REVIEW

Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) affects 1 in 5 women of reproductive age, and is characterized by menstrual irregularities, clinical or biochemical hyperandrogenism, and the presence of polycystic ovary morphology. One of the recommended treatment strategies in the international evidence-based guidelines is lifestyle modification, which includes diet and exercise, with the aim of improving a range of health outcomes. The incurable nature of PCOS reinforces the importance of developing novel and innovative symptomatic relief strategies, which are currently the only available approaches for improving quality of life for these women. Women with PCOS tend to be nutrient deficient in many common vitamins and minerals, thought to be associated with the psychological (depression, anxiety, etc.) and physiological (insulin resistance, diabetes, infertility, etc.) sequelae of the condition. Nutrient supplementation and the integration of complementary medicine as adjuncts to traditional lifestyle-based therapies in PCOS could therefore provide additional benefits to these women. In this review, we synthesize the evidence regarding nutrient supplementation and complementary therapies in PCOS, predominantly from randomized controlled trials, systematic reviews, and meta-analyses, to provide an overview of the state of knowledge in this field. The evidence to date suggests that specific vitamins (B-12, inositols, folate, vitamins D, E, and K), vitamin-like nutrients (bioflavonoids and α-lipoic acid), minerals (calcium, zinc, selenium, and chromium picolinate), and other formulations (melatonin, ω-3 fatty acids, probiotics, and cinnamon), as well as some complementary approaches such as acupuncture and yoga may be beneficial in PCOS. However, there remain areas of uncertainty and key limitations in the literature that must be overcome before these therapies can be integrated into routine clinical practice. *Adv Nutr* 2022;13:1243–1266.

Statement of Significance: This review provides an up-to-date, comprehensive synthesis of the highest level of evidence regarding the effects of nutritional supplements and complementary therapies in the treatment and management of polycystic ovary syndrome.

Keywords: polycystic ovary syndrome, PCOS, nutrition, nutraceutical, diet, supplementation, complementary medicine, vitamins, minerals, review

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder in women of reproductive age, with an incidence rate of 12–18% depending on diagnostic criteria and the demographic studied (1, 2). According to Rotterdam criteria (3), PCOS is diagnosed based on the presence of 2 out of 3 characteristics: oligo- or anovulation, clinical or biochemical hyperandrogenism, and the detection of polycystic ovaries on ultrasound (after excluding other causes) (4). PCOS is also characterized by reproductive (subfertility, infertility, and pregnancy complications) (5), metabolic (higher risk and prevalence of type 2 diabetes and cardiovascular disease), and psychological (anxiety, depression, and worsened quality of life) features (6).

Despite the well-documented adverse health outcomes associated with PCOS, the etiology of the condition remains poorly understood. Putative mechanisms underpinning PCOS include intrinsic insulin resistance (IR), which is PCOS specific and relates to a dysregulated response to insulin in metabolically active peripheral tissues, and extrinsic IR, which is obesity related, where weight gain further worsens PCOS pathology (7–9). To further complicate matters, PCOS is linked with binge-eating symptomatology (10) and food-craving behavior (11), which could intensify body fat accumulation and endocrine perturbations as well as promoting poor body image, self-blame, and related psychosocial anxieties. In line with these factors, one of the recommended treatment strategies for PCOS in the

international evidence-based guidelines (12) is lifestyle modification, which includes diet, exercise, and/or behavioral management, with the aim of improving IR and related health outcomes by preventing weight gain and/or achieving and maintaining modest weight loss (7, 13). The incurable nature of PCOS, coupled with its complex and lifelong adverse biopsychosocial effects, reinforces the importance of developing effective symptomatic relief and component-specific treatment strategies. Currently, these are the only available approaches for improving quality of life for these women.

Recently, there has been growing interest into whether supplementation with vitamins, vitamin-like nutrients or minerals, and the use of complementary medicines and therapies (CM) may promote favorable health outcomes in PCOS (7). Many women with PCOS are already using nutrient supplements and CM, with an Australian study reporting that 70% of women with PCOS had used CM in the preceding 12 mo (14), including 41% who took herbal medicines. Nearly two-thirds (65.5%) of respondents reported using CM to treat PCOS; however, most used CM to improve multiple aspects of their health. Supplements and CM are often perceived to be natural and low-risk adjuncts to conventional PCOS treatment regimens, particularly for some women who have expressed dissatisfaction with certain medical treatments (such as fertility drugs and the oral contraceptive pill) and a desire to explore additional options perceived to be safe and helpful in achieving their desired outcomes (15).

The increased use of nutrient supplements and CM in PCOS has seen a rapid growth in new research exploring the benefits of these treatments. Here, we aim to summarize and evaluate recent evidence, primarily from randomized controlled trials (RCTs) and systematic reviews or meta-analyses, regarding the efficacy of nutrient supplementation and CM in the treatment or management of PCOS. We also describe the key limitations and knowledge gaps that must be overcome before these therapies can be effectively integrated into clinical guidelines and practice.

PCOS: An Overview

PCOS is an oligogenic disorder wherein a number of genetic and environmental factors interact to determine the clinical phenotype (16). Despite a lack of evidence suggesting genetic predisposition to PCOS, a family history of the condition is common. Due to this familial clustering, many researchers have suggested that PCOS may follow an autosomal dominant pattern (17). Moreover, the discovery of PCOS susceptibility loci on specific chromosomes further supports the role of genetics in the progression and/or etiology of the condition (18). Environmental factors thought to influence PCOS progression include food chemicals and environmental toxins, which can be exacerbated by poor diet, sedentary lifestyles, and subsequent weight gain (17, 19). Approximately 40–80% of women with PCOS are classified as overweight or obese, which worsens the reproductive, metabolic, and psychological sequelae of this disorder (6). This further increases the risk of women with PCOS developing chronic diseases including type 2 diabetes and cardiovascular diseases; reproductive dysfunction (menstrual irregularities and infertility problems); and various psychiatric disorders (anxiety, depression, bipolar disorder, etc.) (6, 20). Lim et al. (13), in a Cochrane review in 2019, found that some of these reproductive, metabolic, and psychological features of PCOS are often reversible through lifestyle modification, whether that be diet and/or exercise. However, the benefits of specific nutrient supplements and CM in PCOS remain relatively unknown and could provide helpful insights to facilitate holistic and tailored diet and lifestyle interventions in women with PCOS.

Nutrient Supplements and Complementary Therapies in PCOS: Review of the Evidence

Supplementation with individual nutrients and complementary therapies may be beneficial in improving health outcomes in women with PCOS, by influencing key pathways thought to induce PCOS (e.g., insulin signaling, IR, lipid metabolism, etc.), thereby altering PCOS symptomatology and severity (**Figure 1**). The following keywords were used to search the Medline database from inception until July 2021: "polycystic ovary syndrome," "PCOS," "acupuncture," "dietary supplements," "vitamin∗," "mineral," "micronutrient," "probiotic," "nutritional supplement," "antioxidant," "flavonoid," "herbal," "mindful," "mind-body," "yoga," "meditation," "Chinese medicine," "plant-based," "phytotherapy," "extract," "tea." Reference lists of key reviews and relevant articles were also searched to identify additional articles for review. We excluded articles if they were not pertaining to PCOS, did not evaluate nutrient supplements or CM modalities, did not report original research (e.g.,

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Abbreviations used: α-LA, α-lipoic acid; AMPK, AMP-activated protein kinase; BP, blood pressure; CC, clomiphene citrate; CHM, Chinese herbal medicines; CM, complementary medicines and therapies; CrP, chromium picolinate; DHEAS, dehydroepiandrosterone sulfate; DI, D-chiro-inositol; FBG, fasting blood glucose; FSH, follicle-stimulating hormone; GLUT4, glucose transporter-4; GSH, glutathione; Hcy, homocysteine; HMG, human menopausal gonadotropin; HOMA-β, homeostatic model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; IR, insulin resistance; LH, luteinizing hormone; MD, mean difference; MDA, malondialdehyde; MI, myo-inositol; NAC, N-acetyl cysteine; PCOS, polycystic ovary syndrome; PPARγ, proliferator-activated receptor γ; QUICKI, quantitative insulin-sensitivity check index; RBP4, retinol-binding protein 4; RCT, randomized controlled trial; ROS, reactive oxygen species; SHBG, sex hormone binding globulin; SMD, standardized mean difference; TAC, total antioxidant capacity; TG, triglycerides; WHR, waist-hip ratio; WMD, weighted mean difference.

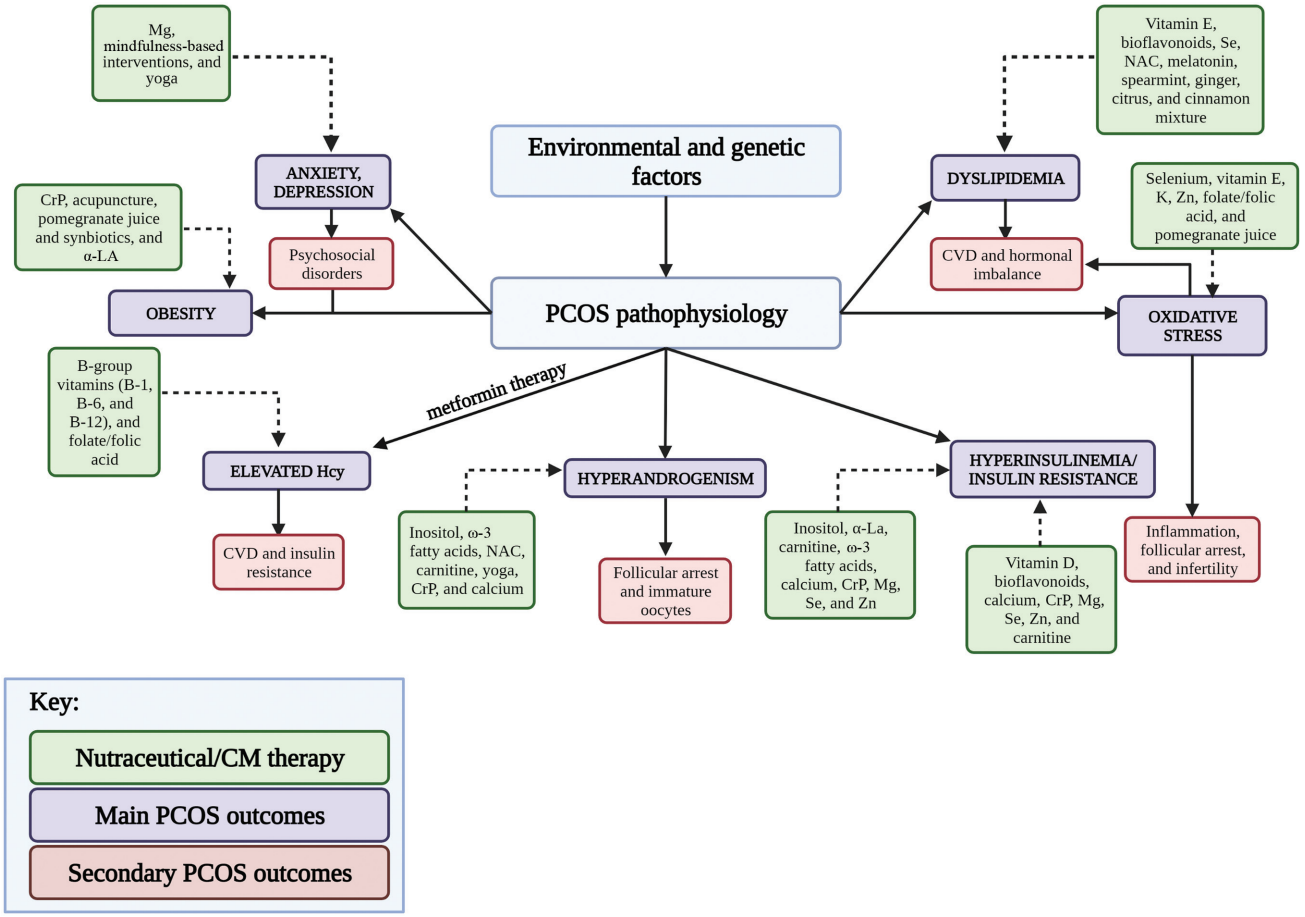

FIGURE 1 Putative effects of various nutritional supplements and complementary therapies on main and secondary health outcomes/risk factors associated with PCOS. Solid arrows indicate an increase or exacerbating effect on the outcome; dashed arrows indicate a decrease or diminishing effect on the outcome. α-LA, α-lipoic acid; CM, complementary medicine; CrP, chromium picolinate; CVD, cardiovascular disease; Hcy, homocysteine; Mg, magnesium; NAC, N-acetyl cysteine; PCOS, polycystic ovary syndrome; selenium, Se; zinc, Zn.

commentaries, editorials), or were observational studies or nonsystematic reviews (in the case where more recent or higher level evidence was available).

As outlined in **Table 1** and described below, we have synthesized recent research primarily from RCTs or systematic reviews of RCTs (or epidemiological studies if no higher level evidence was available), to summarize current evidence pertaining to the efficacy of individual supplements and CM in improving various health outcomes in PCOS (Table 1). The nutrient supplements and CM modalities presented in this review represent the most commonly used nonpharmacological therapies among women with PCOS (14) and the ones for which there is a level of published evidence to synthesize.

Vitamin supplements

Vitamin D.

Vitamin D is a steroid hormone derived primarily from sunlight, with limited amounts from dietary sources such as oily fish or fortified dairy. Vitamin D is critical for calcium metabolism and maintaining skeletal homeostasis, and is posited to also have important metabolic and endocrine functions (21, 22). A meta-analysis by Miao et al. (23) examining various doses of vitamin D supplementation over 8–24 wk in women with PCOS reported improved HOMA-IR and homeostatic model assessment of β-cell function (HOMA-β), and improved total testosterone and LDL cholesterol (23). However, there were no effects on BMI, dehydroepiandrosterone sulfate (DHEAS), triglycerides (TG), or HDL cholesterol. Similarly, a meta-analysis (24) of 13 RCTs with 824 women (with some overlapping studies) reported a reduction in HOMA-IR, VLDL cholesterol, fasting blood glucose (FBG), and fasting insulin, and increased quantitative insulin-sensitivity check index (QUICKI) with vitamin D supplementation compared with placebo. It was noted that glycemic effects were more prominent with daily low doses (compared with intermittent high doses) of vitamin D. There were no effects on other lipids, total testosterone, DHEAS, sex hormone binding globulin (SHBG), or high-sensitivity C-reactive protein (hs-CRP). In contrast, Gao et al. (25) reported that vitamin D

TABLE 1 Study characteristics of recent studies examining nutrient supplements and complementary medicine (CM) in polycystic ovary syndrome, ordered by strength of evidence for each nutrient/CM category

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
Vitamin supplements					
Vitamin D	Miao et al. 2020 (23)	SR + MA	11 RCTs, $n = 483$ women with PCOS	3200 to 12,000 IU/d or 50,000 IU/wk from 8 to 24 wk	Vitamin D supplementation improved HOMA-IR, HOMA-β, LDL-C, and total testosterone. No changes in BMI or other hormones or lipids
	Guo et al. 2020 (24)	SR + MA	13 RCTs, $n = 824$ women with PCOS	3200 to 12,000 IU/d or 50,000 IU/wk from 8 to 24 wk	Vitamin D supplementation improved HOMA-IR, QUICKI, FBG, FBI, and VLDL-C, but no effect on other hormones, lipids, or hs-CRP. Glycemic effects more prominent with low daily doses compared with high intermittent doses
	Gao et al. 2021 (25)	SR + MA	10 RCTs, $n = 543$ women with PCOS	NR	Vitamin D supplementation improved TC, LDL, and TG, but not HDL-C. Effects may be more prominent in women with vitamin D deficiency (<20 ng/mL)
Inositol (Vitamin B-8)	Unfer et al. 2017 (28)	SR + MA	9 RCTs, $n = 496$ women with PCOS (249 control and 247 MI alone or with DI)	MI = 1.1 to 4 g and/or DI = 27.6–2400 mg/d for 2 to 24 wk	MI ± DI decreased HOMA-IR and fasting insulin, but had no effect on androstenedione, testosterone, or SHBG
	Pundir et al. 2017 (30)	SR + MA	10 RCTs, $n = 601$ women with PCOS (257 MI; 105 DI; 179 on placebo and 60 on metformin)	MI = 1.2 to 4 g; DI = 600 mg to 1.2 g for 2 to 24 wk	Inositol improved ovulation rate and increased MC frequency but evidence for pregnancy, miscarriage, and live birth rates is lacking
Folate (vitamin B-9)	Bahmani et al. 2014 (38)	RCT	69 women with PCOS [folate 1 mg/d ($n = 23$) or 5 mg/d ($n = 23$), or placebo ($n = 23$)]	1 mg vs. 5 mg/d folate for 8 wk	Higher folate supplementation reduced Hcy, HOMA-β, hs-CRP, and MDA and increased TAC and GSH
	Asemi et al. 2014 (39)	RCT	81 women with PCOS; [folate 1 mg/d ($n = 27$) or 5 mg/d ($n = 27$) or placebo ($n = 27$)]	1 mg vs. 5 mg/d folate for 8 wk	Higher folate supplementation reduced Hcy, FBI, HOMA-IR, TC/HDL-C ratio and showed differences in serum TC, LDL-C, and non-HDL-C. No effect on FBG or other lipids

(*Continued*)

TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
B-group vitamins (B-1, B-6, B-12)	Kilicdag et al. 2005 (37)	RCT	60 women with PCOS ($n = 20$ metformin only, 20 metformin + B-group vitamins, and 20 metformin + folic acid)	500 mg B-1 + 500 mg B-6 + 2000 mcg B-12 for 12 wk	B-group vitamins and folic acid counteracted the Hcy-increasing effect of metformin therapy, but did not improve HOMA-IR
Vitamin K	Tarkesh et al. 2020 (49)	RCT	79 women ($n = 40$ on vitamin K and 39 on placebo)	90 μg/d of menaquinone-7 (vitamin K_2) for 8 wk	Vitamin K_2 decreased WC, fat mass, FBI, HOMA-IR, HOMA-β, TG, DHT, FAI, and increased skeletal muscle mass, SHBG, and QUICKI
Vitamin E	Chen et al. 2020 (57)	Retrospective cohort	321 women with PCOS and infertility treated with CC or HMG ($n = 110$ no vitamin E, 105 vitamin E in follicular phase, and 106 vitamin E in luteal phase)	100 mg/d from day 3–14 of MC or from ovulation for 14 d	Vitamin E improved oxidative stress, decreased HMG dosage, and increased endometrial thickness and E2 concentration in women with infertility and PCOS. No difference in number of dominant follicles
Vitamin-like nutrients					
Bioflavonoids – quercetin	Pourteymour et al. 2020 (63)	SR	3 RCTs, $n = 246$ women with PCOS with BMI 25–40 kg/m^2	1 g/d quercetin for 12 wk in all trials	Some evidence for improvements in adiponectin-mediated insulin resistance, dyslipidemia, and testosterone concentrations, but no difference in weight loss or WHR compared to placebo. Insufficient evidence to make conclusions
α-Lipoic acid (α-LA)	Masharani et al. 2010 (68)	Prospective	6 lean nondiabetic women with PCOS	Controlled release α-LA 600 mg twice daily for 16 wk	IR (clamp) improved by 13.5%; reduced LDL and TG but no change in plasma antioxidant capacity or plasma oxidation metabolites
	Cianci et al. 2015 (71)	Prospective	46 reproductive age women with PCOS [20 on D-chiro-inositol (DI) and α-LA; 20 controls]	1000 mg/d DI and 600 mg/d α-LA for 180 d	Improved MC, decreased number of ovarian cysts, increased progesterone concentrations; reduced BMI and insulin and increased HDL; no changes in other lipids

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TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
Carnitine	Salehpour et al. 2019 (77)	Prospective	80 reproductive age women with PCOS	3 g/d L-carnitine for 3 mo	Treatment with L-carnitine improved HOMA-IR, decreased LDL, TG, TC, insulin, and BMI and increased HDL
Other bioflavonoids	Romualdi et al. 2008 (62)	Pilot prospective	12 Caucasian women with PCOS and obesity	36 mg/d of genistein soy isoflavone for 6 mo	Soy isoflavone supplementation improved TC, LDL, LDL:HDL ratio, and TG
Mineral supplements					
Chromium picolinate (CrP)	Fazelian et al. 2017 (85)	SR + MA	7 RCTs, $n = 351$ women with PCOS (153 control and 198 CrP)	200 to 1000 μg/d for 2 to 6 mo	CrP supplementation decreased BMI, fasting insulin, and free testosterone in women with PCOS. No effects on FBG or other hormones
	Tang et al. 2018 (86)	SR + MA	6 RCTs, $n = 351$ women with PCOS	200 to 1000 μg/d for 2 to 6 mo	CrP supplementation decreased insulin resistance and increased total and free testosterone. No changes in BMI, FBG, fasting insulin, QUICKI, or hormone or lipid profiles
Calcium	Shojaeian et al. 2019 (104)	SR + MA	6 RCTs, $n = 480$ women with PCOS (MA of 3 trials)	1000 mg/d calcium for 8 to 12 wk (+ vitamin D ± metformin)	Improved lipid profiles, menstrual regularity, and follicular maturation, increased QUICKI; reduced serum insulin, HOMA-IR, FBG, hirsutism, and testosterone concentrations
Magnesium (Mg)	Hamilton et al. 2019 (106)	SR	3 RCTs, $n = 156$ (also identified 4 case control/cross-sectional studies)	200, 400, or 800 mg/d Mg for 12 wk	Serum Mg concentrations were associated with IR but Mg supplementation had inconsistent effects
Selenium (Se)	Hajizadeh-Sharafabad et al. (112)	SR	5 RCTs (also identified 3 case control and 2 in vitro studies)	200 μg/d for 8 to 12 wk	Se improved insulin resistance and inflammation/oxidative stress markers in some RCTs. No effect or inconsistent findings for BMI/weight, FBG, lipids, hormones, acne, hirsutism
Zinc (Zn)	Nasiadek et al. (118)	SR	5 RCTs, $n = 285$ women with PCOS	220 mg of zinc sulfate (50 mg zinc)/d for 8 wk or 8–50 mg zinc/d for 12 wk	Zinc improved insulin resistance (reduced HOMA-IR, HOMA-β, insulin, and increased QUICKI); improved lipids; reduced FSH, free testosterone, 17-OHP, DHEAS; reduced hs-CRP and MDA, increased TAC

(*Continued*)

TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
Other supplements					
Probiotics	Shamasbi et al. 2020 (121)	SR + MA	13 RCTs, $n = 844$ women with PCOS	Mostly *Lactobacillus, Bifidobacterium* strains. Prebiotics included resistant dextrin and inulin for 8–12 wk	Probiotics improve FAI but not hirsutism compared to placebo. Probiotics and synbiotics improved SHBG, NO, and FAI compared to placebo. No difference was reported for testosterone, DHEAS, GSH, hs-CRP, TAC, and hirsutism score
	Liao et al. 2018 (122)	SR + MA	6 RCTs, $n = 406$ women with PCOS	Mostly *Lactobacillus, Bifidobacterium* strains. Prebiotics included resistant dextrin and inulin for 8–12 wk	Probiotics improved FBI, QUICKI, TG, and VLDL-C. No significant changes were found in other markers, including FBG, HOMA-IR, total cholesterol, LDL-C, HDL-C, body weight, CRP, and DHEA concentrations
Melatonin	Hu et al. 2020 (128)	SR + MA	3 studies (2 RCTs, 1 cell culture), $n = 640$ women with PCOS	3 mg melatonin from day 3 to triggering day or day 1 to 14 d after embryo transfer	Improved clinical pregnancy rates in ART, but there was no significant effect in MA of the *in vivo* studies only
	Jamilian et al. 2019 (131)	RCT	56 women with PCOS ($n = 28$ intervention and 28 placebo)	10 mg melatonin/d for 12 wk	Reduced hirsutism, total testosterone, hs-CRP, MDA; increased TAC and total glutathione; downregulated IL-1 and TNF expression. No effect on IL8, VEGF, TGF-β, SHBG, or NO
N-Acetyl-cysteine (NAC)	Thakker et al. 2015 (132)	SR + MA	8 RCTs, $n = 910$ women with PCOS	1200–1800 mg/d from 2 to 12 mo	Higher odds of pregnancy and live births with NAC compared with placebo, but less effective compared with metformin. Reduced FBG but not fasting insulin or HOMA-IR
ω-3 fatty acids	Yang et al. 2018 (135)	SR + MA	9 RCTs, $n = 591$ women with PCOS (238 control and 353 ω-3)	900 to 4000 mg/d ω-3 fatty acids for 6 to 12 wk	ω-3 improves HOMA-IR and reduced TC, LDL-C, and TG. No effects on BMI, FBG, fasting insulin, or hormones
Resveratrol	Shojaei-Zarghani et al. 2021 (137)	SR	3 RCTs, $n = 131$ women with PCOS	Micronized *trans*-resveratrol, 800–1500 mg/d for 40 d to 3 mo	Reduced total testosterone (2 RCTs, $n = 91$), FBI (1 RCT, $n = 30$), increased high-quality oocyte and embryo rate (1 RCT, $n = 61$). No difference for clinical pregnancy rate (2 RCTs, $n = 61$), BMI, lipids, FBG, hirsutism, acne, ISI (1 RCT, $n = 30$)

(*Continued*)

TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
Coenzyme Q10	Samimi et al. 2017 (140)	RCT	60 women with PCOS phenotypes A and D ($n = 30$ intervention and 30 placebo)	Coenzyme Q10 100 mg/d for 12 wk	Improved FBG, FBI, HOMA-IR, HOMA-β, QUICKI, TC, LDL-C in intervention group
Flaxseed	Haidari et al. 2020 (143)	RCT (open label)	41 women with PCOS ($n = 21$ intervention and 20 control)	Milled flaxseed powder 30 g/d for 12 wk with lifestyle modification vs. lifestyle modification alone	No significant differences between groups for QUICKI, FBG, TC, LDL-C, testosterone, inflammatory markers, SHBG, and hirsutism whereas between-group differences were reported for body weight, WC, BMI, insulin, HOMA-IR, TG, leptin, HDL-C, and menstrual regularity
Pomegranate juice and synbiotics	Esmaeilinezhad et al. 2019, 2020 (146, 147)	RCT	86 women with PCOS ($n = 22$ synbiotic pomegranate juice, 22 pomegranate juice, 21 synbiotic juice, and 21 placebo)	Pomegranate juice 300 mL/d or synbiotic juice 300 mL/d; or mixture of pomegranate juice + synbiotics for 8 wk	Synbiotic + pomegranate, and pomegranate juice were better than placebo for TG, HDL, MDA, TAC, and BP. Synbiotics were better than placebo for TC. Synbiotic + pomegranate and synbiotics alone were better than placebo for LDL, insulin sensitivity, weight, BMI, and waist circumference and testosterone. Pomegranate juice alone was better than placebo for lowering hs-CRP. All types of juice were better than placebo for LDL/HDL ratio. There was no change in FBG, LH, or FSH
Herbal medicine					
Cinnamon	Heydarpour et al. 2020 (152)	SR + MA	5 RCTs, $n = 448$ women with PCOS	Dose ranged from 336 to 1500 mg/d and duration from 6 to 24 wk	Cinnamon improved FBG, FBI, HOMA-IR, LDL-C, TC, HDL-C. No difference for body weight
Chinese herbal medicine (CHM)	Zhou et al. 2016 (155)	SR + MA	5 RCTs, $n = 414$ women with PCOS and subfertility	2 trials used patent medicines and 3 used herbal medicines for <6 MC	No difference between CHM and CC for pregnancy rates (2 studies, $n = 90$). Low-quality evidence of higher pregnancy rate for CHM + CC and CC alone (3 studies, $n = 300$). Overall insufficient evidence for CHM for subfertility
Curcumin	Heshmati et al. 2021 (157)	RCT	67 women with PCOS ($n = 34$ intervention and 33 placebo)	500 mg 3 times a day for 12 wk	Curcumin improved FBG and DHEA but not FBI

(*Continued*)

TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
	Sohaei et al. 2019 (158)	RCT	51 women with PCOS and impaired glucose tolerance, BMI 25–30 kg/m^2 ($n = 27$ intervention and 24 placebo)	500 mg twice a day for 6 wk	No between-group differences for FBG, lipids, and insulin sensitivity
Sage	Amini et al. 2020 (160)	RCT	70 women with PCOS ($n = 35$ intervention and 35 placebo)	Sage extract 330 mg/d for 8 wk	Sage improved body weight, BMI, WC, FBG, insulin concentrations, HOMA-IR, and QUICKI. No change in WHR or BP
Fennel and dry cupping	Mokaberinejad et al. 2019 (162)	RCT (open label)	55 women with PCOS ($n = 28$ intervention and 27 control)	Fennel tea (5 g fennel seeds in 200 mL boiling water for 10 min + 4.2 g sugar), once/day after lunch except during menstruation. Dry cupping = 4 cups in lower abdomen, 15–20 min/d from day 14, for 6 MC vs. with 500 mg metformin 3 times/d	Both groups reported a reduction in MC length and BMI at 6 mo with no difference between groups
Spearmint, ginger, citrus, and cinnamon	Ainehchi et al. 2019 (166)	RCT (open label)	60 women with PCOS, primary/secondary infertility, trying to conceive, age 18–35 y ($n = 20$ in each of 3 arms)	Dried plant samples of spearmint, ginger, cinnamon, and citrus in a 5:4:3:2 mixture in 700 mg/d capsules. One group also received CC (50–150 mg) for 3 MC from day 5 for 5 d vs. control group using CC only	Between-group differences were reported for oxidative stress (catalase, GSH, superoxide dismutase but not MDA), HOMA-IR, FBI, and FBG when comparing the herbal mixture or the herbal mixture + CC vs. CC alone. No differences between the herbal mixture and CC and the herbal mixture alone. No difference between groups for MC regularity
Other complementary therapies					
Acupuncture	Wu et al. 2020 (181)	SR + MA	22 RCTs, $n = 2315$ women with PCOS	Electro- or manual acupuncture, daily – once a week vs. sham, no treatment, or medications (CC, metformin, OCP, CHM, and letrozole), for 8 wk to 6 mo	Between-group differences for MC regularity (5 studies, $n = 364$), LH (13 studies, $n = 917$), and testosterone (13 studies, $n = 923$); no difference for live birth, pregnancy, ovulation, LH/FSH. Overall insufficient evidence

(*Continued*)

TABLE 1 (*Continued*)

Supplement	Author, year (Ref)	Study design	Population, *n*	Intervention dose and duration	Main findings
	Qu et al. 2016 (182)	SR + MA	9 RCTs, $n = 531$ women with PCOS, some had infertility or obesity	Electro- or manual acupuncture vs. medications (metformin, OCP, CHM). Duration and frequency NR	Pooled analysis indicated reduction of BMI in the acupuncture group (3 studies, $n = 155$), however, sensitivity analysis revealed this was mainly due to 1 RCT ($n = 80$) which compared acupuncture + the OCP with the OCP alone. No differences for FBI, FBG
Yoga	Anita et al. 2021 (186)	SR + MA	11 experimental studies, $n = 515$ women with PCOS (MA of 2 RCTs)	12 wk of yoga therapy	Yoga therapy may decrease menstrual irregularity, clinical hyperandrogenism, and concentrations of FBG, FBI, and HOMA-IR
	Shele et al. 2020 (185)	SR	2 RCTs ($n = 112$)	12 wk of yoga therapy	Yoga helped lower the concentrations of total and free testosterone (fT), LH, FBI, HOMA-IR, adiponectin, DHEA, and AMH. No difference in FSH, prolactin, androstenedione, and DHEAS. Concentrations of fT remained low even 3 mo after the intervention
	Thakur et al. 2021 (187)	SR	16 studies, $n = 365$ (including 2 RCTs)	Described yoga studies according to year of publication	Yoga may help improve menstrual frequency, lower fatigue, stress, and anxiety, and decrease the concentrations of blood lipids, LH, FBG, and testosterone with or without the use of other treatment measures
	Mohseni et al. 2021 (188)	RCT	67 women with PCOS ($n = 33$ intervention, $n = 34$ control)	90 min/d for 6 wk	Reduction in mFG score, abdominal circumference, and hip circumference scores. No improvement in BMI, SBP, DBP, symptoms of acanthosis nigricans and alopecia
Mindfulness-based interventions	Stefanaki et al. 2015 (194)	RCT	38 women/adolescents with PCOS, aged 15–40 y ($n = 23$ intervention and 15 control)	8-wk mindfulness audio program for 30 min daily with a 30 min individual introduction session vs. no treatment	Improved stress, depression and anxiety symptoms, life satisfaction, and quality of life compared to no treatment

α-LA, α-lipoic acid; AMH, anti-Mullerian hormone; ART, assisted reproductive technology; BP, blood pressure; CC, clomiphene citrate; CHM, Chinese herbal medicine; CrP, chromium picolinate; DBP, diastolic blood pressure; DHEA/DHEAS, dehydroepiandrosterone/-sulfate; DHT, dihydrotestosterone; E2, estradiol; FAI, free androgen index; FBG, fasting blood glucose; FBI, fasting blood insulin; FSH, follicle-stimulating hormone; fT, free testosterone; GSH, glutathione; Hcy, homocysteine; HMG, human menopausal gonadotropin; HOMA-β, homeostatic model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; ISI, insulin sensitivity index; LH, luteal hormone; MA, meta-analysis; MC, menstrual cycle; mcg, microgram; MDA, malondialdehyde; mFG, modified Ferriman–Gallwey; Mg, magnesium; MI, myo-inositol; NAC, N-acetyl cysteine; NR, not reported; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome; SHBG, serum hormone binding globulin; QUICKI, quantitative insulin-sensitivity check index; RCT, randomized controlled trial; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; Se, selenium; SR, systematic review; TAC, total antioxidant capacity; TC, total cholesterol; TG, triglycerides; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor; VLDL-C, very low-density lipoprotein cholesterol; WC, waist circumference; WHR, waist-hip ratio; 17-OHP, 17-hydroxyprogesterone.

improved all lipids except HDL cholesterol following a meta-analysis of 10 RCTs ($n = 543$; also with some overlapping studies) and effects were more pronounced in women with vitamin D deficiency. Based on these findings, vitamin D supplementation may have modest favorable effects in improving glycemic status in women with PCOS when provided in daily doses to women with deficiency (24, 25), but its impact on lipid profile, inflammation, and hyperandrogenism remains uncertain.

Inositol (vitamin B-8).

Inositols naturally occur as 5 stereoisomers, with the most abundant being myo-inositol (MI) and D-chiro-inositol (DI). In the ovary, MI is involved in modulating glucose uptake and follicle-stimulating hormone (FSH) signaling, whereas DI controls glycogen synthesis and insulin-induced androgen synthesis (26, 27). Inositol metabolism is often impaired in women with PCOS (28), typically stemming from imbalances in ovarian MI and DI, which have deleterious effects on glucose metabolism and reproductive health in these women (29). Both MI and DI isomers are second messengers of insulin, via expression of glucose transporters and cellular glucose uptake, or glycogen synthesis and storage, respectively. Inositol is found in many plants and animals, and despite being labeled as vitamin B-8, it is actually not a vitamin, but a carbocyclic sugar found in abundance in brain and muscle tissues (28). Unfer et al. (28) conducted a meta-analysis consisting of 9 RCTs with 496 participants on the variety of effects of MI in women with PCOS. It was consistently found that MI supplementation, alone or combined with DI, significantly reduced fasting insulin [standardized mean difference (SMD): −1.021 μU/mL; 95% CI: −1.791, −0.251] and HOMA-IR (SMD: −0.585; 95% CI: −1.145, −0.025). A substantial increase in SHBG (SMD: 0.425 nmol/L; 95% CI: 0.050, 0.801) was also observed, but only when MI was administered for a minimum of 24 wk, highlighting the importance of assessing the time-dependent effects of inositols on metabolic and hormonal parameters. Other meta-analyses reported improved ovulation rates and regulation of menstrual cycle frequency with MI supplementation (30), while restoring MI: DI ratio normalized hormonal parameters including progesterone, luteinizing hormone (LH), SHBG, estradiol, and testosterone (Table 1). Studies have also highlighted that additional supplementation with α-lactalbumin can optimize the beneficial effects of inositols in women with PCOS and overcome the commonly occurring problem of inositol resistance in these women (31).

Folate/folic acid (vitamin B-9).

Folic acid, also known as vitamin B-9, is the synthetic form of folate derived from fortified foods and supplements as it cannot be synthesized by mammals (32). Folic acid acts as a coenzyme in several key 1-carbon metabolic reactions needed for DNA and RNA synthesis and is essential for methylation reactions such as the remethylation of homocysteine (Hcy) to the amino acid methionine (33). Folic acid is proposed to have antioxidant, anticancer, and cardio- and neuroprotective properties, which could be beneficial in PCOS given the heightened systemic oxidative stress (and increased cardiovascular risk) in these women (34). Moreover, supplementation with folate could normalize the typically elevated Hcy concentration observed in women with PCOS (35–37). Previously, Bahmani et al. (38) observed a beneficial effect of folate supplementation on glycemic, inflammatory, and oxidative stress parameters in women with PCOS and overweight/obesity, marked by a reduction in HOMA-IR, hs-CRP, and malondialdehyde (MDA), and an increase in total antioxidant capacity (TAC) and glutathione (GSH) concentrations after supplementing with folic acid for 8 wk. Similarly, Asemi et al. (39) examined the effects of 1 or 5 mg/d of folic acid or placebo in women with PCOS for 8 wk. They reported a reduction in insulin and HOMA-IR as well as improved lipid profiles, compared with placebo or lower doses.

B-group vitamins (B-1, B-6, B-12).

B-group vitamins are responsible for breaking down Hcy in the blood and recycling it in the methionine cycle for later use (40). Hence, deficiencies in B-group vitamins lead to elevated concentrations of Hcy in the blood, which is potentially damaging to many systems (40). Specifically, elevated concentrations of Hcy are associated with IR and cardiovascular disease (41, 42). B-group vitamins (specifically, vitamin B-12) are often deficient in women with PCOS, which is associated with long-term and/or high-dose intake of metformin, a commonly prescribed medication to treat IR in PCOS (7, 43, 44). Supplementation with B-group vitamins may be effective in regulating Hcy concentrations in women with PCOS, potentially improving cardiometabolic and reproductive health. However, only a single RCT by Kilicdag et al. (37) has explored B-vitamin supplementation in PCOS. They found that 850 mg of metformin dispensed twice daily for 3 mo in 60 women with PCOS resulted in a 26.5% increase in Hcy concentrations, due to metformin-induced malabsorption of B-12. When B-group vitamins (B-1, 250 mg; B-6, 250 mg; B-12, 1000 μg) or folic acid (174 μg) were supplemented (alongside metformin) twice daily for 3 mo, there were reductions of 21.17% and 8.33% in Hcy concentrations, respectively, but no changes in IR measured by HOMA-IR. Therefore, supplementation of B-group vitamins could attenuate the Hcy-increasing effect of metformin in women with PCOS, but effects on IR, if any, remain unclear.

Vitamin K.

Vitamin K [in the form of phylloquinone (K_1) derived from green vegetables or menaquinone (K_2) derived from animal products] is a fat-soluble micronutrient with an unequivocal role in the maintenance of normal coagulation (45). Vitamin K is involved in the calcification of vasculature and bone, as it is a central cofactor for the carboxylation of several vitamin K-dependent proteins including osteocalcin (45). Osteocalcin is the most abundant protein in bone

and is exclusively produced by osteoblasts with downstream effects on metabolism and reproduction (46). Osteocalcin is reported to promote β-cell proliferation and insulin secretion through actions in the pancreas and adipocytes (47), and may therefore act as a mediator between bones and the pancreas in regulating glycemic status. Due to their proposed role in glycemic control, there has been increasing interest in the potential use of vitamins K_1 and K_2 in the management of diseases associated with IR (48). Yet, in women with PCOS, there are only a paucity of trials that have examined the efficacy of vitamin K supplementation. Among these, in an RCT of 79 women with PCOS, Tarkesh et al. (49) found that 90 μg/d of menaquinone-7 (vitamin K_2) for 8 wk decreased waist circumference, fat mass, fasting insulin, HOMA-IR, HOMA-β, TG, dihydrotestosterone, and free androgen index, while increasing skeletal muscle mass, SHBG, and QUICKI. Two other RCTs conducted in 55 (50) and 60 (51) women with PCOS examined vitamin K in combination with vitamin D and calcium. Both trials supplemented 500 mg calcium, 200 IU vitamin D, and 90 μg vitamin K oral formulations or placebo twice a day for 8 wk. The first trial (50) reported improved serum DHEAS, free testosterone (fT), plasma TAC, and MDA concentrations with combined calcium-K-D supplements, but no effect on prolactin, FSH, 17-OH progesterone, inflammatory markers, or GSH. The second trial (51) found that the combined supplement decreased insulin, HOMA-IR, HOMA-β, TG, and VLDL, and increased QUICKI compared with placebo. Vitamin K may be a promising supplement for improving oxidative stress and glycemic control in PCOS, but conclusions cannot be reached at this stage, given only one supplementation trial has been conducted to date.

Vitamin E.

Vitamin E (or tocopherol) is a fat-soluble vitamin stored in the liver, with anticoagulant and antioxidant properties and the ability to neutralize free radicals (52). Vitamin E is often cosupplemented with coenzyme Q10 due to their complementary actions in maintaining mitochondrial function and integrity (53). Vitamin E supplementation has been shown to improve endometrial thickness in women with idiopathic infertility (54), whereas cosupplementation with coenzyme Q10 for 8 wk increased SHBG and reduced free testosterone concentrations in women with PCOS (55). In another study, cosupplementing 400 IU vitamin E with 1000 mg of ω-3 fatty acids for 12 wk led to significant improvements in IR and androgen concentrations (56). Although there are currently no RCTs using vitamin E supplements alone for PCOS, Chen et al. (57) examined the effects of short-term supplementation with vitamin E in a retrospective study of women with PCOS and infertility treated with clomiphene citrate (CC) or human menopausal gonadotropin (HMG). In this study, vitamin E reduced oxidative stress and reduced the dose of exogenous HMG needed (57) but had no effects on ovulation or clinical or ongoing pregnancy rates. Clinical trials using vitamin E alone, at least in 1 intervention group, are needed to clarify its independent effects in PCOS.

Vitamin A.

Vitamin A, also known as retinol, is a fat-soluble vitamin that is thought to contribute to TAC, steroid metabolism, and oocyte maturation (7), although the mechanism of action is not adequately understood. Genes related to retinoic acid synthesis are expressed differentially in PCOS, potentially contributing to suboptimal retinol biosynthesis and a subsequent imbalance in metabolic function and androgen production. Retinol-binding protein 4 (RBP4) has been associated with impaired glucose metabolism and obesity in women with PCOS (58). Moreover, Tan et al. (59) posit that the altered gonadal and adrenal steroid profile in PCOS is attributed to upregulation of the *RBP4* gene (59). Despite being a potentially suitable candidate for supplementation in women with PCOS (7), there are currently no studies directly examining vitamin A supplementation in this population.

Vitamin-like nutrients

Bioflavonoids.

Bioflavonoids consist of plant-derived polyphenolic compounds and include anthacyanides, flovan-3-oils, flavanones, flavones, flavanols, and isoflavones, the latter being of greatest interest due to their reported cardioprotective and neuroplasticity-promoting effects. Bioflavonoids in general have well-established antioxidant, antidiabetic, antiestrogenic, anti-inflammatory, and antiproliferative properties, and some of their metabolites have been shown to improve PCOS pathogenesis at different levels (7). Of these bioflavonoids, quercetin, which is found in apples, berries, grapes, and onions, is thought to have metabolic and anti-inflammatory effects through inhibition of NF-kB and enhancement of glucose uptake through glucose transporter-4 (GLUT4) induction and activation of AMP-activated protein kinase (AMPK) (60). In women with PCOS and metabolic syndrome, Oh et al. (61) analyzed the intakes of the 6 flavonoid classes listed above and found that only flavonol consumption differed between groups (lower in metabolic syndrome) and was inversely associated with metabolic syndrome. In a pilot prospective study, Romualdi et al. (62) found improvements in the lipid profiles of women with PCOS after treatment with 36 mg/d of the soy isoflavone genistein for 6 mo. However, other typical features of PCOS were unchanged, including anthropometry, IR (by euglycemic clamp), hormonal profiles, and menstrual cyclicity. Pourteymour et al. (63) performed a systematic review of the flavonoid quercetin, which included 3 RCTs with a total of 246 participants with a BMI of 25–40 kg/m^2, who received 1 g/d of quercetin for 12 wk. There were improvements in adiponectin-mediated IR and testosterone concentrations compared with placebo, but no differences in weight loss or waist-hip ratio (WHR). The authors concluded that current evidence was insufficient for the efficacy of quercetin for PCOS (63).

α-Lipoic acid.

α-Lipoic acid (α-LA) is a free radical scavenger and potent antioxidant as well as being an essential cofactor in the citric acid cycle (64, 65). α-LA has been suggested to be a regulatory agent of body weight due to its potential in reducing food intake and enhancing energy expenditure via suppression of hypothalamic AMPK activity (66, 67). Masharani et al. (68) found that 1200 mg/d of controlled release α-LA administered to 6 lean nondiabetic women with PCOS for 16 wk resulted in a 13.5% improvement in IR (by hyperinsulinemic clamp) and a reduction in LDL and TG, but no change in antioxidant metabolites or capacity. Although the mechanisms are not fully understood, actions of α-LA may occur through regulation of lipid metabolism in the liver, kidney, and circulation (69). For instance, by promoting weight loss through enhancement of energy expenditure and satiety signals, α-LA could protect against ectopic lipid accumulation in nonadipose tissues such as liver and skeletal muscle, thus preventing lipotoxicities which promote IR (70). Using a randomized prospective study design, Cianci et al. (71) examined the role of α-LA and DI in the short-term management of 46 women with PCOS. Here, 26 women were allocated to receive 1000 mg/d DCI and 600 mg/d α-LA for 180 d, and 20 were untreated controls. Some reproductive characteristics were improved including menstrual cycles, decreased number of ovarian cysts, and increased progesterone concentrations as well as metabolic features including reductions in BMI and insulin and increased HDL cholesterol, but no changes in other lipid measures. Given the limited number of available studies, this area of research awaits further study to clarify the impact of α-LA in PCOS.

Carnitine.

Carnitine is a quaternary ammonium compound synthesized from amino acids lysine and methionine, and is involved in multiple metabolic processes including glucose and fatty acid metabolism, particularly in its active form (L-carnitine) (72, 73). Among its many functions, L-carnitine is responsible for transporting long-chain fatty acids to the inner mitochondrial matrix for β-oxidation. Women with PCOS are reported to have lower concentrations of L-carnitine, which has been associated with oocyte quality (poor oocyte maturation being a source of metabolic and endocrine malfunctions in PCOS) (74, 75). Links with hyperinsulinemic and hyperandrogenic features of PCOS have also been posited (74). Several putative mechanisms have been put forward to explain how reduced insulin sensitivity may be attributed to carnitine deficiency. Reduced carnitine is likely to hinder mitochondrial oxidation, leading to an accumulation of long-chain acyl CoA, resulting in dysregulation of the intramitochondrial acetyl-CoA:CoA ratio (76). This dysregulation is thought to impinge upon the insulin signaling cascade due to perturbations in the expression of glycolytic and gluconeogenic enzymes, as well as insulin-like growth factor-1 (IGF-1) (76). A daily dose of 3 g L-carnitine supplementation for 3 mo was shown to improve insulin sensitivity, BMI, and serum LDL in a prospective study of 80 women with PCOS (77). No other studies have explored carnitine supplementation in PCOS, with the exception of data currently under investigation (78–80).

Mineral supplements

Chromium picolinate.

Chromium picolinate (CrP) contains 12.4% elemental trivalent chromium (Cr^{3+}), an essential compound found in many whole grains, fruits, lean meats, and vegetables. CrP has been shown to improve IR, glycemic control, and metabolic status in women with PCOS in a number of RCTs, as well as systematic reviews and meta-analyses (81–85). Specifically, 200 μg/d CrP administration for 8 wk reduced rates of hirsutism and acne, whilst increasing plasma TAC in women with PCOS (83). Two previous meta-analyses reported mixed results, with one reporting that CrP reduced BMI, fasting insulin, and fT (85), and the other reporting that CrP decreased IR, but not BMI, and increased both free and total testosterone (86) (Table 1). Based on the current evidence, it is possible that CrP supplements may be beneficial in PCOS, but further studies are warranted before clear conclusions can be reached.

Calcium.

Multiple studies have indicated that women with PCOS have abnormalities in calcium concentrations, which is often attributed to deviations in vitamin D and parathyroid hormone (7, 87–89). In fact, Szscuko et al. (90) reported that calcium is the mineral that is at the highest risk of being deficient in women with PCOS. Yet, there is no consensus on the associations between calcium concentrations and IR in metabolic disorders such as PCOS (89, 91–95). Calcium and vitamin D are often cosupplemented together, since vitamin D improves calcium absorption, enabling it to carry out its many functions including the maintenance of bone, nerve transmission, vascular contractions and dilatations, and endocrine secretions, among others (96–99). In women with PCOS and vitamin D deficiency, calcium and vitamin D cosupplementation led to marked improvements in β-cell function, TAC, hs-CRP, and GSH, compared to supplementation with either calcium or vitamin D alone (100). Some RCTs also reported benefits of supplementing vitamin D with varying mixtures of magnesium, zinc, vitamin K, and vitamin E on hormonal profiles, inflammation, and oxidative stress in women with PCOS (51, 101–103). A recent systematic review (104) examined 6 RCTs ($n = 480$) using calcium and vitamin D cosupplementation in women with PCOS, most of whom also used metformin. They reported improved lipid profiles, menstrual regularity, and follicular maturation, increased QUICKI and reduced serum insulin, HOMA-IR, FBG, hirsutism, and testosterone. Although these effects cannot be attributed to calcium alone, the findings are promising and support the increasingly accepted understanding that these micronutrients often act in tandem (either synergistically or

additively) to regulate a variety of reproductive and metabolic systems and improve the negative health outcomes associated with PCOS.

Magnesium.

Magnesium is an intracellular cation and a cofactor of many enzymes involved in insulin metabolism. Hypomagnesemia has been implicated in the impairment of insulin action and development of IR due to a reduction of tyrosine-kinase activity at the insulin receptor level (105). Magnesium is also involved in DNA and RNA synthesis and neuronal protection against cell death. Owing to its mechanisms in regulating glycemic and neurologic functions, magnesium is proposed to have a role in conditions associated with concomitant IR and depression, including PCOS as well as some cardiovascular diseases and diabetes (7, 106), but currently available evidence testing this notion is sparse. Despite some reported benefit of magnesium supplementation on subjective anxiety and stress outcomes in vulnerable groups among the general population (107), there is no data on the effects of magnesium on depressive symptoms in women with PCOS. A systematic review by Hamilton et al. (106) reported that a higher concentration of magnesium was associated with overall reduced IR on the basis of 4 epidemiological studies in women with PCOS. However, when analyzing results from 3 RCTs, the impact of supplementation with magnesium on IR in these women was inconsistent. Given its important metabolic and neurological functions, and since women with PCOS may be more likely to be magnesium deficient and under consume magnesium-rich foods (90), there is a need to further explore whether improving dietary magnesium intake and/or supplementation may be an effective strategy in women with PCOS, particularly for improving IR and depressive symptoms.

Selenium.

Selenium is an essential trace element and key part of selenoproteins which assist in redox processes and have important antioxidant and anti-inflammatory functions (108). For instance, selenoproteins can protect against oxidative stress caused by excessive concentrations of reactive oxygen species (ROS and reactive nitrogen species; RNS) (108). Since embryos are particularly susceptible to oxidative stress due to lower antioxidative capacity as compared to adults, the role of selenium in embryonic gonadal development and reproductive function has been identified (109, 110). Selenium is also involved in metabolic functions, and its plasma concentrations are thought to be decreased in women with PCOS, potentially leading to free radical accumulation and hyperandrogenism (7, 110, 111). A 2019 systematic review (112) of studies of Se in PCOS identified 5 RCTs, where women with PCOS were supplemented with 200 ug Se daily for 8–12 wk. Findings showed reduced IR, inflammation, and oxidative stress, whereas results were inconsistent for BMI, weight, FBG, lipids, hormonal parameters, or other features of PCOS such as acne and hirsutism (112).

Zinc.

Zinc (Zn) is another essential trace element, responsible for the function of over 300 enzymes, with a critical role in insulin synthesis, storage, secretion, and function (113, 114). Zinc is often referred to as an insulin-mimetic, that is, it stimulates lipogenesis and glucose uptake in isolated adipocytes in an insulin-like manner (113, 114). These actions occur through modulation of protein tyrosine phosphatase activity in IGF-1 signaling (115). Previous studies suggest that women with PCOS may be deficient in Zn and that this could underlie the insulin-resistant state seen in some PCOS phenotypes (116, 117). Indeed, deficiencies in Zn could worsen IR in women with PCOS via dysregulation in the insulin-dependent tyrosine phosphatase pathway (7). A recent systematic review conducted by Nasiadek et al. (118) found that 4–50 mg of Zn supplementation 1–2 times daily for 8–12 wk improved HOMA-IR and lipid profiles in women with PCOS, as well as reducing inflammation (hs-CRP) and oxidative stress (MDA and TAC). Reductions in fT, FSH, and DHEAS were also noted in some of the trials (118). Many of the trials, however, cosupplemented Zn with other nutrients such as magnesium, calcium, and vitamin D. Hence, the potential beneficial effects observed cannot be isolated or attributed solely to Zn supplementation.

Other supplements

Probiotics.

The gut microbiome of women with PCOS is less diverse than in women without PCOS, with evidence of higher intestinal permeability (119). This reduction in gut microbial diversity has been linked to hyperandrogenism as well as increased levels of systemic inflammation (120). Shamasbi et al. (121) conducted a meta-analysis of 13 studies with 855 participants with PCOS ($n = 438$ intervention and 417 controls), and showed that SHBG (SMD: 0.56; 95% CI: 0.26, 0.86) and NO (SMD: 0.38; 95% CI: 0.09, 0.68) concentrations increased significantly, whereas free androgen index (SMD: −0.58; 95% CI: 0.95, −0.21) and MDA (SMD: −0.76; 95% CI: 1.46, −0.05) concentrations reduced significantly in the probiotics and synbiotics groups compared with placebo. Other hormonal and inflammatory indices such as testosterone, DHEAS, GSH, hs-CRP, TAC, and hirsutism score did not differ between the groups (121). Interventions were generally given for 12 wk, and strains typically included *Lactobacillus acidophilus/casei/rhamnosus, Bididobacteriumbifidum/longum/breve,* and *Streptococcus thermophiles*, with almost all RCTs including *Lactobacillus acidophilus* in their probiotic. Another meta-analysis (122) pooled data from 6 RCTs involving 406 women with PCOS (aged 25–28.5 y) receiving probiotic supplements for 8–12 wk durations. Probiotic supplements lowered fasting insulin, QUICKI, TG, and VLDL, but there were no differences in other metabolic outcomes including FBG, HOMA-IR, other lipids, body weight, hs-CRP or DHEAS. All RCTs included *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium* species and the pooled results remained significant after the leave-one-out sensitivity analysis (122).

Melatonin.
Melatonin is a neuroendocrine hormone secreted from the pineal gland with potent free radical scavenging properties. Melatonin has an important role in regulating circadian rhythm as well as in ovarian functions including folliculogenesis, ovulation, and oocyte maturation and forming the corpus luteum (123–125). Melatonin may be relevant in PCOS as it is thought to directly reduce testosterone production via its antigonadal effects (126), in addition to its beneficial roles in mitigating IR, hyperglycemia, and dyslipidemia (127). A systematic review (128) identified 3 studies (2 RCTs and 1 cell culture) in women with PCOS undergoing treatment with assisted reproductive technology (ART). Meta-analysis of all 3 studies incorporating both in vivo and ex vivo melatonin administration revealed a significant effect of melatonin treatment on clinical pregnancy rates (in vivo studies = 3 mg of melatonin taken from the day of the first cycle or from day 3 to the triggering day; ex vivo study = 10 μmol/L of melatonin on culture medium for 24–48 h), but this was not significant in meta-analysis of the 2 RCTs alone (in vivo only). Two other prospective studies in women with PCOS reported that melatonin treatment of 2–3 mg/d for 2–6 mo decreased androgens, LH, anti-Müllerian hormone, and BMI, and increased FSH (129, 130). Finally, Jamilian et al. (131) conducted an RCT in 56 women with PCOS and reported reduced hirsutism, total testosterone, hs-CRP, MDA, and increased TAC and total GSH in those receiving 5 g melatonin twice daily for 12 wk, compared with placebo.

N-Acetyl cysteine.
N-Acetyl cysteine (NAC) is the acylated form of the amino acid L-cysteine, and has potent antioxidant properties via enhancing GSH biosynthesis. NAC supplements have been examined in PCOS due to their ability to improve insulin receptor activity and insulin secretion in response to glucose. A 2015 meta-analysis of 8 RCTs (n = 910) (132) showed that women with PCOS receiving 1200–1800 mg/d NAC for 12–24 wk had 3 times higher odds of pregnancy and live births compared with placebo, but were 60% less likely to achieve pregnancy with NAC when compared with metformin. NAC also reduced FBG compared with metformin or placebo, but not fasting insulin or HOMA-IR (132). Although NAC shows promising results, firm conclusions are precluded by the small number of studies with small sample sizes and overall poor quality of the existing evidence.

ω-3 fatty acids.
ω-3 fatty acids, often found in fish oil supplements, are PUFAs, with the most common being α-linolenic acid, EPA, and DHA. ω-3 fatty acids have anti-inflammatory, antioxidant, and antihypertensive properties and regulate abnormal expression of some genes in PCOS (133). For instance, granulosa cell cultures treated with 25–100 μg of the ω-3 fatty acid EPA showed increased IGF-1 and lowered cyclooxygenase 2 (COX2) expression, both essential compounds of follicular differentiation and oocyte maturation (134). A meta-analysis by Yang et al. (135) of 9 RCTs (n = 591) reported that supplementation with ω-3 fatty acids (900–4000 mg/d) for 6–24 wk improved HOMA-IR, whereas total cholesterol, TG, and LDL-C were reduced, but there was no effect on BMI, FBG, fasting insulin, HDL cholesterol, LH, FSH, SHBG, or serum testosterone in women with PCOS. High heterogeneity was noted for most outcomes, with authors concluding (135) that although ω-3 fatty acids could be used in women with PCOS coupled with IR and/or dyslipidemia, further larger scale RCTs with longer follow-up durations were needed to confirm these effects.

Resveratrol.
Resveratrol is a nonflavonoid polyphenol which is found in 72 plant species including berries, grapes, legumes, and nuts. Resveratrol inhibits the production of inflammatory mediators and ROS through a variety of signaling pathways including the arachidonic acid (AA) pathway, NF-kB pathway, and the mitogen-activated protein kinase (MAPK) pathway (136). Resveratrol downregulates vascular endothelial growth factor (VGEF) in granulosa cells therefore reducing angiogenesis, and has been theorized to upregulate GLUT4, increase protein kinase B, and proliferator-activated receptor δ. A systematic review reported on 3 small RCTs (n = 131 participants) that used 800–1500 mg/d micronized *trans*-resveratrol for 40–90 d compared with placebo. There was limited evidence for a reduction in total testosterone and fasting insulin, and an increase in high-quality oocyte and embryo rate with resveratrol, but no corresponding difference between groups for clinical pregnancy rate, hirsutism/acne, or other metabolic markers such as FBG, lipids, and BMI (137).

Coenzyme Q10.
Coenzyme Q10 is a cofactor present in cell membranes and mitochondria, particularly in the heart, kidneys, and liver. One of its functions is to facilitate the production of ATP through participation in the electron transport chain in the mitochondria. It also inhibits peroxidation of cell membrane lipids and reduces oxidation of circulating lipids, therefore acting as a potent antioxidant. Exogenous supplementation may improve markers of insulin sensitivity through modulation of insulin, glucose uptake, and adiponectin receptors and reduction of ROS concentrations (138, 139). Supplementation with 100 mg/d of coenzyme Q10 for 12 wk in an RCT of 60 women with PCOS (140) resulted in improved HOMA-IR, QUICKI, serum insulin, FBG, and lipids (TC and LDL cholesterol). This was thought to be due to an upregulation in the gene expression of proliferator-activated receptor γ (PPARγ) and a downregulation in the gene expression of oxidized LDL receptor-1 and inflammatory markers (IL-1, IL-8, and TNF-α) in peripheral blood mononuclear cells of women who received coenzyme Q10 supplements; however, the exact mechanisms of action are as yet unknown (140).

Flaxseed.

The active compounds of flaxseed (*Linum usitatissimum*) include α-linolenic acid, lignans, and dietary fiber. Lignans and fiber may improve insulin sensitivity by reducing glucose uptake speed and insulin release, and ω-3 fatty acids may increase adiponectin concentrations (141, 142). Haidari et al. (143) conducted an open-label RCT in 41 women with PCOS who were either given milled flaxseed powder (30 g/d) and advice on lifestyle modification (provision of healthy diet recommendations from the American Heart Association and advice to increase physical activity to 30 min moderate intensity 3 times a week) or provided with advice on lifestyle modification alone for a period of 12 wk. There were small improvements in body weight, waist circumference, insulin, HOMA-IR, TG, hs-CRP, leptin, and QUICKI (143), although these differences are unlikely to be clinically significant, warranting more research on the use of this supplement in PCOS.

Pomegranate juice and synbiotics.

The fruit juice of *Punica granatum L.,* or pomegranate, is rich in polyphenols including flavonoids. Preclinical studies suggest that pomegranate juice improves gut microbial diversity, and reduces oxidative stress and the inflammatory response (144, 145). In a triple-blind 4-arm RCT of 86 women with PCOS, 300 mL/d of pomegranate juice for 8 wk, with or without synbiotics, improved lipids (TG, HDL), blood pressure (BP), and oxidative stress (TAC, MDA) compared with placebo. Synbiotics, with or without pomegranate juice, lowered LDL, IR, weight, BMI, waist circumference, and testosterone, whereas symbiotic juice alone reduced total cholesterol and pomegranate juice alone lowered inflammatory markers (146, 147).

Iron.

Iron is a trace mineral oligoelement and is critical for human life given its key role in electron and oxygen transport. Serum ferritin concentrations are increased in some women with PCOS, especially in phenotypes associated with glucose intolerance irrespective of obesity status (148), suggesting possible iron excess. This mild iron overload may be due to acquired or genetic iron-sparing mechanisms due to chronic oligomenorrhea, or increased iron absorption from decreased hepcidin (the main negative regulator of iron absorption), respectively (149). No RCTs have examined iron supplementation in PCOS; however, 1 RCT of women with PCOS using metformin compared with an antiandrogenic contraceptive pill showed that it was the improved insulin sensitivity, not the restoring of menstrual regularity, that decreased serum ferritin concentrations in these women (150). This suggests that regulation of body iron stores in PCOS may be driven more by IR and hyperinsulinemia than by menstrual losses. However, studies examining the relations between iron metabolism and PCOS and any potential benefits of iron supplementation in this context remain relatively scant, meriting further inquiry.

Herbal medicine

Cinnamon.

Cinnamomum cassia, or cinnamon, may exert hypoglycemic effects through insulin receptor autophosphorylation and dephosphorylation; GLUT-4 receptor synthesis and translocation; modulation of hepatic glucose metabolism through changes in pyruvate kinase and phosphenol pyruvate carboxykinase; and/or inhibition of intestinal glucosidases and altering the expression of PPAR-γ through multiple active compounds including eugenol, cinnamaldehyde, copane, cinnamyl acetate, and camphor (151). Heydarpour et al. (152) conducted a meta-analysis on cinnamon for metabolic parameters in women with PCOS and identified 5 trials (n = 448), all of which were deemed to be of high quality. Improvements in FBG [weighted mean difference (WMD): −5.32 mg/dL; 95% CI: −10.46, −0.17], fasting insulin (WMD: −4.10 μIU/dL; 95% CI: −6.76, −0.144), and HOMA-IR (WMD: −0.69; 95% CI: −1.37, −0.004) were reported as well as differences in lipids (LDL cholesterol, HDL cholesterol, total cholesterol), but there were no differences in body weight or BMI, compared with placebo (152). Doses of cinnamon ranged from 336 mg/d of cinnamon extract or 1500 mg/d of cinnamon capsules, with durations ranging from 6 to 24 wk. Although these studies provide some indication of the potential benefits of cinnamon supplements for glucose and lipid metabolism, there remains a need for further clarification on optimal doses and durations, as well as the underlying mechanisms of action in the context of PCOS.

Chinese herbal medicine.

Chinese herbs may have physiological effects on IR, glycemic control, inflammation, ovarian morphology, and androgens through active compounds such as glucosides, ginsenosides, alkaloids, and cryptotanshinone (153, 154). Zhou et al. (155) conducted a Cochrane review and concluded that, overall, there is insufficient evidence to support the use of Chinese herbal medicines (CHM) for women with PCOS and subfertility. The authors identified 5 RCTs (n = 414) of low to very low quality, finding that there was low-quality evidence of a higher pregnancy rate for CHM + CC compared with CC alone (OR: 2.62; 95% CI: 1.65, 4.14), but no difference between CHM and CC. No data on live birth rates were reported in any of the trials (155).

Curcumin.

Turmeric is a spice derived from the root of *Curcuma longa* and is commonly used in Ayurveda and Traditional Chinese Medicine. The main active compound derived from turmeric is curcumin, which may exert hypoglycemic effects through attenuating TNF-α concentrations and plasma free fatty acids; inhibiting NF-kB activation and protein carbonyl, lipid peroxidation, and lysosomal enzyme activities; reducing TBARs; and activating PPARγ and hepatic glycolysis (156). A previous RCT in 67 women reported that FBG [mean difference (MD): −4.11 mg/dL; 95% CI: −8.35, −0.35] and DHEA (MD: −26.53 μg/dL; 95% CI: −47.99, −4.34) decreased

with 500 g curcumin 3 times daily for 12 wk compared with placebo, with no change in fasting insulin (157). Another RCT of 51 women reported that some measures of IR (QUICKI) improved in the curcumin group receiving 500 mg daily for 6 wk, but not in the placebo group; however, there were no between-group differences in lipid parameters or glycemic indices (158).

Sage (Salvia officinalis).

Salvia officinalis, or sage, is a herb that is commonly used in Iranian traditional medicine. Active compounds include multiple phenolic compounds such as rosmarinic acid and flavonoids such as carnosic acid as well as terpenoids and coumarins, which exert antioxidant effects and therefore effects on glucose metabolism and insulin sensitivity (159). An RCT by Amini et al. (160) examined 70 euglycemic women with PCOS who were given sage extract or placebo for 8 wk. A reduction in BMI (MD: −0.64 kg/m^2; 95% CI: −1.00, −0.28) and improved IR (MD: −0.69; 95% CI: −0.87, −0.51) and insulin (MD: −2.81 mIU/L; 95% CI: −3.59, −2.02) were reported in the intervention group (160), but there were no differences in WHR or BP.

Fennel infusion and dry cupping.

Fennel, or *Foeniculum vulgare*, may act as a phytoestrogen (161), weakly mimicking estrogen with potential metabolic and hormonal benefits in PCOS. Mokaberinejad et al. (162) conducted an open-label RCT in 55 women with PCOS and compared fennel tea combined with dry cupping (a suction technique to promote blood circulation and healing) against 1.5 g of metformin daily. The intervention was provided for 6 menstrual cycles and was as effective as metformin for reducing menstrual cycle length and BMI at 6 mo (162).

Spearmint, ginger, cinnamon, and citrus mixture.

Mentha spicata (spearmint), *zingiber officinale roscoe* (ginger), and *citrus silences* (citrus) may have anti-inflammatory and hypoglycemic effects through active compounds that include zingiberene, camphene, p-cymene, menthone, flavonoids, and terpenoids (163–165). Ainehchi et al. (166) conducted an open-label RCT of a herbal mixture containing spearmint, ginger, cinnamon, and citrus with CC, herbal mixture alone, or CC alone (50–150 mg) for 3 menstrual cycles in 60 women with PCOS and primary/secondary infertility. This herbal mixture, with or without CC, improved serum antioxidant concentrations (including catalase, glutathione peroxidase, and MDA), HOMA-IR, insulin, and FBG compared to CC alone (166). However, there was no difference between groups for menstrual regularity.

Other CM modalities

Acupuncture.

In non-PCOS populations, acupuncture, in particular, auricular and electro-acupuncture, is more efficacious than sham acupuncture for reducing BMI, body fat mass, and waist and hip circumference (167). These effects are mediated through multiple responses including appetite suppression (168, 169), modulation of leptin and ghrelin (170–172), and improved insulin sensitivity (173–178). Acupuncture may have an impact on sympathetic function in women with PCOS (179) and may also increase ovarian blood flow (180). Wu et al. (181) conducted a meta-analysis on the effectiveness of acupuncture in PCOS and found 22 trials (n = 2315), all of which had either unclear or high risk of bias. When compared to sham acupuncture, there were no differences in ovulation, LH, and LH/FSH ratios (2 studies, n = 1683) or pregnancy rates (3 studies, n = 583), with 1 study (n = 29) reporting an improvement in testosterone, but not live birth rates. When compared with conventional medication, 2 studies (n = 80) reported improvements in LH concentrations compared to CC. Although pooled analyses reported between-group differences for menstrual regularity and some hormonal markers (testosterone and LH), the authors concluded that there was overall insufficient evidence to support acupuncture as an effective treatment in PCOS (181).

Another meta-analysis by Qu et al. (182) examined acupuncture for metabolic outcomes in women with PCOS and reported a reduction in BMI, but not IR, in a pooled analysis of 3 studies (n = 155). However, sensitivity analysis revealed that this difference was mainly due to 1 RCT (n = 80) which compared acupuncture and the oral contraceptive pill to the pill alone (182). Hence, it is unclear whether these effects can be attributed to acupuncture or the contraceptive pill or both. Overall, there is insufficient evidence to draw conclusions about the benefits of acupuncture in PCOS, and further research that overcomes methodological challenges, such as small sample sizes and lack of allocation concealment, is needed.

Yoga.

Yoga is a mind-body therapy that originated in India (183). Today, there are several styles/schools of yoga practices globally, each having its own aim and form of practice, such as traditional Hatha yoga, Iyengar, Ashtanga, Bikram, Sivananda, Kripalu, Viniyoga, Kundalini, and integrated yoga therapy (184). Shele et al. (185) conducted a systematic review on yoga for women with PCOS and identified 2 RCTs (n = 112), with findings that suggested benefits for testosterone and IR. A meta-analysis of the same 2 RCTs reported that yoga therapy may decrease menstrual irregularity, clinical hyperandrogenism, and concentrations of FBG, fasting insulin, and HOMA-IR (186). Another systematic review which identified 16 studies (2 RCTs) that were organized chronologically and reviewed narratively, suggested that yoga may have promising benefits for the management of stress, anxiety, fatigue, menstrual irregularity, concentrations of LH, FBG, lipids, testosterone, and IR (187). In a more recent RCT, Mohseni et al. (188) enrolled 67 women with PCOS and reported that 90 min of daily yoga practice for 6 wk reduced hirsutism and waist and hip circumference, but without improvements in BMI, BP, symptoms of acanthosis nigricans or alopecia. Although

yoga could be a potentially feasible, sustainable, and low-cost lifestyle intervention for women with PCOS, possibly helping to reduce the risk of developing PCOS (136, 189), the evidence remains limited and methodological quality is low, with small sample sizes, high attrition rates, and poor adherence. Well-designed and adequately powered RCTs are warranted to strengthen the evidence base in this area and refute or corroborate these initial findings.

Mindfulness-based interventions.

Mindfulness-based interventions aim to cultivate the practice of mindfulness, defined as nonjudgmental, present-moment awareness (190). In the general (non-PCOS) population, mindfulness-based interventions demonstrate reductions in body weight (191), stress (192), and anxiety and depression symptoms (193). Stefanaki et al. (194) conducted a small RCT exploring the impact of an 8-wk mindfulness stress management program on depression, anxiety, stress, and quality of life in 38 women with PCOS. Stress, depression, and anxiety symptoms were reduced in the intervention group, with a concomitant increase in life satisfaction and quality of life compared with no treatment (194). In a pilot study of 86 women with PCOS and a BMI $\geq$25 kg/m^2 (195), mindfulness-based stress reduction (MBSR), a standardized 8-wk mindfulness program, was trialed in comparison with a control group receiving health education. There were between-group differences favoring the intervention group for negative affectivity at 8 wk and perceived stress at 16 wk, but there were no significant differences in BP, weight, or IR (195).

Limitations and Future Directions

Whilst the preliminary data for the potential utility of nutritional and complementary therapies for ameliorating the negative health effects of PCOS is promising, there are some notable limitations that must be discussed and overcome before these therapies can be considered for integration into clinical practice.

First, the vast diversity of interventions and treatment regimens examined across the literature makes interpretation difficult, precluding firm conclusions from being reached. There is a lack of consistency in nutrient and herbal formulations, dosages, comparators, and intervention durations, as well as significant heterogeneity in the styles and frequencies of interventions such as acupuncture and yoga. This makes it particularly challenging for developing systematic reviews or meta-analyses with appropriate inclusion criteria that are both broad enough to capture all the relevant research on the intervention and specific enough to avoid unsuitable comparisons being made between studies. Where nutrients are cosupplemented, which occurs quite frequently, it is difficult to identify the relative effects of each nutrient on the outcomes, potentially (and likely) confounding or over- or underestimating the potential benefits of a given nutrient or treatment. Further, incorporating adequate control methods for interventions such as yoga, acupuncture, and mindfulness programs is challenging, and it is not possible to blind participants or practitioners to allocation. Although sham acupuncture methods have been trialed, and some attempts to blind investigators and personnel involved in outcome measurement can be utilized, these shortcomings increase the risk of bias in RCTs of these interventions and limit confidence in their results.

Second, the present review illustrates that although meta-analyses exist for some interventions including MI, vitamin D, ω-3 fatty acids, and NAC in women with PCOS, other interventions such as vitamin K and carnitine have little to no available data testing their efficacy in PCOS. The quality of the evidence therefore ranges from higher levels of evidence with meta-analyses of RCTs to single retrospective observational studies. Sample sizes are also problematic and, as shown in Table 1, of the 45 studies and systematic reviews included, 19 (42%) included <100 participants, bringing into question the statistical power of these studies to detect effects.

A third problem pertains to the degree of interstudy and interindividual heterogeneity present within and across the currently available PCOS studies. For instance, there are critical differences among study participants in factors such as age, BMI, ethnicity, and diagnostic method/criteria of PCOS. These factors can influence nutrient sufficiency, disease phenotypes, and clinical outcomes, potentially resulting in third variable effects — a key problem for observational studies if appropriate adjustment for confounding has not been incorporated. Varied intervention settings, study designs, participant medication use and comorbidities, and a lack of data on nutrient sufficiency in general in women with PCOS, can further complicate this issue. Moreover, certain environmental exposures cannot be sufficiently controlled in RCTs, affecting internal validity. For example, seasonality or sunlight exposure (the main source of vitamin D) has rarely been accounted for when examining the effects of vitamin D supplements in PCOS, so the placebo groups are not "true" placebos if control participants can receive vitamin D from sun exposure. Reproductive and metabolic outcomes studied also vary across the literature, with different diagnostic criteria or cut-offs and outcome measures (e.g., clamp versus HOMA-IR, etc.), making direct comparisons difficult. Finally, Günalan et al. (7) highlights that PCOS has many diverse clinical manifestations, ranging from reproductive to metabolic to psychological dysfunction. There is thus a need for research in this field to explore the potential mechanisms and benefits of nutrient supplementation and complementary therapies on the wide range of clinical manifestations of PCOS. At present, the evidence is not sufficiently robust to support supplementation clinically, and a more nuanced and case-specific approach of nutrient supplementation for PCOS is needed to encapsulate the variety of pathologies associated with this condition.

Future research should endeavor to address these above limitations to clarify the benefits (and possible harms) of nutritional supplements and CM for women with PCOS. The use of RCTs that have standardized criteria (e.g., diet, dosage, and timeframe; or using a standardized acupuncture, yoga, or mindfulness protocol) with suitable inclusion criteria

(standardized diagnostic criteria for PCOS, age range, BMI groups, and specific phenotypes) is essential to allow for reliable results. Moreover, the use of validated tools and gold-standard methods instead of indirect proxy measures, such as using hyperinsulinemic clamps instead of HOMA-IR, with cohorts that are sufficiently powered will allow for meaningful and reliable comparisons to be made between studies. As previously suggested, certain nutrients have a paucity of data (iron, magnesium, zinc, flaxseed, etc.) and more high-quality research on these nutrients is needed before their efficacy can be established. Some supplements may theoretically enhance the hypoglycemic actions of metformin (which is commonly used by women with PCOS); for example, sage, curcumin, quercetin, inositol, and some CHM (196). However, apart from potential synergistic or additive effects with metformin, no other known herb-drug interactions have been reported (197). Future research on biologically based therapies should include an investigation of potential herb- or nutrient-drug interactions and any immediate or long-term risks associated with these interactions.

At present, the etiology and mechanisms underpinning PCOS remain incompletely understood. However, it is likely that as more women with PCOS adopt supplements and CM as adjunct therapies to traditional treatments, the scientific community will be urged to broaden current knowledge and employ innovative methods to clarify if and how these therapies can influence the metabolic, reproductive, and psychological characteristics of this condition. Such research would help generate an essential platform to promote a better understanding of these therapeutic approaches in PCOS and a more rigorous evidence base for practitioners, patients, and policymakers.

Conclusions

Based on this review of the literature, supplementation with nutrients including minerals, vitamins, vitamin-like nutrients, and complementary therapies may be beneficial in ameliorating some of the adverse health outcomes associated with PCOS. However, current literature is inconsistent and sparse or of poor quality, making it difficult to ascertain whether these therapies, together or separately, are effective in managing or treating PCOS symptoms and outcomes. Further research is therefore needed, particularly by means of well-designed, adequately powered RCTs, in addition to mechanistic studies, to determine the efficacy of these therapies and their actions and interactions with the biological processes underpinning PCOS.

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References

1. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90(4):1929–35.
2. Wolf WM, Wattick RA, Kinkade ON, Olfert MD. Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. Int J Environ Res Public Health 2018;15(11):2589.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19(1):41–7.
4. Teede HJ, Misso ML, Boyle JA, Garad RM, McAllister V, Downes L, Gibson M, Hart RJ, Rombauts L, Moran L, et al. Translation and implementation of the Australian-led PCOS guideline: clinical summary and translation resources from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Med J Aust 2018;209(S7):S3–S8.
5. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 2016;37(5):467–520.
6. Sam S. Obesity and polycystic ovary syndrome. Obes Manag 2007;3(2):69–73.
7. Gunalan E, Yaba A, Yilmaz B. The effect of nutrient supplementation in the management of polycystic ovary syndrome-associated metabolic dysfunctions: a critical review. J Turk Ger Gynecol Assoc 2018;19(4):220–32.
8. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. Hum Reprod 2016;31(11):2619–31.
9. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33(6):981–1030.
10. Krug I, Giles S, Paganini C. Binge eating in patients with polycystic ovary syndrome: prevalence, causes, and management strategies. Neuropsychiatr Dis Treat 2019;15:1273–85.
11. Jeanes YM, Reeves S, Gibson EL, Piggott C, May VA, Hart KH. Binge eating behaviours and food cravings in women with polycystic ovary syndrome. Appetite 2017;109:24–32.
12. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ, International PICOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod 2018;33(9):1602–18.
13. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2019;3:CD007506.
14. Arentz S, Smith CA, Abbott JA, Bensoussan A. A survey of the use of complementary medicine by a self-selected community group of Australian women with polycystic ovary syndrome. BMC Complement Alternat Med 2014;14(1):472.
15. Sills ES, Perloe M, Tucker MJ, Kaplan CR, Genton MG, Schattman GL. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. BMC Women's Health 2001;1(1):3.
16. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P T 2013;38(6):336–55.
17. Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. Endocrine 2006;30(1):19–26.
18. Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, Li Z, You L, Zhao J, Liu J, et al. Genome-wide association study identifies susceptibility loci for

polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet 2011;43(1):55–9.
19. Rutkowska AZ, Diamanti-Kandarakis E. Polycystic ovary syndrome and environmental toxins. Fertil Steril 2016;106(4):948–58.
20. Brutocao C, Zaiem F, Alsawas M, Morrow AS, Murad MH, Javed A. Psychiatric disorders in women with polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine 2018;62(2): 318–25.
21. Mousa A. Prevention and management of gestational diabetes using vitamin D supplementation: an overview and appraisal of applied sciences. Appl Sci 2020;10(22):8141.
22. Mousa A, Naderpoor N, de Courten MP, Scragg R, de Courten B. 25-hydroxyvitamin D is associated with adiposity and cardiometabolic risk factors in a predominantly vitamin D-deficient and overweight/obese but otherwise healthy cohort. J Steroid Biochem Mol Biol 2017;173:258–64.
23. Miao C-Y, Fang X-J, Chen Y, Zhang Q. Effect of vitamin D supplementation on polycystic ovary syndrome: a meta-analysis. Exp Ther Med 2020;19(4):2641–9.
24. Guo S, Tal R, Jiang H, Yuan T, Liu Y. Vitamin D supplementation ameliorates metabolic dysfunction in patients with PCOS: a systematic review of RCTs and insight into the underlying mechanism. Int J Endocrinol 2020;2020:1.
25. Gao H, Li Y, Yan W, Gao F. The effect of vitamin D supplementation on blood lipids in patients with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Int J Endocrinol 2021; 2021:1.
26. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 1998;83(6):2001–5.
27. Nestler JE, Unfer V. Reflections on inositol(s) for PCOS therapy: steps toward success. Gynecol Endocrinol 2015;31(7):501–5.
28. Unfer V, Facchinetti F, Orru B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocrine Connections 2017;6(8):647–58.
29. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: a systematic review of randomized controlled trials. Int J Endocrinol 2016;2016:1.
30. Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, Coomarasamy A, Thangaratinam S. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG: An International Journal of Obstetrics & Gynaecology 2018;125(3):299–308.
31. Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. J Ovarian Res 2018;11(1):38.
32. Greenberg JA, Bell SJ, Guan Y, Yu Y-H. Folic acid supplementation and pregnancy: more than just neural tube defect prevention. Rev Obstet Gynecol 2011;4(2):52–9.
33. Asbaghi O, Ghanavati M, Ashtary-Larky D, Bagheri R, Rezaei Kelishadi M, Nazarian B, Nordvall M, Wong A, Dutheil F, Suzuki K, et al. Effects of folic acid supplementation on oxidative stress markers: a systematic review and meta-analysis of randomized controlled trials. Antioxidants 2021;10(6):871.
34. González F, Rote NS, Minium J, Kirwan JP. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91(1):336–40.
35. Kazerooni T, Asadi N, Dehbashi S, Zolghadri J. Effect of folic acid in women with and without insulin resistance who have hyperhomocysteinemic polycystic ovary syndrome. Int J Gynecol Obstet 2008;101(2):156–60.
36. Guzelmeric K, Alkan N, Pirimoglu M, Unal O, Turan C. Chronic inflammation and elevated homocysteine levels are associated with increased body mass index in women with polycystic ovary syndrome. Gynecol Endocrinol 2007;23(9):505–10.
37. Kilicdag EB, Bagis T, Tarim E, Aslan E, Erkanli S, Simsek E, Haydardedeoglu B, Kuscu E. Administration of B-group vitamins reduces circulating homocysteine in polycystic ovarian syndrome patients treated with metformin: a randomized trial. Hum Reprod 2005;20(6):1521–8.
38. Bahmani F, Karamali M, Shakeri H, Asemi Z. The effects of folate supplementation on inflammatory factors and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled clinical trial. Clin Endocrinol (Oxf) 2014;81(4):582–7.
39. Asemi Z, Karamali M, Esmaillzadeh A. Metabolic response to folate supplementation in overweight women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Mol Nutr Food Res 2014;58(7):1465–73.
40. Kennedy DO. B vitamins and the brain: mechanisms, dose and efficacy–a review. Nutrients 2016;8(2):68.
41. Loverro G, Lorusso F, Mei L, Depalo R, Cormio G, Selvaggi L. The plasma homocysteine levels are increased in polycystic ovary syndrome. Gynecol Obstet Invest 2002;53(3):157–62.
42. Badawy A, State O, El Gawad SSA, El Aziz OA. Plasma homocysteine and polycystic ovary syndrome: the missed link. Eur J Obstetr Gynecol Reprod Biol 2007;131(1):68–72.
43. Yarali H, Yildirir A, Aybar F, Kabakci G, Bukulmez O, Akgul E, Oto A. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. Fertil Steril 2001;76(3): 511–16.
44. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore) 2019;98(46):e17918.
45. Bartstra JW, Draaisma F, Zwakenberg SR, Lessmann N, Wolterink JM, van der Schouw YT, de Jong PA, Beulens JWJ. Six months vitamin K treatment does not affect systemic arterial calcification or bone mineral density in diabetes mellitus 2. Eur J Nutr 2021;60(3): 1691–9.
46. Zoch ML, Clemens TL, Riddle RC. New insights into the biology of osteocalcin. Bone 2016;82:42–9.
47. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, et al. Endocrine regulation of energy metabolism by the skeleton. Cell 2007;130(3):456–69.
48. Schwalfenberg GK. Vitamins K1 and K2: the emerging group of vitamins required for human health. J Nutr Metab 2017;2017:1.
49. Tarkesh F, Namavar Jahromi B, Hejazi N, Tabatabaee H. Beneficial health effects of menaquinone-7 on body composition, glycemic indices, lipid profile, and endocrine markers in polycystic ovary syndrome patients. Food Sci Nutr 2020;8(10):5612–21.
50. Karamali M, Ashrafi M, Razavi M, Jamilian M, Akbari M, Asemi Z. The effects of calcium, vitamins D and K co-supplementation on markers of insulin metabolism and lipid profiles in vitamin D-deficient women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2017;125(05):316–21.
51. Razavi M, Jamilian M, Karamali M, Bahmani F, Aghadavod E, Asemi Z. The effects of vitamin D-K-calcium co-supplementation on endocrine, inflammation, and oxidative stress biomarkers in vitamin D-deficient women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Horm Metab Res 2016;48(07):446–51.
52. Palamanda JR, Kehrer JP. Involvement of vitamin E and protein thiols in the inhibition of microsomal lipid peroxidation by glutathione. Lipids 1993;28(5):427–31.
53. Wang XL, Rainwater DL, Mahaney MC, Stocker R. Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. Am J Clin Nutr 2004;80(3):649–55.
54. Cicek N, Eryilmaz OG, Sarikaya E, Gulerman C, Genc Y. Vitamin E effect on controlled ovarian stimulation of unexplained infertile women. J Assist Reprod Genet 2012;29(4):325–8.
55. Izadi A, Ebrahimi S, Shirazi S, Taghizadeh S, Parizad M, Farzadi L, Gargari BP. Hormonal and metabolic effects of coenzyme Q10

and/or vitamin E in patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2019;104(2):319–27.
56. Ebrahimi FA, Samimi M, Foroozanfard F, Jamilian M, Akbari H, Rahmani E, Ahmadi S, Taghizadeh M, Memarzadeh MR, Asemi Z. The effects of omega-3 fatty acids and vitamin E co-supplementation on indices of insulin resistance and hormonal parameters in patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Exp Clin Endocrinol Diabetes 2017;125(06):353–9.
57. Chen J, Guo Q, Pei YH, Ren QL, Chi L, Hu RK, Tan Y. Effect of a short-term vitamin E supplementation on oxidative stress in infertile PCOS women under ovulation induction: a retrospective cohort study. BMC Women's Health 2020;20(1):69.
58. Hahn S, Backhaus M, Broecker-Preuss M, Tan S, Dietz T, Kimmig R, Schmidt M, Mann K, Janssen OE. Retinol-binding protein 4 levels are elevated in polycystic ovary syndrome women with obesity and impaired glucose metabolism. Eur J Endocrinol 2007;157(2): 201–7.
59. Tan BK, Chen J, Lehnert H, Kennedy R, Randeva HS. Raised serum, adipocyte, and adipose tissue retinol-binding protein 4 in overweight women with polycystic ovary syndrome: effects of gonadal and adrenal steroids. J Clin Endocrinol Metab 2007;92(7):2764–72.
60. Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and metabolic syndrome: a review. Phytother Res 2021;35(10)5352–64.
61. Oh JS, Ahn MJ, Han CJ, Kim H, Kwon O, Chung HW, Chang N. Relationship between flavonoids intake and metabolic syndrome in Korean women with polycystic ovary syndrome. J Nutr Health 2014;47(3):176–85.
62. Romualdi D, Constantini B, Campagna G, Lanzone A, Guido M. Is there a role for soy isoflavones in the therapeutic approach to polycystic ovary syndrome? Results from a pilot study. Fertil Steril 2008;90(5):1826–33.
63. Pourteymour Fard Tabrizi F, Hajizadeh-Sharafabad F, Vaezi M, Jafari-Vayghan H, Alizadeh M, Maleki V. Quercetin and polycystic ovary syndrome, current evidence and future directions: a systematic review. J Ovarian Res 2020;13(1):11.
64. Salehi B, Berkay Yilmaz Y, Antika G, Boyunegmez Tumer T, Fawzi Mahomoodally M, Lobine D, Akram M, Riaz M, Capanoglu E, Sharopov F, et al. Insights on the use of alpha-lipoic acid for therapeutic purposes. Biomolecules 2019;9(8):356.
65. Packer L, Cadenas E. Lipoic acid: energy metabolism and redox regulation of transcription and cell signaling. J Clin Biochem Nutr 2010;48(1):26–32.
66. Prieto-Hontoria PL, Perez-Matute P, Fernandez-Galilea M, Alfredo Martinez J, Moreno-Aliaga MJ. Effects of lipoic acid on AMPK and adiponectin in adipose tissue of low- and high-fat-fed rats. Eur J Nutr 2013;52(2):779–87.
67. Wang Y, Li X, Guo Y, Chan L, Guan X. alpha-Lipoic acid increases energy expenditure by enhancing adenosine monophosphate-activated protein kinase-peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling in the skeletal muscle of aged mice. Metabolism 2010;59(7):967–76.
68. Masharani U, Gjerde C, Evans JL, Youngren JF, Goldfine ID. Effects of controlled-release alpha lipoic acid in lean, nondiabetic patients with polycystic ovary syndrome. J Diabetes Sci Technol 2010;4(2):359–64.
69. Packer L, Kraemer K, Rimbach G. Molecular aspects of lipoic acid in the prevention of diabetes complications. Nutrition 2001;17(10): 888–95.
70. Haghighatdoost F, Hariri M. Does alpha-lipoic acid affect lipid profile? A meta-analysis and systematic review on randomized controlled trials. Eur J Pharmacol 2019;847:1–10.
71. Cianci A, Panella M, Fichera M, Falduzzi C, Bartolo M, Caruso S. d-chiro-Inositol and alpha lipoic acid treatment of metabolic and menses disorders in women with PCOS. Gynecol Endocrinol 2015;31(6): 483–6.
72. Vigerust NF, Bohov P, Bjorndal B, Seifert R, Nygard O, Svardal A, Glintborg D, Berge RK, Gaster M. Free carnitine and acylcarnitines in obese patients with polycystic ovary syndrome and effects of pioglitazone treatment. Fertil Steril 2012;98(6):1620–6.e1.
73. Bene J, Hadzsiev K, Melegh B. Role of carnitine and its derivatives in the development and management of type 2 diabetes. Nutr Diabetes 2018;8(1):8.
74. Fenkci SM, Fenkci V, Oztekin O, Rota S, Karagenc N. Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome. Hum Reprod 2008;23(7):1602–6.
75. Dunning KR, Robker RL. Promoting lipid utilization with l-carnitine to improve oocyte quality. Anim Reprod Sci 2012;134(1–2):69–75.
76. Ringseis R, Keller J, Eder K. Role of carnitine in the regulation of glucose homeostasis and insulin sensitivity: evidence from in vivo and in vitro studies with carnitine supplementation and carnitine deficiency. Eur J Nutr 2012;51(1):1–18.
77. Salehpour S, Nazari L, Hoseini S, Moghaddam PB, Gachkar L. Effects of L-carnitine on polycystic ovary syndrome. JBRA Assist Reprod 2019;23(4):392–5.
78. Expression of concern: oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial and the effects of coenzyme Q10 supplementation on gene expression related to insulin, lipid and inflammation in patients with polycystic ovary syndrome. Gynecol Endocrinol 2020:1. doi: 10.1080/09513590.2020.1841983.
79. Expression of concern: comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial and the effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. J Psychosom Obstet Gynaecol 2020;41(4):I.
80. Jamilian H, Jamilian M, Samimi M, Afshar Ebrahimi F, Rahimi M, Bahmani F, Aghababayan S, Kouhi M, Shahabbaspour S, Asemi Z. Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Gynecol Endocrinol 2017;33(6):442–7.
81. Ashoush S, Abou-Gamrah A, Bayoumy H, Othman N. Chromium picolinate reduces insulin resistance in polycystic ovary syndrome: randomized controlled trial. J Obstet Gynaecol Res 2016;42(3): 279–85.
82. Jamilian M, Asemi Z. Chromium supplementation and the effects on metabolic status in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Ann Nutr Metab 2015;67(1):42–8.
83. Jamilian M, Bahmani F, Siavashani MA, Mazloomi M, Asemi Z, Esmaillzadeh A. The effects of chromium supplementation on endocrine profiles, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2016;172(1): 72–8.
84. Jamilian M, Zadeh Modarres S, Amiri Siavashani M, Karimi M, Mafi A, Ostadmohammadi V, Asemi Z. The influences of chromium supplementation on glycemic control, markers of cardio-metabolic risk, and oxidative stress in infertile polycystic ovary syndrome women candidate for in vitro fertilization: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2018;185(1):48–55.
85. Fazelian S, Rouhani MH, Bank SS, Amani R. Chromium supplementation and polycystic ovary syndrome: a systematic review and meta-analysis. J Trace Elem Med Biol 2017;42:92–6.
86. Tang XL, Sun Z, Gong L. Chromium supplementation in women with polycystic ovary syndrome: systematic review and meta-analysis. J Obstet Gynaecol Res 2018;44(1):134–43.
87. Kadoura S, Alhalabi M, Nattouf AH. Effect of calcium and vitamin D supplements as an adjuvant therapy to metformin on menstrual cycle abnormalities, hormonal profile, and IGF-1 system in polycystic ovary syndrome patients: a randomized, placebo-controlled clinical trial. Adv Pharmacol Sci 2019;2019:9680390.
88. Panidis D, Balaris C, Farmakiotis D, Rousso D, Kourtis A, Balaris V, Katsikis I, Zournatzi V, Diamanti-Kandarakis E. Serum parathyroid

hormone concentrations are increased in women with polycystic ovary syndrome. Clin Chem 2005;51(9):1691–7.
89. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, Kimmig R, Mann K, Janssen OE. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2006;114(10):577–83.
90. Szczuko M, Skowronek M, Zapalowska-Chwyc M, Starczewski A. Quantitative assessment of nutrition in patients with polycystic ovary syndrome (PCOS). Rocz Panstw Zakl Hig 2016;67(4):419–26.
91. Ahn C, Kang JH, Jeung EB. Calcium homeostasis in diabetes mellitus. J Vet Sci 2017;18(3):261–6.
92. Gagnon C, Daly RM, Carpentier A, Lu ZX, Shore-Lorenti C, Sikaris K, Jean S, Ebeling PR. Effects of combined calcium and vitamin D supplementation on insulin secretion, insulin sensitivity and beta-cell function in multi-ethnic vitamin D-deficient adults at risk for type 2 diabetes: a pilot randomized, placebo-controlled trial. PLoS One 2014;9(10):e109607.
93. van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. Diabetes Care 2006;29(10): 2238–43.
94. Sun G, Vasdev S, Martin GR, Gadag V, Zhang H. Altered calcium homeostasis is correlated with abnormalities of fasting serum glucose, insulin resistance, and beta-cell function in the Newfoundland population. Diabetes 2005;54(11):3336–9.
95. Voznesenskaya A, Tordoff MG. Low-calcium diet prevents fructose-induced hyperinsulinemia and ameliorates the response to glucose load in rats. Nutr Metab 2015;12(1):38.
96. Cormick G, Belizan JM. Calcium intake and health. Nutrients 2019;11(7):1606.
97. Yim HE, Yoo KH. Renin-angiotensin system – considerations for hypertension and kidney. Electrolyte Blood Press 2008;6(1): 42–50.
98. Belizan JM, Villar J, Self S, Pineda O, Gonzalez I, Sainz E. The mediating role of the parathyroid gland in the effect of low calcium intake on blood pressure in the rat. Arch Latinoam Nutr 1984;34(4):666–75.
99. Christakos S, Dhawan P, Porta A, Mady LJ, Seth T. Vitamin D and intestinal calcium absorption. Mol Cell Endocrinol 2011;347(1–2): 25–9.
100. Foroozanfard F, Jamilian M, Bahmani F, Talaee R, Talaee N, Hashemi T, Nasri K, Asemi Z, Esmaillzadeh A. Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Clin Endocrinol (Oxf) 2015;83(6):888–94.
101. Maktabi M, Jamilian M, Asemi Z. Magnesium-zinc-calcium-vitamin D co-supplementation improves hormonal profiles, biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2018;182(1):21–8.
102. Pal L, Berry A, Coraluzzi L, Kustan E, Danton C, Shaw J, Taylor H. Therapeutic implications of vitamin D and calcium in overweight women with polycystic ovary syndrome. Gynecol Endocrinol 2012;28(12):965–8.
103. Shokrpour M, Asemi Z. The effects of magnesium and vitamin E co-supplementation on hormonal status and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. Biol Trace Elem Res 2019;191(1):54–60.
104. Shojaeian Z, Sadeghi R, Latifnejad Roudsari R. Calcium and vitamin D supplementation effects on metabolic factors, menstrual cycles and follicular responses in women with polycystic ocvary syndrome: a systematic review and meta-analysis. Caspian J Intern Med 2019;10(4):359–69.
105. Rodríguez-Morán M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects. Diabetes Care 2003;26(4):1147.
106. Hamilton KP, Zelig R, Parker AR, Haggag A. Insulin resistance and serum magnesium concentrations among women with polycystic ovary syndrome. Curr Dev Nutr 2019;3(11):nzz108.
107. Boyle NB, Lawton C, Dye L. The effects of magnesium supplementation on subjective anxiety and stress – a systematic review. Nutrients 2017;9(5):429.
108. Tinggi U. Selenium: its role as antioxidant in human health. Environ Health Prev Med 2008;13(2):102–8.
109. Qazi IH, Angel C, Yang H, Pan B, Zoidis E, Zeng CJ, Han H, Zhou GB. Selenium, selenoproteins, and female reproduction: a review. Molecules 2018;23(12):3053.
110. Mirone M, Giannetta E, Isidori AM. Selenium and reproductive function. A systematic review. J Endocrinol Invest 2013;36(10 Suppl):28–36.
111. Coskun A, Arikan T, Kilinc M, Arikan DC, Ekerbicer HC. Plasma selenium levels in Turkish women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2013;168(2):183–6.
112. Hajizadeh-Sharafabad F, Moludi J, Tutunchi H, Taheri E, Izadi A, Maleki V. Selenium and polycystic ovary syndrome; current knowledge and future directions: a systematic review. Horm Metab Res 2019;51(05):279–87.
113. Maret W. Zinc in cellular regulation: The nature and significance of "zinc signals" Prev Nutr Food Sci 2017;22(1):1–8.
114. Coulston L, Dandona P. Insulin-like effect of zinc on adipocytes. Diabetes 1980;29(8):665–7.
115. Haase H, Maret W. Intracellular zinc fluctuations modulate protein tyrosine phosphatase activity in insulin/insulin-like growth factor-1 signaling. Exp Cell Res 2003;291(2):289–98.
116. Guler I, Himmetoglu O, Turp A, Erdem A, Erdem M, Onan MA, Taskiran C, Taslipinar MY, Guner H. Zinc and homocysteine levels in polycystic ovarian syndrome patients with insulin resistance. Biol Trace Elem Res 2014;158(3):297–304.
117. Jamilian M, Foroozanfard F, Bahmani F, Talaee R, Monavari M, Asemi Z. Effects of zinc supplementation on endocrine outcomes in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2016;170(2): 271–8.
118. Nasiadek M, Stragierowicz J, Klimczak M, Kilanowicz A. The role of zinc in selected female reproductive system disorders. Nutrients 2020;12(8):2464.
119. Lindheim L, Bashir M, Munzker J, Trummer C, Zachhuber V, Leber B, Horvath A, Pieber TR, Gorkiewicz G, Stadlbauer V, et al. Alterations in gut microbiome composition and barrier function are associated with reproductive and metabolic defects in women with polycystic ovary syndrome (PCOS): a pilot study. PLoS One 2017;12(1): e0168390.
120. Torres PJ, Siakowska M, Banaszewska B, Pawelczyk L, Duleba AJ, Kelley ST, Thackray VG. Gut microbial diversity in women with polycystic ovary syndrome correlates with hyperandrogenism. J Clin Endocrinol Metab 2018;103(4):1502–11.
121. Shamasbi SG, Ghanbari-Homayi S, Mirghafourvand M. The effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indices in women with polycystic ovary syndrome: a systematic review and meta-analysis. Eur J Nutr 2020;59(2):433–50.
122. Liao D, Zhong C, Li C, Mo L, Liu Y. Meta-analysis of the effects of probiotic supplementation on glycemia, lipidic profiles, weight loss and C-reactive protein in women with polycystic ovarian syndrome. Minerva Med 2018;109(6):479–87.
123. Adriaens I, Jacquet P, Cortvrindt R, Janssen K, Smitz J. Melatonin has dose-dependent effects on folliculogenesis, oocyte maturation capacity and steroidogenesis. Toxicology 2006;228(2–3):333–43.
124. Tamura H, Nakamura Y, Korkmaz A, Manchester LC, Tan DX, Sugino N, Reiter RJ. Melatonin and the ovary: physiological and pathophysiological implications. Fertil Steril 2009;92(1):328–43.
125. Wei D, Zhang C, Xie J, Song X, Yin B, Liu Q, Hu L, Hao H, Geng J, Wang P. Supplementation with low concentrations of melatonin improves nuclear maturation of human oocytes in vitro. J Assist Reprod Genet 2013;30(7):933–8.

126. Sirotkin AV, Schaeffer HJ. Direct regulation of mammalian reproductive organs by serotonin and melatonin. J Endocrinol 1997;154(1):1–5.
127. Raygan F, Ostadmohammadi V, Bahmani F, Reiter RJ, Asemi Z. Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: a randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38(1):191–6.
128. Hu KL, Ye X, Wang S, Zhang D. Melatonin application in assisted reproductive technology: a systematic review and meta-analysis of randomized trials. Front Endocrinol 2020;11:160.
129. Al-Q HI. Effect of melatonin supplementation on serum LH level and BMI in women with polycystic ovary syndrome. J Pharm Sci Res 2018;10(1):1–4.
130. Tagliaferri V, Romualdi D, Scarinci E, Cicco S, Florio CD, Immediata V, Tropea A, Santarsiero CM, Lanzone A, Apa R. Melatonin treatment may be able to restore menstrual cyclicity in women with PCOS: a pilot study. Reprod Sci 2018;25(2):269–75.
131. Jamilian M, Foroozanfard F, Mirhosseini N, Kavossian E, Aghadavod E, Bahmani F, Ostadmohammadi V, Kia M, Eftekhar T, Ayati E, et al. Effects of melatonin supplementation on hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome. Front Endocrinol 2019;10:273.
132. Thakker D, Raval A, Patel I, Walia R. N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Obstet Gynecol Int 2015;2015:817849.
133. Poudyal H, Panchal SK, Diwan V, Brown L. Omega-3 fatty acids and metabolic syndrome: effects and emerging mechanisms of action. Prog Lipid Res 2011;50(4):372–87.
134. Shahnazi V, Zaree M, Nouri M, Mehrzad-Sadaghiani M, Fayezi S, Darabi M, Khani S, Darabi M. Influence of omega-3 fatty acid eicosapentaenoic acid on IGF-1 and COX-2 gene expression in granulosa cells of PCOS women. Iran J Reprod Med 2015;13(2):71–8.
135. Yang K, Zeng L, Bao T, Ge J. Effectiveness of omega-3 fatty acid for polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biol Endocrinol 2018;16(1):27.
136. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-inflammatory action and mechanisms of resveratrol. Molecules (Basel, Switzerland) 2021;26(1):229.
137. Shojaei-Zarghani S, Rafraf M. Resveratrol and markers of polycystic ovary syndrome: a systematic review of animal and clinical studies. Reprod Sci 2021. doi: 10.1007/s43032-0.
138. Amin MM, Asaad GF, Abdel Salam RM, El-Abhar HS, Arbid MS. Novel coq10 antidiabetic mechanisms underlie its positive effect: modulation of insulin and adiponectine receptors, tyrosine kinase, PI3K, glucose transporters, sRAGE and visfatin in insulin resistant/diabetic rats. PLoS One 2014;9(2):e89169.
139. Martelli A, Testai L, Colletti A, Cicero AFG. Coenzyme Q(4): clinical applications in cardiovascular diseases. Antioxidants 2020;9(4):341.
140. Samimi M, Zarezade Mehrizi M, Foroozanfard F, Akbari H, Jamilian M, Ahmadi S, Asemi Z. The effects of coenzyme Q10 supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf) 2017;86(4):560–6.
141. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest 2013;123(7):2764–72.
142. Mani UV, Mani I, Biswas M, Kumar SN. An open-label study on the effect of flax seed powder (*Linum usitatissimum*) supplementation in the management of diabetes mellitus. J Diet Suppl 2011;8(3): 257–65.
143. Haidari F, Banaei-Jahromi N, Zakerkish M, Ahmadi K. The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial. Nutr J 2020;19(1):8.
144. Hou C, Zhang W, Li J, Du L, Lv O, Zhao S, Li J. Beneficial effects of pomegranate on lipid metabolism in metabolic disorders. Mol Nutr Food Res 2019;63(16):1800773.
145. Rom O, Korach-Rechtman H, Hayek T, Danin-Poleg Y, Bar H, Kashi Y, Aviram M. Acrolein increases macrophage atherogenicity in association with gut microbiota remodeling in atherosclerotic mice: protective role for the polyphenol-rich pomegranate juice. Arch Toxicol 2017;91(4):1709–25.
146. Esmaeilinezhad Z, Barati-Boldaji R, Brett NR, de Zepetnek JOT, Bellissimo N, Babajafari S, Sohrabi Z. The effect of synbiotics pomegranate juice on cardiovascular risk factors in PCOS patients: a randomized, triple-blinded, controlled trial. J Endocrinol Invest 2020;43(4):539–48.
147. Esmaeilinezhad Z, Babajafari S, Sohrabi Z, Eskandari MH, Amooee S, Barati-Boldaji R. Effect of synbiotic pomegranate juice on glycemic, sex hormone profile and anthropometric indices in PCOS: a randomized, triple blind, controlled trial. Nutr Metab Cardiovasc Dis 2019;29(2):201–8.
148. Martinez-Garcia MA, Luque-Ramirez M, San-Millan JL, Escobar-Morreale HF. Body iron stores and glucose intolerance in premenopausal women: role of hyperandrogenism, insulin resistance, and genomic variants related to inflammation, oxidative stress, and iron metabolism. Diabetes Care 2009;32(8):1525–30.
149. Escobar-Morreale HF. Iron metabolism and the polycystic ovary syndrome. Trends Endocrinol Metab 2012;23(10):509–15.
150. Luque-Ramirez M, Alvarez-Blasco F, Botella-Carretero JI, Sanchon R, San Millan JL, Escobar-Morreale HF. Increased body iron stores of obese women with polycystic ovary syndrome are a consequence of insulin resistance and hyperinsulinism and are not a result of reduced menstrual losses. Diabetes Care 2007;30(9):2309–13.
151. Medagama AB. The glycaemic outcomes of cinnamon, a review of the experimental evidence and clinical trials. Nutr J 2015;14(1):108.
152. Heydarpour F, Hemati N, Hadi A, Moradi S, Mohammadi E, Farzaei MH. Effects of cinnamon on controlling metabolic parameters of polycystic ovary syndrome: a systematic review and meta-analysis. J Ethnopharmacol 2020;254:112741.
153. Ong M, Peng J, Jin XL, Qu XQ. Chinese herbal medicine for the optimal management of polycystic ovary syndrome. Am J Chin Med 2017;45(03):405–22.
154. Chang C-C, Yuan W, Lin Y-L, Liu R-S, Juan Y-C, Sun W-H, Tsay HJ, Huang H-C, Lee Y-C, Liu H-K. Evaluation of the in vivo therapeutic effects of radix paeoniae rubra ethanol extract with the hypoglycemic activities measured from multiple cell-based assays. Evid Based Complement Alternat Med 2016;2016:3262790.
155. Zhou K, Zhang J, Xu L, Wu T, Lim CE. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database Syst Rev 2016;10(10):CD007535.
156. Zhang D-W, Fu M, Gao S-H, Liu J-L. Curcumin and diabetes: a systematic review. Evid Based Complement Alternat Med 2013;2013:636053.
157. Heshmati J, Moini A, Sepidarkish M, Morvaridzadeh M, Salehi M, Palmowski A, Mojtahedi MF, Shidfar F. Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Phytomedicine 2021;80:153395.
158. Sohaei S, Amani R, Tarrahi MJ, Ghasemi-Tehrani H. The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled clinical trial. Complement Ther Med 2019;47:102201.
159. Ghowsi M, Yousofvand N, Moradi S. Effects of *Salvia officinalis* L. (common sage) leaves tea on insulin resistance, lipid profile, and oxidative stress in rats with polycystic ovary: an experimental study. Avicenna J Phytomed 2020;10(3):263–72.
160. Amini L, Mojab F, Jahanfar S, Sepidarkish M, Raoofi Z, Maleki-Hajiagha A. Efficacy of *Salvia officinalis* extract on the prevention of insulin resistance in euglycemic patients with polycystic ovary syndrome: a double-blinded placebo-controlled clinical trial. Complement Ther Med 2020;48:102245.
161. Badgujar SB, Patel VV, Bandivdekar AH. . Biomed Res Int 2014;2014:842674.

162. 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;39(5): 652–8.
163. Sadeghi Ataabadi M, Alaee 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;7(4):651–4.
164. Chen Z-T, Chu H-L, Chyau C-C, Chu C-C, Duh P-D. Protective effects of sweet orange (*Citrus sinensis*) peel and their bioactive compounds on oxidative stress. Food Chem 2012;135(4):2119–27.
165. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale roscoe*): a review of recent research. Food Chem Toxicol 2008;46(2):409–20.
166. 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;9(6):215.
167. Zhang RQ, Tan J, Li FY, Ma YH, Han LX, Yang XL. Acupuncture for the treatment of obesity in adults: a systematic review and meta-analysis. Postgrad Med J 2017;93(1106):743–51.
168. Richards D, Marley J. Stimulation of auricular acupuncture points in weight loss. Aust Fam Physician 1998;27 Suppl 2:S73–7.
169. Li H, Zhang JB, Xu C, Tang QQ, Shen WX, Zhou JZ, Chen JD, Wang YP. Effects and mechanisms of auricular vagus nerve stimulation on high-fat-diet-induced obese rats. Nutrition 2015;31(11–12): 1416–22.
170. Firouzjaei A, Li G-C, Wang N, Liu W-X, Zhu B-M. Comparative evaluation of the therapeutic effect of metformin monotherapy with metformin and acupuncture combined therapy on weight loss and insulin sensitivity in diabetic patients. Nutr Diabetes 2016;6(5):e209.
171. Gucel F, Bahar B, Demirtas C, Mit S, Cevik C. Influence of acupuncture on leptin, ghrelin, insulin and cholecystokinin in obese women: a randomised, sham-controlled preliminary trial. Acupunct Med 2012;30(3):203–7.
172. Hsu CH, Wang CJ, Hwang KC, Lee TY, Chou P, Chang HH. The effect of auricular acupuncture in obese women: a randomized controlled trial. J Women's Health 2009;18(6):813–18.
173. Lin RT, Tzeng CY, Lee YC, Chen YI, Hsu TH, Lin JG, Chang SL. Acupoint-specific, frequency-dependent, and improved insulin sensitivity hypoglycemic effect of electroacupuncture applied to drug-combined therapy studied by a randomized control clinical trial. Evid Based Complement Alternat Med 2014;2014:371475.
174. Lin RT, Chen CY, Tzeng CY, Lee YC, Cheng YW, Chen YI, Ho WJ, Cheng JT, Lin JG, Chang SL. Electroacupuncture improves glucose tolerance through cholinergic nerve and nitric oxide synthase effects in rats. Neurosci Lett 2011;494(2):114–18.
175. Lin RT, Tzeng CY, Lee YC, Ho WJ, Cheng JT, Lin JG, Chang SL. Acute effect of electroacupuncture at the Zusanli acupoints on decreasing insulin resistance as shown by lowering plasma free fatty acid levels in steroid-background male rats. BMC Complement Altern Med 2009;9(1):26.
176. Liang F, Koya D. Acupuncture: is it effective for treatment of insulin resistance? Diabetes Obes Metab 2010;12(7):555–69.
177. Peplow PV, Baxter GD. Electroacupuncture for control of blood glucose in diabetes: literature review. J Acupunct Meridian Stud 2012;5(1):1–10.
178. Wang F, Tian DR, Han JS. Electroacupuncture in the treatment of obesity. Neurochem Res 2008;33(10):2023–7.
179. Stener-Victorin E, Jedel E, Manneras L. Acupuncture in polycystic ovary syndrome: current experimental and clinical evidence. J Neuroendocrinol 2008;20(3):290–8.
180. Stener-Victorin E, Fujisawa S, Kurosawa M. Ovarian blood flow responses to electroacupuncture stimulation depend on estrous cycle and on site and frequency of stimulation in anesthetized rats. J Appl Physiol (Bethesda, MD: 2006) 2006;101(1):84–91.
181. Wu J, Chen D, Liu N. Effectiveness of acupuncture in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2020;99(22):e20441.
182. Qu F, Wu Y, Hu X-Y, Barry JA, Zhou J, Wang F-F, Ye Y-H, Zhang R, Han S-P, Han J-S, et al. The effects of acupuncture on polycystic ovary syndrome: a systematic review and meta-analysis. Eur J Integr Med 2016;8(1):12–18.
183. Monro R. Yoga therapy. J Bodyw Mov Ther 1997;1(4):215–18.
184. De Michelis E. A History of Modern Yoga: Patanjali and Western Esotericism. London, UK: A&C Black; 2005.
185. Shele G, Genkil J, Speelman D. A systematic review of the effects of exercise on hormones in women with polycystic ovary syndrome. J Funct Morphol Kinesiol 2020;5(2):35.
186. Verma A, Upadhyay V, Saxena V. Effect of yoga therapy on health outcomes in women with polycystic ovary syndrome: a systematic review and meta-analysis. Am J Lifestyle Med 2021. doi:10.1177/15598276211029221.
187. Thakur D, Saurabh Singh DS, Tripathi DM, Lufang D. Effect of yoga on polycystic ovarian syndrome: a systematic review. J Bodyw Mov Therap 2021;27:281–6.
188. Mohseni M, Eghbali M, Bahrami H, Dastaran F, Amini L. Yoga effects on anthropometric indices and polycystic ovary syndrome symptoms in women undergoing infertility treatment: a randomized controlled clinical trial. Evid Based Complement Alternat Med 2021;2021:5564824.
189. Selvaraj V, Vanitha J, Dhanaraj FM, Sekar P, Babu AR. Impact of yoga and exercises on polycystic ovarian syndrome risk among adolescent schoolgirls in South India. Health Sci Rep 2020;3(4):e212.
190. Kabat-Zinn J, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. J Behav Med 1985;8(2):163–90.
191. Carriere K, Khoury B, Gunak MM, Knauper B. Mindfulness-based interventions for weight loss: a systematic review and meta-analysis. Obesity 2018;19(2):164–77.
192. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. J Alternat Complement Med 2009;15(5):593–600.
193. Strauss C, Cavanagh K, Oliver A, Pettman D. Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. PLoS One 2014;9(4):e96110.
194. Stefanaki C, Bacopoulou F, Livadas S, Kandaraki A, Karachalios A, Chrousos GP, Diamanti-Kandarakis E. Impact of a mindfulness stress management program on stress, anxiety, depression and quality of life in women with polycystic ovary syndrome: a randomized controlled trial. Stress (Amsterdam, Netherlands) 2015;18(1):57–66.
195. Raja-Khan N, Agito K, Shah J, Stetter CM, Gustafson TS, Socolow H, Kunselman AR, Reibel DK, Legro RS. Mindfulness-based stress reduction in women with overweight or obesity: a randomized clinical trial. Obesity (Silver Spring, Md) 2017;25(8):1349–59.
196. Therapeutic Research Center. Natural Medicines. Somerville, MA: Therapeutic Research Center; 2021.
197. Gupta RC, Chang D, Nammi S, Bensoussan A, Bilinski K, Roufogalis BD. Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications. Diabetol Metab Syndr 2017;9:59.