reduce blood glucose and insulin resistance by inhibiting alpha-amylase and sucrose activity [74, 75]. Moreover, *Trigonella foenum-graecum* L. extract reduces blood lipid and cholesterol storage by decreasing carbohydrate reabsorption and increasing the secretion of natural sterols [76, 77]. Fenugreek compounds, including linoleic acid, decrease the level of LH by reducing leptin, nitric oxide, and gonadotropin-releasing hormone release [78]. Also, the findings showed that progesterone levels increased in PCOS mice treated with *Trigonella foenum-graecum* L. seed extract, which might be attributed to the presence of diosgenin compounds in *Trigonella foenum-graecum* L. seeds as progesterone precursors [79].

Cimicifuga racemosa decreases LH due to the selective inhibition of alpha-estrogen receptors in PCOS patients [80].

Soybeans may improve insulin resistance markers by inhibiting protein tyrosine kinase as a regulator of insulin secretion from pancreatic beta cells [81]. Soy also reduces lipid synthesis by decreasing glucose conversion to fat and increasing lipolysis [82]. Isoflavones in soybean may regulate the function of steroidogenic enzymes, such as P450 aromatase and 3 β -steroid dehydrogenase, by binding to estrogen receptors. Inhibition of 3 β -steroid dehydrogenase enzyme by phytoestrogens, including soy, also reduces the serum testosterone level [83–85]. This enzyme acts as a catalyst for the conversion of androstenedione to testosterone [84, 85]. Phytoestrogens also decrease the serum level of androgens by increasing the level of sex hormone binding globulin (SHBG) [86, 87]. However, some articles reported no change in SHBG level [88]. Differences in sample size, dosage, duration of use, and different drug forms appear to contribute to different effects of soy on testosterone level in PCOS patients.

Moreover, use of some herbs (e.g., *Cimicifuga racemosa*), along with conventional treatments (e.g., clomiphene citrate, letrozole, and metformin), has several advantages, such as improvement of ovulation, increased pregnancy rate, increased live birth rate, improvement of uterine wall thickness, and improvement of menstrual cycle. On the other hand, mild and reversible adverse effects were reported in some studies.

Conclusion

According to the present study, several medicinal plants, such as *Vitex agnus-castus*, cinnamon species, *Cimicifuga racemosa* (L.) Nutt., and *Trigonella foenum-graecum* L. could be helpful in the management of PCOS, based on current clinical evidence. However, their effectiveness is not certain due to some limitations, such as small sample size and short duration of studies. Therefore, further preclinical and clinical studies are essential with a larger sample size and a more structured methodology in order to evaluate the safety and pharmacological mechanisms of herbal medicines in PCOS.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest or financial relationships.

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