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REVIEW

Clinical and Biochemical Potential of Antioxidants in Treating Polycystic Ovary Syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is the most common cause of infertility in reproductive-age women. Increased reactive oxygen species levels and decreased antioxidant capacity in PCOS patients can lead to metabolic disorders and damage the ovarian tissues, resulting in the occurrence of related symptoms. Antioxidants have been used in the treatment of PCOS and have yielded satisfactory outcomes due to their ability to counter oxidative stress. Many experiments on PCOS patients have proved that antioxidants can not only improve the ovarian environment, promote follicular maturation, and elevate oocyte quantities but can also regulate lipid and glucose metabolism as well as vascular endothelial cell function in PCOS patients, thereby attenuating adiposity and reducing the occurrence rate of chronic complications to ensure that patients can obtain long-term benefits. This review describes the use of antioxidants in PCOS, which have been used in the treatment.

Keywords: PCOS, oxidative stress, antioxidants, α-lipoic acid

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disease that affects 5–10% of reproductive-age females.[1] It is characterized by irregular menses, anovulatory infertility, and hyperandrogenism, accompanied by metabolic abnormalities, such as obesity, insulin resistance (IR), hyperinsulinemia, dyslipidemia, and glucometabolic disorders. Currently, the primary treatment strategies for PCOS are lifestyle changes and medications,[2] which help control weight, induce ovulation, reduce IR, regulate the menstrual cycle, and reduce serum androgen levels.[3] Clomiphene citrate (CC), metformin, ethinylestradiol, and cyproterone are among the traditional drugs used for PCOS treatment. However, these drugs may induce numerous adverse effects, including ovarian hyperstimulation syndrome (OHSS), gastrointestinal side effects, abnormal glucose and lipid metabolism, mental disorder, hair loss, vision loss, and allergic dermatitis.[4–6] In addition, they may not substantially improve IR and metabolic disorders when used as a single therapy,[7] requiring them to be combined with other treatment agents.

Although the pathophysiology of PCOS is quite complex,[8] there is increasing evidence that oxidative stress (OS) is involved in its pathogenesis. Many studies have shown that the levels of OS markers are elevated in PCOS patients.[14,15] There are also indications that genetic variability in gene coding for antioxidant enzymes modifies the risk of PCOS.[9] In addition, OS in PCOS patients possibly enhance the risk of long-term complications, such as type 2 diabetes (T2DM) and endometrial cancer.[9] This article therefore summarizes the relationship between OS and PCOS, and explores the application of antioxidants as treatment, with the aim of providing an effective reference for new drug research and development and for the clinical treatment of PCOS.

OS in PCOS

OS is an expression used to describe various deleterious processes resulting from an imbalance between the excessive formation of reactive oxygen species (ROS) and/or reactive nitrogen species and limited antioxidant defenses.[10] The data collected by Herman et al indicate that genetic variability in gene coding for antioxidant enzymes not only modifies the

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risk of PCOS but also influences the metabolic characteristics of PCOS patients.[11] Malondialdehyde (MDA) is a decomposition product of peroxidized polyunsaturated fatty acids, used as a biological marker for OS.[12,13] Bannigida et al[14] determined serum MDA, CRP, insulin levels, along with IR in 100 women diagnosed with PCOS (50 obese and 50 non-obese), and found that women with PCOS had higher CRP and MDA levels than their respective controls did, irrespective of whether they were obese or not. In addition, Özer et al[15] found that PCOS patients have high MDA levels, low antioxidant indices, such as low zinc serum levels, and catalase activity, appearing to be more pronounced in patients with IR and infertility. Total antioxidant status (TAOS), which is defined as the ability of plasma/serum to inhibit free radical production, is a cumulative index of plasma antioxidant status and carbonyl content and should be considered when evaluating the effects of OS on the risk of developing cardiovascular diseases in women with PCOS.[16] The presence of carbonyl groups in proteins has been used as a marker of ROS-mediated protein oxidation.[17] In a study by Fenkci et al,[16] which included 30 women with PCOS and 31 healthy women, the TAOS was significantly lower in women with PCOS than that in healthy women, and that protein carbonyl levels were significantly higher in women with PCOS than those in healthy women, which indicated that these proteins were attacked by ROS.[16] Moreover, they found that high-density lipoprotein levels were inversely associated with protein carbonyl levels; this led them to the speculation that increased OS and decreased antioxidant capacity may increase the risk of cardiovascular disease in women with PCOS.[16] Chattopadhayay et al[18] examined 326 oocytes from 35 women with PCOS (group A) and 208 oocytes from 32 women with tubal infertility (group B) for meiotic spindles using PolScope. They found that the number of oocytes, which failed to form spindles and OS markers, was significantly higher in group A than those in group B.[18] Furthermore, fertilization rate, the number of good-quality embryos, and clinical pregnancy rates were lower in group A than they were in group B; however, these differences were not statistically significant.[18] Thus, they showed that oocyte development could be affected by increased OS, as high follicular fluid (FF) ROS levels tended to decrease the fertilization potential of oocytes, consequently lowering pregnancy rates.[18] The studies by Yalcinkaya et al[19] and Calonge et al[20] have shown that imbalance between oxidant and antioxidant levels in the ovary may not only reduce ovarian reserve and oocyte quality but also have a negative impact on placental growth. In summary, in PCOS patients, ROS production increases, whereas antioxidant capacity decreases, and this may have adverse effects on ovarian function and body metabolism.

Antioxidants in PCOS

Alpha Lipoic Acid (ALA)

ALA, 1, 2-dithiolane-3-pentanoic acid, which has been termed "the universal antioxidant," is one of the most powerful natural antioxidants.[21] LA is an essential cofactor for the pyruvate dehydrogenase complex, and belongs to the class of metabotropic antioxidants, with both its oxidized (disulfide) and reduced (di-thiol: dihydro-lipoic acid) forms showing antioxidant activity.[22,23] In addition, LA lowers blood glucose levels by enhancing the expression of glucose transporter 4 (GLUT-4), which can initiate glucose transport.[24]

Masharani et al[25] administered 600 mg of controlled-release LA (CRLA) twice daily to six lean, nondiabetic PCOS patients, and the subjects did not develop any adverse reactions to LA over the study period. At the end of 16 weeks, they found a decrease in triglyceride levels and shift in the distribution of low-density lipoprotein (LDL) particles toward the larger, more buoyant LDL subclass fraction, thus decreasing the proportion of LDL-4, which is the most atherogenic of all LDL subfractions.[25] Therefore, it was hypothesized that CRLA may have a significant anti-atherogenic effect in PCOS patients.[25] In addition, there was a significant improvement in insulin sensitivity as determined by the euglycemic hyperinsulinemic clamp technique, and two subjects who were not on oral contraception had an increased frequency of menstrual cycles.[25] Based on these findings, they hypothesized that improvements in insulin sensitivity may be associated with better reproductive capacity, and that CRLA may be useful in normalizing menstrual cycles in women with PCOS.[25] In a study by Ivanova et al,[26] 45 PCOS patients were randomly allocated to an LA (n = 25) or high-protein diet (n = 20) group. Patients in the experimental group received one tablet of ALA (Thioctacid-HR) 30 minutes before breakfast, and after 3 months of intervention. A considerable decrease in basal and/or glucose-stimulated hyperinsulinemia as well as in IR index was observed in patients who received ALA as compared to those who received the high-

protein diet.[26] Furthermore, 16 (64%) patients in the ALA group with amenorrhea had their menstruation induced, developed dominant follicles, and the average ovarian volume was normalized.[26] Another study by Genazzani et al[27] also showed that low-dose integrative administration of ALA could improve insulin sensitivity in obese PCOS patients. In addition, PCOS patients with diabetic relatives showed decreased triglyceride and glutamic oxaloacetic transaminase levels, suggesting that the integrative administration of ALA improved metabolic impairment, especially in those with familial diabetes, who are potentially at high risk of developing non-alcoholic fatty liver disease and have a greater predisposition to diabetes.[27] Based on the findings of these studies, ALA therapy is efficacious in both obese and non-obese PCOS patients, delaying the onset of complications, such as atherosclerosis and chronic liver injury.[27] It is hence expected that ALA may be the drug of choice for the treatment of PCOS and hyperinsulinemia accompanied by liver disease (hepatitis, cirrhosis, and decompensated steatosis).[26]

LA and inositol can act on GLUT-4 synergistically. Genazzani et al[28] and Fruzzetti et al[29,30] administered ALA doses of 400 mg/day, 800 mg/day, and 600 mg/day in combination with inositol were administered to PCOS patients and found that the efficacy of the therapeutic combination was superior to that of the individual molecules; however, their optimal doses need to be determined by further research.

Vitamin C and Vitamin E

Vitamin E (α-tocopherol), which is a lipid-soluble vitamin with antioxidant properties, can activate intracellular antioxidant enzymes known as "radical scavengers," thereby protecting the cell membrane from lipid peroxidation.[31,32] Vitamin C (L-ascorbic acid; VC), another potent antioxidant, acts as a cofactor in essential enzyme reactions, and is an important nutrient for the human body.[33] It elicits its antioxidant effects by directly reacting with aqueous peroxyl radicals or by indirectly restoring fat-soluble antioxidant vitamin levels.[34]

Olaniyan et al[35] evaluated the effects of vitamin C in a dehydroepiandrosterone (DHEA)-induced mouse PCOS model and found that there was a significant decrease in MDA and cytokine levels and an increase in antioxidant and metabolic enzyme levels in the DHEA and vitamin C co-treated group as compared to the cytokine and metabolic enzyme levels in the DHEA-treated group. In addition, histopathological analyses showed a reduction in the number of cystic and atretic ovaries, and a significant downregulation of androgen receptor mRNA gene expression, which confirms that vitamin C plays a protective role against DHEA-induced PCOS via its antioxidant effects.[35] Shirazi et al[36] enrolled 43 PCOS patients and randomized them into two groups, subjects in the vitamin E and placebo groups received 400 IU/day of vitamin E as alpha tocopheryl acetate (n = 22) and cellulose capsules (n = 21), respectively, for eight weeks. After adjusting for potential confounders, vitamin E supplementation significantly reduced body weight, fat mass, Ang-1 levels, the Ang-1/Ang-2 ratio, and vascular endothelial growth factor (VEGF) levels, thereby improving blood circulation in ovarian tissues and normalizing ovarian follicular growth and ovulation.[36] Clomiphene citrate (CC) is a commonly used ovulation-inducing drug, and OS plays a vital role in CC resistance.[37] In a study by Morsy et al[37] which included 60 PCOS patients, it was found that the patients who received vitamin E in addition to metformin and CC had higher clinical pregnancy rates, ovulation rates, and endometrial thickness than those who did not receive vitamin E. However, this trial did not support the hypothesis that vitamin E may increase ovulation and pregnancy rates in women with CC-resistant PCOS, but suggested that higher doses of vitamin E may be needed to enhance its effects.[37] Furthermore, combined treatment with vitamin E, ethinyl estradiol, and cyproterone or metformin has facilitated ovulation more effectively and induced higher pregnancy rates than their separate application.[38–41]

Coenzyme Q (CoQ_{10})

CoQ_{10}, also known as ubiquinone, plays an important role in cell energy supply and exhibits significant antioxidant activity.[42] In addition, it is a component of the electron-transport chain, and participates in cellular aerobic respiration and generating cellular energy in the form of ATP.[43]

In the study by Taghizadeh et al.[44] PCOS patients were randomized into two groups; subjects in group 1 (n = 22) received a 200 mg CoQ_{10} supplement tablet daily, while those in group 2 (n = 21) received a placebo tablet daily, over a period of eight weeks. They found that CoQ_{10} supplementation has a beneficial effect on inflammatory and endothelial dysfunction marker levels in overweight and obese PCOS patients, and therefore improves ovarian function.[44] Impaired

glucose tolerance and T2DM are common in women with PCOS. A study by Izadi et al[45] showed that supplementation with CoQ_{10} alone or in combination with vitamin E had considerable effects on fasting plasma glucose (FPG) and homeostasis model assessment-IR (HOMA-IR) as compared to those under the placebo treatment, whereas only co-supplementation affected sex hormone-binding globulin concentrations, which decreased total serum testosterone levels. In a meta-analysis, Liu et al[46] concluded that CoQ_{10} administration can significantly reduce FPG and HOMA-IR, and effectively improve glucose and lipid metabolism, inflammation, and sex hormone levels. Refaeey et al[47] evaluated the combined ovulation induction effects of oral CoQ_{10} and CC in CC-resistant PCOS patients through a prospective randomized controlled trial, and found that clinical pregnancy rate was significantly higher in the CoQ_{10} group than in the control group. The researchers concluded that CoQ_{10} could improve ovarian functions in CC-resistant PCOS and that in combination with CC was an effective and safe option to be considered before gonadotrophin therapy or laparoscopic ovarian drilling (LOD).[47] However, the appropriate CoQ_{10} dosage and the optimal duration of treatment need to be further investigated.

N-Acetylcysteine (NAC)

NAC is a safe and commonly used mucolytic drug; at high doses, it induces an increase in cellular antioxidant levels and reduces glutathione levels.[48]

In a study by Fulghesu et al,[49] 37 PCOS patients were treated for up to six weeks with oral NAC at a dose of 1.8 g/day, and a dose of 3 g/day was arbitrarily chosen for significantly obese subjects. They found that NAC was well tolerated by all patients and no adverse effects were observed.[49] At the end of the treatment, hyperinsulinemic subjects showed a significant increase in insulin sensitivity as well as a concomitant decrease in circulating insulin levels, which was followed by a significant reduction in T levels and free androgen index.[49] However, similar results were not obtained for normoinsulinemic subjects.[49] In addition, studies on the effects of insulin-sensitizing agents on lipidic patterns found a significant decrease in plasma lipid levels, including cholesterol, triglyceride, and LDL levels after NAC-mediated insulin-level reduction, indicating a possible additional benefit of this drug on long-term health outcomes in PCOS patients.[49–51] The efficacy of metformin in PCOS was compared with that of NAC by Chandil et al,[52] and they showed that NAC improved the clinical features of PCOS, IR biochemical marker levels, hormonal levels, and anovulation, in addition to the improved peripheral IR, more effectively than metformin did. Moreover, due to the absence of adverse effects, NAC can be regarded as an appropriate substitute for insulin sensitizer in the treatment of PCOS.[52] In a study by Cheraghi et al,[53] 60 women with PCOS who underwent intracytoplasmic sperm injection (ICSI) were divided into four groups and received either metformin (1500 mg/day), NAC (1800 mg/day), metformin + NAC, or a placebo for six weeks. They found that the number of immature and abnormal oocytes substantially decreased with a concomitant increase in the number of good-quality embryos in the NAC group as compared to that of the placebo group.[53] In addition, leptin, MDA, insulin, and LH levels were significantly lower in the NAC and NAC+MET groups.[53] In another study by Nasr et al.[54] NAC was administered as an adjunct therapy following unilateral LOD in women with CC-resistant PCOS, and they found a significant increase in ovulation, pregnancy, and live birth rates, indicating that NAC could be used as a novel adjunct therapeutic agent after unilateral LOD and may improve the overall reproductive outcome. Rizk et al[55] and Badawy et al[56] investigated the combined effects of NAC and clomiphene on PCOS and found that this combination helped increase pregnancy and ovulation rates and decreased OHSS rates compared with those after a single application. Sacchinelli et al[57] also found that the combination of NAC + Inositol + folic acid improved ovarian function in PCOS patients, regardless of IR state, indicating that inositol and NAC may have additional non-insulin-related mechanisms of action that could allow them to elicit beneficial effects in patients with negative HOMA-indices.

Resveratrol (RSV)

RSV, a polyphenolic compound, which is found in grapes, red wine, peanuts, and some berry species, is regarded as a powerful antioxidant with anti-Inflammatory, anti-coagulant, anti aging, and anti-cancer properties.[58] Its protective effects against oxidative injury are probably due to the upregulation of cellular antioxidant enzyme activity, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[59]

In a study by Ergenoglu et al,[60] a PCOS model was formed in 14 rats using subcutaneous dihydrotestosterone, and the rats were randomly divided into two groups, treated with 1 mL/kg/day of isotonic saline or 10 mg/kg/day of resveratrol. They found a significant decrease in antral follicle counts, plasma anti-Mullerian hormone, insulin-like growth factor 1 levels, and superoxide dismutase activity, and a significant increase in glutathione peroxidase content in the resveratrol treatment group, indicating that it could be effective in the treatment of PCOS due to its antioxidant properties.[60] IR in PCOS is associated with chronic low-grade inflammation. In a 3-month randomized controlled trial conducted by Banaszewska et al,[61] treatment with resveratrol resulted in lower serum levels of both T and DHEA in women with PCOS, while fasted insulin levels significantly decreased and insulin sensitivity was improved following RSV treatment.[61] Another study reported a significant downregulation of LH and total testosterone levels, as well as an upregulation of FSH and thyroid stimulating hormone levels in patients treated with RSV.[62] Therefore, RSV may be effective in increasing FSH levels by reducing steroid-derived androgen levels, thus facilitating follicular maturity and growth, and contributing to improving oocyte quality and better pregnancy outcomes.[62]

Melatonin

Melatonin is a tryptophan-derived molecule with pleiotropic activities; it is secreted from the pineal gland, with a circadian rhythm that peaks at night and is low during the day.[63,64] The original and primary function of melatonin in early life forms such as unicellular organisms was to serve as a free radical scavenger and an antioxidant with several unique features that differ from those of classic antioxidants, including the ability to undergo cascade reactions with free radicals, and capacity to be induced under moderate OS conditions.[64]

Basheer et al[65] observed a downregulation of melatonin (MT1 and MT2), estrogen (ER-α), and cytokine (IL-2R and IL-6R) receptor expression levels, and high circulation levels of IL-6 and TNF-α in female Wistar rats induced by letrozole; however, these alterations were reversed after melatonin treatment. In a study by Pai et al.[66] PCOS was induced in 21-day-old female rats by daily subcutaneous administration of testosterone (20 mg/kg) over a period of 35 d. The PCOS mice were administered metformin (500 mg/kg), 1 mg/kg of melatonin, or 2 mg/kg of melatonin, in combination with testosterone, over a period of 36 d.[66] Both doses of melatonin significantly reduced body weight, body mass index, intra-abdominal fat (IAF), and insulin and CRP levels; in addition, a favorable lipid profile was observed.[66] Moreover, histopathological examination of the ovary, uterus, and IAF tissues revealed a decrease in the number of cystic follicles, neoplastic endometrial glands, and adipocyte hypertrophy, respectively.[66] Jamilian et al[67] showed that melatonin administration to women with PCOS can significantly reduce hirsutism, total testosterone, high-sensitivity hs-CRP, and MDA levels, while increase TAC and GSH levels. In addition, melatonin administration was found to reduce IL-1 and TNF-α gene expression.[67] In a study by Tagliaferri et al,[68] after 6 months of melatonin administration in 40 normal-weight women with PCOS, menstrual irregularities and biochemical hyperandrogenism were improved, possibly through a direct insulin-independent effect on the ovaries. In a study by Shabani et al,[69] 58 subjects were randomized into two groups and were administered either 10 mg of melatonin or placebo once a day, 1 h before bedtime, for 12 weeks. They found that melatonin exhibited beneficial effects on mental health parameters, insulin levels, HOMA-IR, quantitative insulin sensitivity check index, total cholesterol and LDL-cholesterol levels, and gene expression of the peroxisome proliferator-activated receptor gamma (PPAR-γ) and the low-density lipoprotein receptor in women with PCOS, which indicated that melatonin supplementation may confer potential therapeutic advantages in women with PCOS.[69] Based on the finding that the addition of melatonin to IVM media improves cytoplasmic maturation in human immature oocytes and subsequent clinical outcomes, Kim et al[70] hypothesized that follicular melatonin may be released from luteinizing granulosa cells during late folliculogenesis, and that melatonin supplementation could hence be used to improve the clinical outcomes of in vitro maturation (IVM). Similarly, the findings by Mokhtari et al[71] showed that treating PCOS patients undergoing intrauterine insemination (IUI) with melatonin significantly improves the rate of chemical pregnancy. Kun Yu et al[72] showed that melatonin promoted CYP19A1 and HO-1 expression and decreased IL-18 levels in human ovarian GCs obtained from a patient with PCOS with hyperandrogenia, thereby facilitating oocyte maturation. Hence, melatonin supplementation could be beneficial for women with PCOS due to its effects on steroidogenesis, through which it regulates ovulation, reverses IR and dyslipidemia, prevents hyperplastic changes in the endometrium, and protects against endometrial cancer.[66]

Carnitine

Carnitine is a quaternary ammonium compound that can be synthesized from the two amino acids lysine and methionine.[73] It plays important roles in carbohydrate and lipid metabolism, and improves IR and depression states.[74,75]

In a study by Jamilian et al,[76] 60 patients diagnosed with PCOS were randomized into two groups to receive either 250 mg of carnitine supplements or a placebo for 12 weeks. They found that carnitine supplementation had favorable effects on mental health, which was judged with Beck Depression Inventory (BDI), General Health Questionnaire-28 (GHQ-28) and Depression Anxiety and Stress Scale (DASS) at the beginning and the end of study, and OS biomarker levels.[76] Tauqir et al[77] evaluated 147 women with PCOS for 12 weeks that were randomly assigned into a combo group (n = 72) that received a combination of metformin, pioglitazone (pio), and acetyl-L-Carnitine (ALC), or the Met + Pio group (n = 75) that received metformin plus pioglitazone and placebo. They concluded that addition of ALC to metformin plus pioglitazone further ameliorates IR, polycystic ovaries, and stress burden, along with normalization of regular menstrual cycles.[77] A study by Ismail et al[78] included a total of 170 women with clomiphene-resistant PCOS who were divided into two groups. Group (A) included patients who received 100 to 150 mg clomiphene citrate from day three until day seven of the cycle and L-carnitine (LC) 3 g daily until a positive pregnancy test; group (B) received 100 to 150 mg clomiphene citrate with a placebo. The results show that adding LC to clomiphene from the follicular phase and extending through the luteal phase in patients with clomiphene-resistant PCOS, at the given dose and duration, may benefit the quality of ovulation and clinical pregnancy rate.[78]

In general, as an antioxidant, carnitine can improve IR, ovulation, and even mental health in PCOS patients.

Other Antioxidants

Selenium is an essential trace element, which is essential for human biology and health.[79] In a study by Razavi et al,[79] 64 women with PCOS were randomized into two groups and received either 200 μg of selenium daily or a placebo. After eight weeks of intervention, patients who received selenium exhibited markedly decreased serum DHEA levels, hirsutism (modified Ferriman–Gallwey scores), serum hs-CRP levels, and plasma MDA levels compared to the levels of those who received the placebo.[79] In addition, selenium elicited beneficial effects on reproductive outcomes, which indicate that PCOS-related symptoms can be improved via the antioxidant effects of selenium.[79] Similar findings have been obtained for combined magnesium and zinc supplementation.[80] Jamilian et al[81] also reported that chromium administration in infertile women with PCOS, who were candidates for IVF, for eight weeks, had beneficial effects on glycemic control and OS. Various pharmacological studies have demonstrated that crocetin has a wide range of antioxidant, anti-cancer, hypolipidemic, and anti-atherosclerotic effects.[82] Hu et al[82] confirmed the attenuation of PCOS by crocetin in prenatal mice exposed to DHT. They suggested that the therapeutic effect of crocetin was likely due to the revise in kisspeptin expression in the anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC), serum levels of estradiol (E2), progesterone (P4), T, LH, and FSH, as well as the structural and functional changes in ovaries.[82] Furthermore, based on both experimental and analytical proof, Bahmani et al[83] concluded that folate supplementation (5 mg/d) in women with PCOS had beneficial effects on inflammatory factor and OS biomarker levels.

Conclusion

PCOS is the most common cause of anovulatory infertility in women of reproductive age. Antioxidants can not only improve OS and IR in PCOS patients but also improve the ovarian environment, reduce androgen levels, and promote follicular maturation. In addition, they can induce better outcomes when used in combination with traditional ovulation-inducing regimens and assisted reproductive technologies, effectively improving pregnancy outcomes. As endothelial dysfunction and dyslipidemia are early signs of cardiovascular disease, antioxidants can regulate lipid metabolism and vascular endothelial cell function in PCOS patients, thereby attenuating adiposity and reducing the occurrence rate of chronic complications. Moreover, some antioxidants, including carnitine and melatonin, can enhance the quality and psychological status of PCOS patients. The reviewed articles are summarized in Table 1. In summary, numerous antioxidants with significant beneficial effects and low adverse reaction rates can significantly improve the symptoms of PCOS and prevent or treat the long-term complications. Therefore, as a drug class with useful potential, antioxidant

Table 1 Characteristics of Included Articles

Study ID	PCOS Population	Intervention	Control	Duration	Observation Index
Masharani et al., 2010[25]	Lean patients	ALA (n=6)	N/A	16 weeks	Metabolic parameters menstrual cycles
Ivanova et al., 2015[26]	Average-weight patients	ALA (n=25)	High-protein diet (n=20)	12 weeks	Basal and/or glucose-stimulated metabolic parameters average ovarian volume menstrual cycles
Genazzani et al., 2018[27]	Obese patients	ALA (n=32)	N/A	12 weeks	Hormonal and metabolic parameters
Genazzani et al., 2019[28]	Overweight/obese patients	MI + ALA (n=56)	MI (n=48) ALA (n=48)	12 weeks	Hormonal and metabolic parameters
Fruzzetti et al., 2019[29]	Average-weight patients	MI + ALA (n=57)	N/A	24, 48, and 96 weeks	Menstrual cycles and histopathological evaluation Hormonal and metabolic parameters
Fruzzetti et al., 2018[30]	Average-weight patients	D-chiro-inositol + ALA (n=41)	Healthy subjects (n=30)	24 weeks	Menstrual cycle metabolic parameters
Olaniyan et al., 2019[35]	Rats	Vitamin C (n=7) DHEA (n=7) DHEA and Vitamin C (n=7)	Water (n=7)	15 d	Oxidative stress parameters cytokines hormonal parameters and histopathological evaluation
Shirazi et al., 2021[36]	Average-weight patients	Vitamin E (n=22)	Placebo (n=21)	8 weeks	Anthropometric indices serum angiogenic markers
Morsy et al., 2020[37]	Average-weight patients	Vitamin E + metformin + CC (n=30)	Metformin (n=30)	4 weeks	Hormonal parameters Ovulation frequency Pregnancy frequency histopathological evaluation
Taghizadeh et al., 2020[44]	Average-weight patients	CoQ10 (n=22)	Placebo tablet (n=21)	8 weeks	Inflammatory and endothelial dysfunction markers
Izadi et al., 2018[45]	Overweight/obese patients	CoQ_{10} + vitamin E placebo (n=22) vitamin E + CoQ_{10} placebo (n=22) CoQ_{10} + vitamin E (n=21)	CoQ_{10} placebo + vitamin E placebo (n=21)	8 weeks	Hormonal and metabolic parameters
Refaeey et al., 2014[47]	CC-resistant patients	CoQ_{10} +CC (n=51)	CC (n=50)	12 weeks	Hormonal parameters histopathological evaluation clinical pregnancy and miscarriage rates
Fulghesu et al., 2002[49]	Average-weight patients	NAC (n=31)	placebo (n=6)	5–6 weeks	Hormonal parameters metabolic parameters

(*Continued*)

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Table 1 (Continued).

Study ID	PCOS Population	Intervention	Control	Duration	Observation Index
Chandil et al., 2019[52]	Average-weight patients	NAC (n=45)	Metformin (n=45)	24 weeks	Hormonal parameters metabolic parameters
Cheraghi et al., 2016[53]	Average-weight patients	Metformin (n=15) NAC (n=15) metformin+NAC (n=15)	Placebo (n=15)	6 weeks	Histopathological evaluation Hormonal, oxidative stress, and metabolic parameters
Nasr et al., 2009[54]	CC-resistant patients	NAC (n=30)	Placebo (n=30)	5 d	Clinical and reproductive outcomes
Rizk et al., 2005[55]	CC-resistant patients	NAC (n=75)	Placebo (n=75)	5 d	Hormonal and metabolic parameters reproductive outcomes
Badawy et al., 2011[56]	Average-weight patients	NAC + CC (n=470)	CC (n=103)	5 d	Hormonal parameters the histopathological evaluation reproductive outcomes
Sacchinell et al., 2014[57]	Average-weight patients	NAC + Inositol + folic acid (n=91)	N/A	24 weeks/ 48 weeks	Hormonal and menstrual cycle metabolic parameters
Ergenoglu et al., 2015[60]	Rats	RSV (n=7)	Isotonic saline (n=7)	4 weeks	Oxidative stress parameters Hormonal parameters
Banaszewska et al., 2016[61]	Average-weight patients	RSV (n=17)	Placebo (n=17)	12 weeks	Hormonal parameters histopathological evaluation metabolic parameters
Bahramrezaie et al., 2019[62]	Average-weight patients	RSV (n=31)	Placebo (n=31)	40 d	Hormonal parameters histopathological evaluation *VEGF* & *HIF1* genes
Basheer et al., 2018[65]	Rats	Melatonin + letrozole	Letrozole	2–3 weeks	Hormonal parameters cytokine (IL-2R and IL-6R)
Pai et al., 2014[66]	Rats	Melatonin	Metformin	36 d	Hormonal and metabolic parameters anthropometrical and histopathological evaluation
Jamilian et al., 2019[67]	Average-weight patients	Melatonin (n=28)	Placebo (n=28)	12 weeks	Hormonal and Oxidative stress parameters cytokines
Tagliaferri et al,2018[68]	Average-weight patients	Melatonin (n=40)	Non	24 weeks	Hormonal parameters metabolic parameters menstrual cycles anthropometrical and histopathological evaluation
Shabani et al., 2019[69]	Average-weight patients	Melatonin (n=29)	Placebo (n=29)	12 weeks	Metabolic, Mental health and genetic parameters

Kim et al,2012[70]	Average-weight patients	Melatonin (n=21)	No melatonin (n=24)	2 days	Clinical outcomes of IVM IVF-embryo transfer
Mokhtari et al., 2019[71]	Average-weight patients	Melatonin (n=94)	Placebo (n=100)	10 d	Chemical pregnancy rates
Kun Yu et al., 2019[72]	Average-weight patients	Melatonin (n=15)	Non-melatonin (n=17)	16–18 hours	Hormonal parameters histopathological evaluation oxidative stress and inflammatory parameters
Jamilian et al., 2017[76]	Average-weight patients	Carnitine (n=30)	Placebo (n=30)	12 weeks	Mental health parameters oxidative stress biomarker levels
Tauqir et al., 2021[77]	Average-weight patients	Metformin + pioglitazone + acetyl-L-carnitine (n=75)	Metformin + pioglitazone + placebo (n=75)	12 weeks	Anthropometric, metabolic, and endocrine parameters stress score
Ismail et al., 2014[78]	Clomiphene-resistant patients	Clomiphene citrate + L-carnitine (n=85)	CC + placebo (n=85)	5 d	Clinical outcomes metabolic parameters
Razavi et al., 2016[79]	Average-weight patients	Selenium (n=32)	Placebo (n=32)	8 weeks	Clinical outcomes metabolic parameters hormonal parameters oxidative stress parameters
Afshar et al., 2018[80]	Average-weight patients	Magnesium oxide + zinc sulfate (n=30)	Placebo (n=30)	12 weeks	Metabolic parameters
Jamilian et al., 2018[81]	Average-weight patients	Chromium (n= 20)	Placebo (n=20)	8 weeks	Glycemic control cardio-metabolic risk markers oxidative stress parameters metabolic parameters
Hu Q et al., 2018[82]	Rats	Crocetin (n=28)	Vehicle (n=28)	8 weeks	Estrous cycle hormonal parameters histopathological evaluation hypothalamic kisspeptin and GnRH neurons
Bahmani et al., 2014[83]	Average-weight patients	Folate (1 mg/d) (n=23) folate (5 mg/d) (n=23)	Placebo (n=23)	8 weeks	Oxidative stress parameters metabolic parameters

Abbreviations: PCOS, polycystic ovary syndrome; ALA, alpha lipoic acid; MI, myo-inositol; DHEA, dehydroepiandrosterone; CC, clomiphene citrate; CoQ_{10}, coenzyme Q_{10}; NAC, N-acetyl cysteine; RSV, resveratrol; VEGF, vascular endothelial growth factor; HIF, hypoxia-inducible factor; GnRH, gonadotropin-releasing hormone; IL, interleukin.

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use in clinical settings should be encouraged following careful review of the Medical history and disease profile of each individual patient with PCOS. However, the potential of antioxidants in the treatment of PCOS remains to be further explored, such as the impact on pregnancy outcomes and offspring growth and development in women with PCOS pregnancy. Optimal dosage of various antioxidants also remains to be studied.

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Disclosure

The authors report no conflicts of interest for this work.

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