

PHYTOESTROGENS AND THE POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW OF CLINICAL EVIDENCE AND LABORATORY FINDINGS

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Abstract

The aim of this review was to identify the effect of phytoestrogens on polycystic ovary syndrome (PCOS) (clinical evidence and laboratory findings) in women of reproductive age. Major databases were systematically searched until 1st July 2017. The Jadad scale was used for evaluating the quality of trials. Compared to placebo, there is a variable and inconclusive result regarding the effect of soy on testosterone. The luteinizing hormone (LH), the follicular stimulating hormone (FSH), and dehydroepiandrosterone sulphate (DHEAS) are not affected significantly either. No significant changes in the menstrual cycle were observed following treatment with soy. Following the administration of flaxseed, testosterone and DHEAS levels did not change significantly but 33.3% of patients had a normal menstrual cycle and 10% of patients become pregnant. *Cimicifuga racemosa* alone, or in combination with clomiphene, had a beneficial effect on decreasing serum LH. Ninety-five percent of patients reported irregular cycle at baseline, while 71.4% of patients receiving fenugreek seed extract (*Trigonella foenum-graecum*) had a normal cycle at the end of the study. There is scientific evidence that phytoestrogens, such as flaxseed and the fenugreek seed extract, may have effects on ovulation regulation. However, the currently available evidence on the effect of phytoestrogens on PCOS endocrine disorder is inconclusive.

Rezumat

Scopul acestui studiu a fost de a identifica efectul fitoestrogenilor asupra sindromului ovarului polichistic la femeile aflate în perioada reproductivă, pe baza dovezilor clinice și de laborator. S-a realizat o căutare sistematică a studiilor reprezentative publicate în bazele de date internaționale până la 1 iulie 2017. Scala Jadad a fost utilizată pentru evaluarea calității studiilor clinice. În comparație cu *placebo*, rezultatele legate de efectul pe care soia l-ar avea asupra testosteronului sunt variabile și neconcludente, în timp ce hormonul luteinizant (LH), hormonul foliculostimulant (FSH) și dehidroepiandrosteron-sulfat (DHEA-S) nu sunt afectați semnificativ. Nici o modificare semnificativă legată de ciclul menstrual nu a fost observată după tratamentul cu soia. După administrarea semințelor de in, nivelul testosteronului și al DHEA-S nu s-au modificat semnificativ, dar 33,3% dintre paciente au prezentat un ciclu menstrual normal, iar 10% dintre acestea au rămas însărcinate. *Cimicifuga racemosa* singură sau în combinație cu clomifen prezintă un efect benefic asupra scăderii nivelului seric de LH. Nouăzeci și cinci la sută dintre paciente au raportat un ciclu menstrual neregulat inițial, în timp ce 71,4% dintre cele care au primit extract de semințe de fenugreek (*Trigonella foenum-graecum*) au prezentat o normalizare a ciclului menstrual la finalul studiului. Există dovezi științifice care arată că fitoestrogenii precum semințele de in și extractul de semințe de fenugreek au efecte asupra reglării ovulației. Cu toate acestea, dovezile actuale în ceea ce privește efectul fitoestrogenilor în sindromul ovarului polichistic sunt neconcludente.

Keywords: polycystic ovary syndrome, phytoestrogens, genistein, flax seed, *Cimicifuga racemosa*, *Trigonella foenum-graecum*

Introduction

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine abnormality encountered

in 6 - 14% of women of reproductive age [2]. The diagnosis of the disease is confirmed in the presence of two out of three symptoms, including oligo and/or anovulation, clinical and/or biochemical hyper-

androgenism, and polycystic ovaries on ultrasound, after excluding other aetiologies [11]. Women with PCOS present a serious risk of ischemic heart disease, insulin resistance, hyperlipidaemia, obesity, high blood pressure and metabolic disorders [4, 21]. The history of premature adrenarche and perimenarchal weight gain and a family history of PCOS are the leading risk factors for the disease [14].

The medications used in these patients for attenuating insulin resistance, androgen levels, inflammatory symptoms and menstrual irregularity, as well as promoting ovarian function are metformin, thiazolidinediones, and insulin-sensitizing agents. Nevertheless, many side-effects have been reported for these drugs; for example, safety concerns have been reported for thiazolidinediones and poor toleration, due to nausea (61%), vomiting (30%), and diarrhoea (65%) have been reported for metformin [16]. A statistically significant difference was observed between the placebo and the metformin group in the Cochrane review with an odds ratio of 1.81 for the live birth rate. Moreover, the metformin group showed lower rates for ovulation, clinical pregnancy and live birth compared to the clomiphene citrate group [17].

One of the recent therapeutic approaches for PCOS is the complementary and alternative medicine (CAM), including lifestyle modification, acupuncture, yoga, meditation, aromatherapy, homeopathy, Ayurveda, weight loss, herbal medicine, and antioxidants, especially vitamins [2]. Among these, the phytoestrogens seem to be of great importance [1, 18]. In this regard, it could be noted that since long ago, it was known that nutrition influences the humans' health. During the past decades, several human studies have shown the effect of high quality nutrition on people's health; in other words, it was indicated that nutritional components can avert and/or slow down the progress of chronic diseases development [6]. Phytoestrogens, as a nutritional ingredient have a functional or structural similarity to oestrogens [8]; and some of them such as fennel could be used for menstruation regulation or dysmenorrhea [10]. Despite the existence of scientific evidence on medicinal plants, such as *Glycyrrhiza glabra*, *Paeonia lactiflora*, *Menta spicata*, *Cinnamomum* and berberine [24], to the best of our knowledge there is no systematic review currently available on the possible therapeutic effects of phytoestrogens in PCOS. The present systematic review evaluates the efficacy of phytoestrogens on clinical evidence and laboratory findings in women of a reproductive age with PCOS.

Methods

Database Search

The following databases were used in the initial screening: PubMed, Scopus, ISI Web of Science, and Cochrane Library. These databases were systematically

searched until 1st July 2017. The following keywords were used: (PCO OR PCOS OR Polycystic ovary disease OR Polycystic ovarian disease OR Polycystic ovarian syndrome OR Polycystic ovary syndrome OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Sclerocystic Ovarian Degeneration OR Sclerocystic Ovary Syndrome OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Sclerocystic Ovary) AND (Complementary medicine OR Complementary Therapies OR alternative Therapies OR Alternative Medicine OR phytomedicine OR herb OR natural product OR traditional medicine OR Phytoestrogen OR evening primrose oil OR soy OR ginseng OR *Trigonella foenum-graecum* OR fennel OR *Foeniculum vulgare* OR *Trifolium* OR fenugreek husk OR *Pueraria mirifica* OR maca OR flaxseed OR red clover OR *Vitex agnus castus* OR Quercetin OR Resveratrol OR *Cimicifuga racemosa*).

Inclusion criteria

All clinical trials were included in this systematic review if the phytoestrogen was orally administrated as mono-therapy or complementary therapy with other drugs, at any dose, in women of reproductive age (18 - 45 years old). In this systematic review, semi-experimental studies (before-after studies) and randomized clinical trials were included. There was no limit for the control group. Multi-drug herbal medicines such as traditional Chinese medicines, non-English papers, and animal studies were excluded.

Outcome measures

The outcome measures included menstrual cycle regularity, an occurrence of pregnancy, and changes in hormone levels (luteinizing hormone (LH), follicular stimulating hormone (FSH), dehydroepiandrosterone sulphate (DHEAS) thyroid-stimulating hormone (TSH), insulin, and homeostatic model assessment of insulin resistance (HOMA-IR)).

Quality assessment

The Jadad scale [12] was used for evaluating the quality of trials. The items evaluated with this scale included: expression of randomization and blinding and appropriate method for them, reporting the frequency of patients' drop-out rate and the reason for this. The total score of Jadad ranged from 3 to 5 points.

Data extraction

The characteristics and general information were extracted and tabulated including the authors, location, time and design of study, diagnostic criteria for PCOs, patients age, type of intervention, comparison group, duration of treatment, number of subjects in each group, patients drop-out rate (%), main outcomes and possible side effects.

Statistical analyses

Considering the heterogeneity of the studies and the fact that the data were not adequate in order to

perform a meta-analysis, studies were presented qualitatively.

Results

The initial search yielded 1803 records, which were reduced to 1089 after excluding duplicates. Following title and abstract screening, 20 full-text articles were assessed for eligibility. Finally, 16 articles were included in the qualitative synthesis. The procedure followed is shown in the PRISMA flow chart (Figure 1).

In this review, 13 trials were randomised controlled trials (RCT) and 3 trials were single-arm studies

(before-after). All controlled trials were parallel, only one of them was cross-over designed. Duration of treatment with phytoestrogens ranged from 1 to 6 months. Three studies among RCTs did not mention if they were blind or not, and one of them was open labelled. One trial did not report withdrawal or drop-out rate. The randomization procedure was not described in 2 trials. Most of the trials did not report or clearly explained the intention to treat and concealment. Baseline comparability was reported in all RCTs. The characteristics of the studies are shown in Tables I and II.

Table I

The characteristics of the included studies and the effect of phytoestrogens on clinical evidence in polycystic ovary syndrome

First author/ country/year	Study design	Duration	Subjects	Age	Type of intervention	Control	Number of subjects in intervention/control	Drop-out %	Primary Outcome		Adverse event
									Menstrual Cycle	Pregnancy	
Romualdi D [23]; Italy 2007	Single arm	6 m	Rotterdam Criteria	18 - 32	Genistein 36 mg/d	-	12	0	No significant changes in menstrual cyclicity	-	Not mention
Khani B [15]; Iran 2011	RCT	3 m	Rotterdam criteria	18 - 35	Genistein 36 mg/d	Placebo	73/73	5.5/6.8	-	-	Gastrointestinal complication: 4
Jamilian M [13]; Iran 2016	RCT	3 m	Rotterdam criteria	18 - 40	Soy isoflavones 50 mg/d (37.5 mg genistein + 10 mg daidzein + 2.5 mg glycitein)	Placebo	35/35	0/0	-	-	None
Forouhari S [7]; Iran 2013	Cross over	2m and 1 m for wash out	Rotterdam criteria	18 - 35	Soy bread, Each loaf: 75 g soy flour + 40 g wheat flour	Wheat bread	28/28	?	-	-	?
Vargas ML [27]; USA 2011	RCT	6 w	NIH criteria	20 - 45	1. Fish oil 2. Flax seed oil	Soybean oil	21/23/18	19/26/5.5	-	-	None
Farzana F [5]; India 2015	single arm	3 m	Rotterdam criteria	18 - 35	Flax seed powder 15 g/d	-	30	2/30	Regular menses in 10 (33.3%)	3 (10%)	Transient nausea
Mimasoumi G [20]; Iran 2017	RCT	3 m	Rotterdam criteria	18 - 40	Flax seed oil 2 g/d	Placebo	30/30	0/0	-	-	None
Maged A [19]; Egypt 2015	RCT	1 m	Rotterdam criteria	20 - 37	G1. CR + CC G2. Estradiol + CC	G3. CC	50/50/50	0/0/0	-	Significant more pregnancy rate in G1 (36%), and G2 (34%) vs. G3 (18%)	?
Shahin AY [25]; Egypt 2014	RCT	1 m	Rotterdam criteria	< 35	CC + CR 120 mg/d	CC	103/103	6.8/4.8	-	38.2% in intervention group vs. 19.8% in control group (p < 0.01)	?
Kamel HH [14]; Egypt 2013	RCT	3 m	Clinical and ultrasonography	21 - 27	CR 20 mg/d	CC 100 mg/d	50/50	14/8	-	14% vs. 8% (p = 0.1)	Mild hyper-stimulation: 1
Swaroop A [26]; India 2015	Single arm	3 m	Rotterdam criteria	18 - 45	<i>T. foenum-graecum</i> seed extract enriched in furostanolic saponins 1 g/day	-	50	?	regular menses in 71.43% of cases	6 (12%)	None
Banaszewska B [3]; Poland 2016	RCT	3 m	Rotterdam criteria	Mean: 26.8	Resveratrol 1.5 g/d	Placebo	17/17	11.8/11.8	-	-	None
Rezvan N [22]; Iran 2016	RCT	3 m	Rotterdam criteria	20 - 40	Quercetin 1 g/d	Placebo	42/42	0/4.8	-	-	None
Hajimonfarednejad M [9]; Iran 2017	RCT	3 m	Rotterdam criteria	18 - 45	Cinnamon cap 1.5 mg/d	Placebo	30/30	3.3/0	-	-	Rash/itchiness: 1
Kort DH [16]; USA 2014	RCT	6 m	Rotterdam criteria	18 - 38	Cinnamon 1.5 g/d	Placebo	23/22	52/73	More menstrual cyclicity in intervention vs. placebo (p = 0.008)	-	Headache: 4 Heartburn: 2 Menstrual cramps: 2 Nausea/diarrhea: 1
Wang JG [28]; USA 2006	RCT	2 m	Clinical and ultrasonography	Mean: 31.1	Cinnamon 333 mg/three times/d	Placebo	7/8	14.2/12.5	-	-	None

m = month, d = day, RCT = randomised controlled trial, CR = *Cimicifuga racemosa*, CC = clomiphene citrate, MPA = medroxyprogesterone acetate, Cap = capsules

Table II

The laboratory findings of the effect of phytoestrogens on sexual hormones, insulin and HOMA-IR in polycystic ovary syndrome

Authors	Intervention Control	Primary outcome					
		LH	FSH	Total Testosterone	DHEAS	Insulin	HOMA-IR
Romualdi D [23]	Single arm (Genistein)	No significant change	No significant change	No significant change	No significant change	No significant change	-
Khani B [15]	Genistein placebo	Sig decreased	No significant change	Sig decreased	Sig decreased	-	-
Jamilian M [13]	Soy Isoflavones Placebo	-	-	Sig decreased	No significant change	Sig decreased	Sig decreased
Forouhari S [7]	Soy bread Wheat bread	-	No significant change	No significant change	-	-	-
Vargas ML [27]	G1 Fish oil G2 Flaxseed oil G3 Soy been oil	-	-	G3: Sig decreased G1, G2: No significant change	No significant change	No significant change	No significant change
Farzana F [5]	Single arm (flax seed)	-	-	-	-	-	-
Mirmasoumi G [20]	Flax seed oil Placebo	-	-	No significant change	No significant change	Sig decreased	Sig decreased
Maged A [19]	1.CR+CC 2.estradiol+CC 3.CC	-	-	-	-	-	-
Shahin AY [25]	CC+ CR CC	Sig lower in Int. group vs. cont. after treatment	No sig difference between 2 groups after treatment	-	-	-	-
Kamel HH [14]	CR CC	Sig decreased	No significant change in Int. group	-	-	-	-
Swaroop A [26]	Single arm (<i>T. foenum graecum</i>)	Sig decreased	Sig decreased	-	-	-	-
Banaszewska B [3]	Resveratrol placebo	No significant change	No significant change	Sig decreased	Sig decreased	Sig decreased in Int. group after treatment but no difference between 2 groups	-
Rezvan N [22]	Quercetin placebo	Sig decreased	-	Sig decreased	-	Sig decreased	Sig decreased
Hajimonfarednejad M [9]	Cinnamon placebo	-	-	Sig decreased in both groups	No significant change	Sig decreased	Sig decreased
Kort DH [16]	Cinnamon placebo	-	-	No significant change	-	-	No significant change
Wang JG [28]	Cinnamon placebo	-	-	No significant change	-	-	Sig decreased In Int. group

Int = intervention, Cont = control, FSH = follicular stimulating hormone, LH = luteinizing hormone, DHEAS = dehydroepiandrosterone sulphate, Sig = significantly, CR = *Cimicifuga racemosa*, CC = clomiphene citrate, MPA = medroxyprogesterone acetate

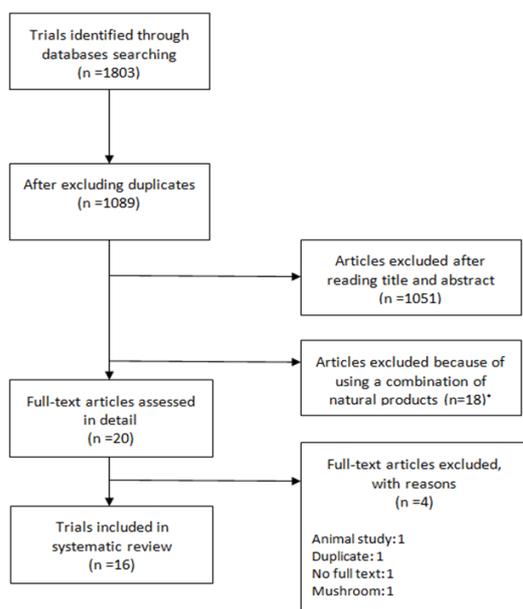


Figure 1.

PRISMA flow chart of study

*Articles excluded due to using traditional Chinese medicine in which a combination of natural products were used not a single medication.

Soy

Five studies assessed the effect of soy on the hormonal profile. Khani *et al.* [15] assessed the effect of soy phytoestrogens on the hormonal disturbance in

women with PCOS. Patients were randomized into two groups to receive 18 mg of genistein or placebo twice a day. LH ($p < 0.001$), testosterone ($p < 0.001$) and DHEAS ($p < 0.001$) decreased significantly following the administration of genistein. Furthermore, the above hormones did not differ from baseline following placebo administration.

Romualdi *et al.* [23] conducted a pretest - posttest design and assessed the effect of genistein on the hormonal profile. FSH increased at 3 months and then decreased at 6 months. LH, testosterone, fasting insulin and DHEAS decreased at 3 months and then increased at 6 months. No significant change in the menstrual cycle was observed during the 6 months of treatment.

Jamilian *et al.* [13] randomized 70 women with PCOS, aged 18 - 40 years old, into two groups: the soy and the placebo. Treatment with soy supplementation decreased significantly the insulin levels ($p < 0.001$), serum testosterone ($p = 0.01$) and HOMA-IR ($p < 0.001$) compared to placebo. DHEAS showed a greater decrease in the soy group compared to placebo, although this difference was not significant.

Forouhari *et al.* [7] conducted a cross-over study and assessed the effect of soy on endocrine disturbance in women affected with PCOS. Patients were randomized in two groups: soy bread (75 mg soy flour + 40 g wheat) and wheat flour. FSH and testosterone showed

a non-significant decrease in the treatment group. The difference between the two groups was not significant regarding FSH ($p = 0.827$) and testosterone ($p = 0.807$).

Vargas *et al.* [27] compared three groups: fish oil, flaxseed oil and soybean oil. Total testosterone decreased significantly from 3.33 to 3.05 (nmol/L) only in the soybean group. DHEAS, insulin, and HOMA-IR did not change significantly.

Flaxseed

Three studies assessed the effect of flaxseed on the hormonal profile, the pregnancy rate and the normal menstrual cycle. Farzana *et al.* [5] assessed the effect of flaxseeds in 32 women affected with PCOS. At the end of study, 33.3% of patients had a normal menstrual cycle, 16.7% reported a change and 10% of patients became pregnant following administration of flaxseed. Mirmasoumi *et al.* [20] randomized 60 women with PCOS into two groups to receive flaxseed oil omega-3 fatty acids supplementation ($n = 30$) or placebo ($n = 30$) for 12 weeks. Flaxseed resulted in a significant decrease in insulin ($p = 0.01$) and HOMA-IR ($p = 0.01$) and a non-significant decrease in DHEA ($p = 0.20$) and total testosterone ($p = 0.96$) compared to placebo. In Vargas *et al.* [27], DHEAS levels and insulin did not change significantly in the flaxseed group. Total testosterone decreased non-significantly, from 2.95 to 2.78 (nmol/L) in the flaxseed group. Flaxseed administration led in a non-significant increase in insulin and HOMA-IR.

Black cohosh (*Cimicifuga racemosa*)

Shahin *et al.* [25] compared *C. racemosa* plus clomiphene (group A) with clomiphene alone (group B). Patients were randomized into two groups: A ($n = 98$) and B ($n = 96$). On the day of human chorionic gonadotropin (hCG) injection, serum LH was significantly lower in group A compared to group B ($p < 0.001$). Clinical pregnancy *per cycle* was significantly higher in group A (38.2%) compared to group B (19.8%) ($p < 0.01$).

Kamel *et al.* [14] assessed the effect of phytoestrogens in ovulation induction. One hundred women were randomized in two equal groups to receive phytoestrogens ($n = 50$) and clomiphene ($n = 50$). A gradual increase was seen in FSH in both groups: *C. racemosae* (5.3, 5.6, 5.2 and 5.92 (IU/mL)) and clomiphene (4.9, 5.3, 5.3 and 5.65 (IU/mL)). The difference between the two groups was significant ($p < 0.001$). A gradual decrease was seen in LH in both groups: *C. racemosae* (9.5, 8.5, 5.5 and 3.45 (IU/mL)) and clomiphene (9.6, 8.9, 6.9 and 4.55 (IU/mL)). The difference between the two groups was significant ($p = 0.007$). The intervention ($n = 7$) was associated with a higher rate of pregnancy compared to clomiphene ($n = 4$), although this difference was not significant.

Meged *et al.* [19] compared three groups: the first group received clomiphene citrate (CC) alone, the

second group received 20 mg of *C. racemosa* plus CC and the third group received estradiol plus CC. The group of estradiol plus CC (34%) and the group of phytoestrogen plus CC (36%) showed a higher pregnancy rate compared to the group of CC alone (18%).

One trial showed that CC plus *C. racemosa* was superior to CC alone regarding LH [25]. Another trial showed that *C. racemosa* had a better effect compared to CC [20]. In conclusion, *C. racemosa* alone or in combination with CC have beneficial effects on serum LH.

Fenugreek Seed Extract (*Trigonella foenum-graecum*)

Swaroop *et al.* assessed the effect of fenugreek seed extract, 2 capsules/500 mg once a day, in fifty women, aged 18 - 45 years, affected with PCOS. The patients received fenugreek seed extract LH decreased from 10.33 to 8.98 at 1 month ($p = 0.241$) and returned to baseline at 2 months ($p = 0.825$) and then increased significantly ($p = 0.045$). A gradual increase was seen in FSH (5.36, 5.49, 6.38 and 8.36 (IU/L)). This increase was significant when a comparison was made between baseline and 2 months ($p = 0.010$) and between baseline and 3 months ($p < 0.001$). As far as menstrual cycles are concerned, 95% of patients reported having an irregular cycle at baseline. The irregular cycle rate remained unchanged after 1 month. At 2 months, 33.33% of patients reported a regular cycle, whereas after 3 months (end of the study period) 71.43% of patients had a regular cycle [26].

Cinannamon

Kort *et al.* [16] compared the efficacy of cinnamon with placebo in 45 women diagnosed with PCOS. The groups received either Cinnamon supplements (1.5 g/day) or placebo for a period of six months. Total testosterone levels mildly increased in both groups. HOMA-IR showed a non-significant increase. The number of cycle was more frequent in women receiving cinnamon compared to placebo ($p = 0.008$). Wang *et al.* [28] compared the effect of cinnamon extract on insulin resistance parameters in women with PCOS. HOMA-IR did not change in the placebo group. However, HOMA-IR showed a significant decrease in the cinnamon extract group compared to baseline ($p = 0.03$). Hajimonfarednejad *et al.* [9] conducted a randomized placebo-controlled trial on 66 women with PCOS. All patients received 10 mg medroxyprogesterone acetate *per day* for 10 days consecutively. Then the patients were divided into two groups: placebo and cinnamon. The latter group received 1.5 mg/day of cinnamon. Insulin ($p = 0.02$) and HOMA-IR ($p = 0.04$) decreased significantly in the cinnamon group compared to the placebo group. Total testosterone decreased significantly in both groups: cinnamon ($p = 0.001$) and placebo ($p = 0.04$). However, the difference between the two groups was not significant.

Quercetin

Rezvan *et al.* [22] randomized patients into two groups: the quercetin group and the placebo group. LH decreased significantly both in the quercetin group ($p = 0.013$), as well as in the placebo group ($p = 0.050$) compared to baseline. The difference between the two groups was significant ($p = 0.009$). There was a significant decrease in testosterone ($p < 0.001$), insulin ($p < 0.001$) and HOMA-IR ($p < 0.001$) in the quercetin group, compared to the placebo group.

Resveratrol

Banaszewska *et al.* [3] compared resveratrol vs. placebo. A significant decrease in DHEAS ($p = 0.002$) and total testosterone ($p = 0.04$) and a non-significant decrease in FSH ($p = 0.85$) were observed in intervention group. Only a significant decrease in fasting insulin was found in the Resveratrol group ($p = 0.007$). Placebo caused an increase in LH compared to placebo, although it was non-significant ($p = 0.52$).

Discussion

As far as we know, this is the first systematic review on the effect of phytoestrogens on the hormonal profile and the reproductive outcome. In the current review, the effect of seven phytoestrogens, including quercetin, resveratrol, soy, cinnamon, fenugreek seed and *C. racemosa*, was presented and discussed.

As far as flaxseed oil is concerned, it seems that it acts in a dose and duration dependent manner as the higher dose of flaxseed and the longer administration caused a significant decrease in insulin and HOMA-IR. The improvement in insulin and HOMA-IR is consistent with the findings of a study suggesting that a dose of 2 g flaxseed/day may result in a significant improvement in gene expression related to insulin [24].

As far as cinnamon is concerned, there seems to be some inconsistent findings between different studies [9, 16, 28], although this inconsistency may be attributed to treatment duration, dosage and sample size. In general, cinnamon does not induce significant changes in testosterone. The findings on HOMA-IR are inconsistent.

The results on the effect of soy on testosterone are variable and inconclusive [7, 13, 15, 23, 27]. Soy does not induce significant changes on LH [15, 23], FSH [7, 15, 23] and DHEAS [13, 23, 27].

Other phytoestrogens have variable effects. Quercetin caused a significant decrease in LH, testosterone, insulin, and HOMA-IR [22]. Resveratrol decreased DHEAS, total testosterone and fasting insulin and the fenugreek seed extract caused a significant increase in LH and FSH [3].

As far as the reproductive outcome is concerned, the fenugreek seed extract [26] and flaxseed [5] contributed towards the normalization of irregular cycles. Soy did not induce significant changes in

the menstrual cycle [23]. *C. racemosa* alone, or in combination with CC, had a beneficial effect on serum LH, but *C. racemosa* didn't significantly decrease serum FSH [14, 25].

Limitations

The current systematic review presents some limitations that are worthy to be addressed. Some of the studies did not control the placebo effect. Others reported a high placebo response that did not allow reliable conclusions. Future trials should include a placebo group and patients with a high placebo response should be excluded from the study. The dose-dependent effect of phytoestrogens was shown in some trials, while in other studies the phytoestrogen showed various effects at various times. This indicates that studies should include enough patients to allow for subgroups with different doses and different treatment durations. According to the available literature, phytoestrogens exert their effects after 3.2 months of treatment [24]. Therefore, in some trials, the duration of treatment was too short and this could explain the insignificant findings reported. In general, the methodological quality of the reviewed studies (small sample size, a method of randomization, concealment of randomization, blinding, intention to treat) was inadequate. Future studies should be more appropriately designed and should report their findings in accordance to the Consolidated Standards of Reporting Trials (CONSORT) statements.

Conclusions

Following the systematic review of the available scientific literature, there is evidence that phytoestrogens, including flaxseed and fenugreek seed extract, but not soy, may regulate ovulation. The currently available knowledge is inconclusive regarding the effect of phytoestrogens on the endocrine disorder of PCOS. These findings should be interpreted with caution due to various limitations/methodological weaknesses of the currently available studies.

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