

Evidence-Based Nutritional Supplementation in Polycystic Ovary Syndrome: A Comprehensive Review of Clinical Outcomes, Mechanisms, and Recommendations

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a prevalent and multifactorial endocrine-metabolic disorder among women of reproductive age. Recent research indicates that nutritional supplementation may play a valuable adjunctive role in PCOS management, particularly in addressing metabolic, hormonal, and inflammatory disturbances. This review synthesizes evidence from randomized controlled trials and meta-analyses published up to 2024, evaluating the efficacy and safety of commonly used supplements such as myo-inositol, vitamin D, omega-3 fatty acids, selenium, and coenzyme Q10. The analysis demonstrates that several supplements can improve insulin sensitivity, lipid profiles, hormonal balance, and oxidative stress markers in women with PCOS. Mechanistic insights suggest these effects are mediated through the modulation of metabolic and inflammatory pathways, including AMPK, NF- κ B, PPAR- γ , and VDR.

Nevertheless, the heterogeneity of study designs, sample sizes, and a paucity of long-term safety data highlight the need for standardized protocols and further high-quality trials. Overall, nutritional supplements offer a promising strategy for personalized PCOS management, especially for women with insulin resistance or those seeking alternatives to conventional pharmacotherapy. Continued research into optimal dosing, duration, and co-supplementation effects will be essential to refine clinical recommendations and maximize patient outcomes. This is the most comprehensive synthesis, combining clinical outcomes with mechanistic insights across 13 key nutritional supplements in PCOS management.

Keywords. Polycystic Ovary Syndrome, Nutritional Supplements, Inositol, Omega-3 Fatty Acids, Coenzyme Q10, Vitamin D, Selenium, Insulin Resistance, Clinical Trials, Evidence-Based Review, Endocrine Metabolism

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a multifactorial endocrine-metabolic disorder that affects approximately 6–20% of women of reproductive age, depending on diagnostic criteria¹. It is characterized by hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology, often accompanied by insulin resistance,

dyslipidemia, and low-grade chronic inflammation². Due to its complex etiology and heterogeneous presentation, PCOS requires a multidisciplinary management approach³. While pharmacological treatments remain the standard of care, there is growing interest in adjunctive non-pharmacological strategies, including dietary and lifestyle modifications⁴. Various nutritional supplements have emerged as potential modulators of metabolic, hormonal, and inflammatory pathways involved in PCOS pathophysiology⁵. These supplements are thought to exert their effects through various mechanisms, including improving insulin sensitivity, reducing oxidative stress, and modulation of androgen production and inflammatory cytokine levels⁶. A comprehensive evaluation of these supplements within evidence-based frameworks is essential to guide their safe and effective integration into clinical practice⁷.

Supplements And Polycystic Ovary Syndrome

The treatment for polycystic ovary syndrome (PCOS) has focused on drugs that allow control over androgen production and insulin resistance. However, a comprehensive treatment is required, as it is a condition that can trigger various metabolic complications⁵. Traditionally, in PCOS, one of the main aspects to consider is hyperglycemia, as it can trigger type 2 diabetes mellitus, cardiovascular diseases, the production of inflammatory factors, and reactive oxygen species that cause oxidative stress and tissue damage⁵; Moreover, hyperandrogenism and insulin resistance significantly affect lipid metabolism in PCOS⁶. So, women with PCOS are prone to developing dyslipidemia⁷, which includes elevated concentrations of a variety of serum lipids but reduced levels of HDL cholesterol⁸. To date, various supplements have been used as part of the treatment and management of PCOS to achieve a better therapeutic response and reduce complications⁵. Next, we describe them:

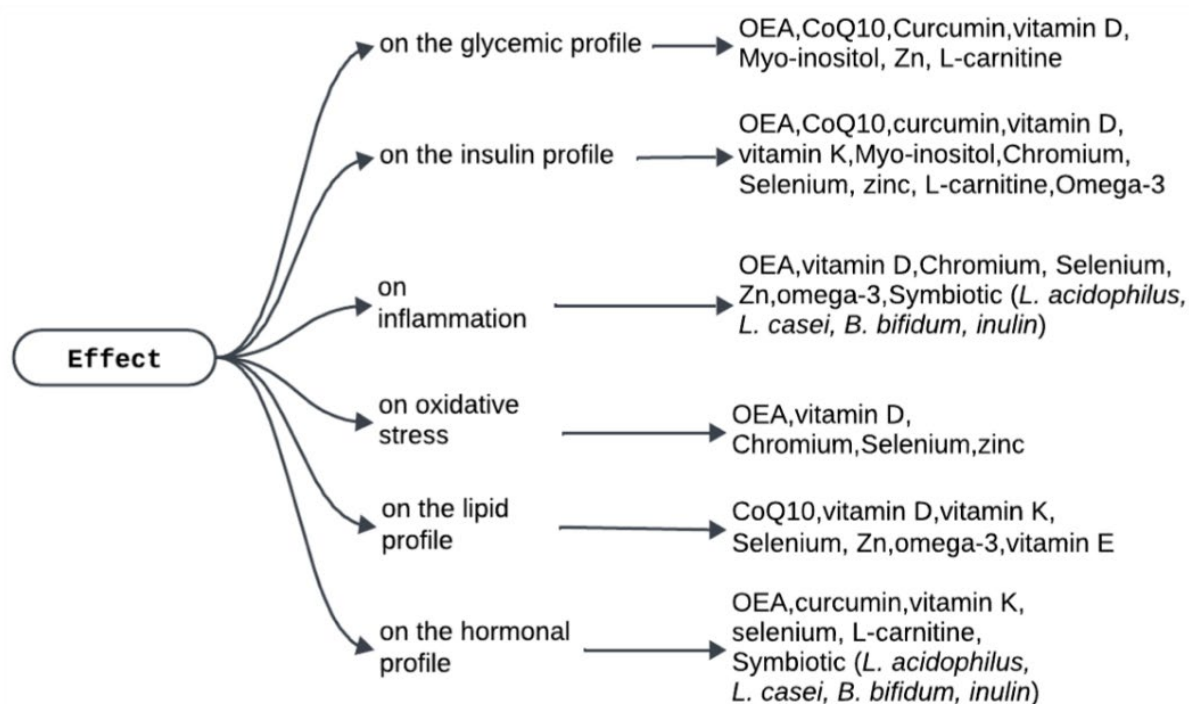


Figure 1. Represents the effect of various supplements on polycystic ovary syndrome. Five impact areas are identified: glyceimic profile, inflammation, oxidative stress, lipid profile, and hormonal profile, each linked to metabolic and endocrine alterations characteristic of PCOS. Within each category, supplements with therapeutic potential are listed.

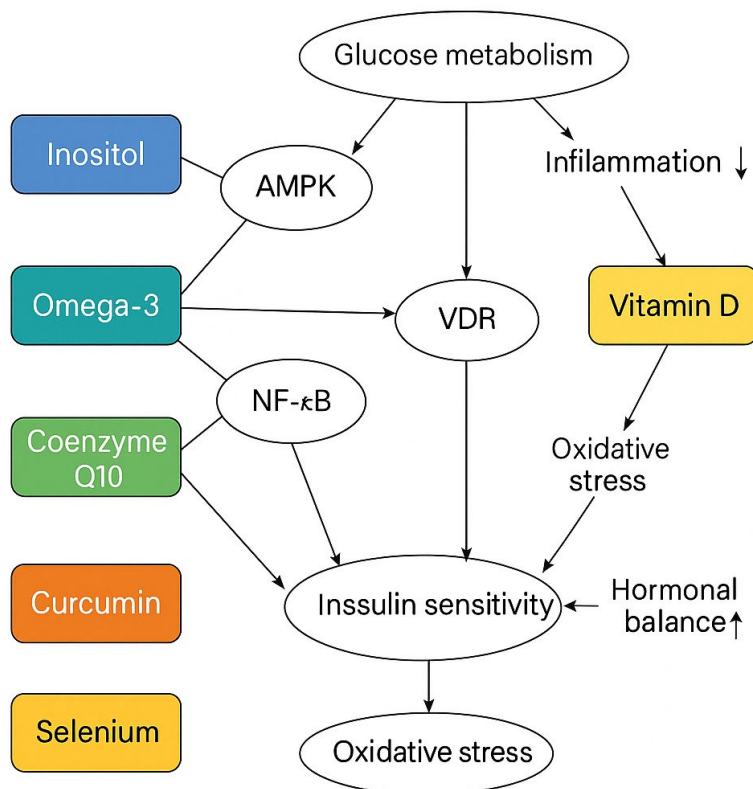


Figure 2. Mechanisms of action of dietary supplements in PCOS treatment.

A simplified schematic representation of the molecular and physiological pathways influenced by the main supplements reviewed. The illustration highlights their interaction with key metabolic and endocrine targets such as AMPK, PPAR- γ , NF- κ B, VDR, and oxidative stress markers. These mechanisms improve glucose metabolism, hormonal balance, and inflammation and reduce insulin resistance.

OLEOILETANOLAMIDE

Oleylethanolamide (OEA) is a lipid derived from oleic acid, possessing anti-inflammatory and antioxidant properties. It can be absorbed from the diet or synthesized by the human body from oleic acid⁵. Oral supplementation with OEA has been shown to influence the levels of Anti-Müllerian Hormone (AMH), fasting blood sugar (FBS), the Homeostasis Model Assessment for Insulin Resistance (HOMA IR), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP), significantly decreasing their serum concentration starting from a dose of 125 mg/day, over eight weeks⁵. The effect on blood glucose is associated with increased insulin sensitivity⁵. Regarding the levels of CRP and TNF- α , different studies suggest that their decrease is due to the suppression of the NF- κ B pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) and the activation of signals through PPAR- α (peroxisome proliferator-activated receptor alpha). Regarding the effects on oxidation, it has been shown to decrease malondialdehyde (MDA) and, in turn, increase total antioxidant capacity (TAC) levels⁵. According to various authors, this reduction is significant when administering 125 to 300 mg of OEA 5 doses.

COENZYME Q10

Coenzyme Q10 (CoQ10) is a liposoluble benzoquinone that supplements by scavenging free radicals, inhibiting protein oxidation, and regulating lipid metabolism markers and glycemic control in patients with type 2 diabetes mellitus⁹. A study conducted by Samimi et al.⁹ demonstrated that a dose of 100 mg/day of CoQ10 to patients with PCOS for 12 significantly improved glycemic control, insulin metabolism markers, total cholesterol, and LDL. CoQ10 acts under a blocking effect on interleukins such as IL-1B, inhibiting insulin secretion stimulated by glucose. Its intake contributes to improving insulin resistance through the modulation of

insulin and adiponectin receptors and the enhancement of glucose transporters¹⁰. Regarding the lipid profile, the consumption of CoQ10 could lead to an improvement by reducing oxidative stress and its implication in endothelial metabolism⁹.

CURCUMIN

Curcumin (diferuloylmethane) is an active polyphenolic pigment from *Curcuma longa*, and it possesses antioxidant and anti-inflammatory properties¹¹. Due to its pharmacological and biological characteristics, its hypoglycemic and hypolipidemic effects made it a supplement of interest¹². Different mechanisms are proposed to explain curcumin's effect on glucose homeostasis, which are mainly based on the activation of the gamma receptor, which is activated by the peroxisome proliferator (PPAR- γ). This exerts control over genes involved in metabolic homeostasis and simultaneously stimulates the action of enzymes such as glucokinase¹². According to the study by Heshmati et al.¹¹, curcumin increases glucose absorption by activating AMP-activated protein kinase, thereby increasing phosphorylation. The intake of capsules containing 500 mg of curcumin powder (1500 mg per day) for 12 weeks significantly decreases glucose and DHEA levels in patients with PCOS¹¹. In the study by Sohaei et al.¹² 1 g of curcumin (500 mg twice a day) was administered daily for 6 weeks, resulting in a significant decrease in serum insulin levels and QUICK, although no statistical significance was observed in other glycemic parameters.

VITAMIN D

Vitamin D is a steroid hormone whose function is regulated by the vitamin D receptor (VDR), which is found in various tissues of the human body, including the ovaries, playing an important role in female reproductive physiology¹³. It has been evidenced that vitamin D improves glucose metabolism, as it increases insulin production and receptor expression reduces the production of pro-inflammatory cytokines⁷. Various studies, including a bibliographic review, indicate that the most favorable results were achieved with high doses of vitamin D (≥ 4000 IU/d) over a minimum period of 12 weeks. This dosage improved glucose levels, insulin sensitivity, hyperlipidemia, and hormonal function¹⁴. Insulin resistance correlates in most cases where there is a vitamin D deficiency, as it has been shown to be capable of modulating the homeostasis between glucose and insulin due to the action it exerts on the VDR. These receptors activate the transcription of the human insulin receptor gene, thereby stimulating the expression of insulin receptors improving insulin-mediated glucose transport¹⁴. Significant changes have been recorded in glucose levels, serum insulin, HOMA-IR, CRP, and MDA following supplementation with doses of 50,000 IU of vitamin D every two weeks for 12 weeks¹⁵. A meta-analysis demonstrated that vitamin D supplementation in women with PCOS affects hs-CRP, MDA, and TAC but did not affect NO or GSH¹⁶ levels.

Vitamin D may have a reducing effect on lipid metabolism parameters⁶. Studies suggest an association between low serum vitamin D concentrations and an unfavorable lipid profile in patients with PCOS⁸. However, supplementation has a greater hypolipidemic effect in patients with metabolic disorders and varies by population⁶. A study showed that vitamin D supplemented for 12 weeks in women with PCOS yielded significant results in reducing insulin concentration and HOMA-IR at fasting, 1 hour, 2 hours, and 3 hours after the OGTT⁷. The lipid profile showed a significant reduction in triglycerides, total cholesterol, and lipoprotein compared to the control group⁷. The exact mechanism by which vitamin D improves lipid markers is still under debate⁶. It is attributed to vitamin D stimulating the expression of the LPL gene in muscles and adipose tissue, increasing the clearance of circulating lipoprotein particles⁶. Wen et al.⁷ indicated that vitamin D can increase hepatic intracellular calcium, which stimulates microsomal triglyceride transfer protein (MTP), which is involved in the formation and secretion of VLDL, resulting in a decrease in serum levels of triglycerides and VLDL cholesterol. Other studies associate the effect of vitamin D with the reduction of parathyroid hormone and the improvement of insulin sensitivity⁶, suggesting that vitamin D intake could reduce cholesterol absorption, thereby affecting the serum concentration of Total Cholesterol and the endogenous synthesis of cells⁶.

VITAMIN K

It is a fat-soluble vitamin synthesized naturally, phylloquinone (vitamin K1) from green vegetables and menaquinone (vitamin K2) produced by intestinal bacteria¹⁷. Studies indicate that osteocalcin mediates between bones and the pancreas in regulating glycemic status, promoting the proliferation of β cells and insulin secretion through actions in the pancreas and adipocytes¹⁷. It, in turn, helps increase insulin sensitivity through adiponectin expression in fat cells¹⁸. Recently, evidence has emerged linking the absence of the osteocalcin gene with metabolic dysfunctions such as hyperglycemia, glucose intolerance, increased fat mass and serum triglyceride levels, and decreased production of β cells, insulin secretion, and adiponectin expression.¹⁸ Tarkesh et al.¹⁸ demonstrated that 8 weeks with a dose of 90 $\mu\text{g}/\text{day}$ of menaquinone-7 (vitamin K2) reduced waist circumference, fasting insulin, HOMA-IR, triglycerides, DHT, SHBG, and HOMA- β while increasing the QUICKI index, compared to placebo. To date, there is little evidence of vitamin K action in PCOS¹⁸.

MELATONIN

Melatonin is a hormone secreted by the pineal gland; it performs various functions, controlling sleep patterns, adjusting the circadian rhythm, contributing to the immune response, protecting oocytes from ROS, and is also considered a free radical eliminator and an endogenous antioxidant¹⁹. It regulates oxidative damage and attenuates the inflammatory state through anti-inflammatory enzymes and eliminating free radicals in the tissues¹⁹. To date, no significant changes have been observed in glucose, insulin, cholesterol, triglycerides, LDL, or HDL; however, there are heterogeneous results regarding the changes that may occur in PCR and MDA levels¹⁹. The doses of melatonin that have been used range between 3 and 10 mg/day for 3 to 12 weeks¹⁹.

INOSITOL

Inositols belong to the B vitamin complex; there are nine stereoisomers, the most important being Myo-inositol and D-chiro-inositol. These are considered an alternative treatment to metformin, as their function lies in the modulation of the components that signal the insulin pathways, thus influencing processes such as the regulation of the menstrual cycle, carbohydrate metabolism, and hyperandrogenism²⁰. Myo-inositol in the human body promotes the translocation of glucose transporter type 4 to the plasma membrane for glucose uptake and, in turn, reduces the release of free fatty acids²¹. Additionally, it produces messengers of inositol triphosphates, which regulate the production of hormones such as TSH and FSH and are also responsible for glucose absorption, thereby benefiting insulin sensitivity²². It has been demonstrated that administering myo-inositol for 12 weeks in women with PCOS influences glucose, insulin, HOMA IR, and QUICKI levels, as well as the expression of the PPAR- γ gene, which is involved in the function of metabolic pathways such as insulin and lipid metabolism. Also, it participates in regulating steroidogenesis, which is of great importance for the proper functioning of the ovaries²². Regarding the D-chiro-inositol isoform, it has a positive effect on hyperandrogenism indices, but it does not significantly reduce glucose levels²³. However, both isoforms have demonstrated their effectiveness in ovarian function and metabolism in patients with PCOS²³.

CHROMIUM

Chromium is a trace element that benefits the endocrine profile, inflammation biomarkers, and oxidative stress²⁴. These effects are attributed to the action of enzymes, such as the activation of glutathione reductase, the improvement of insulin resistance, and the inhibition of protein glycosylation²⁴. It has been demonstrated that the intake of 200 $\mu\text{g}/\text{day}$ of chromium picolinate for 8 weeks significantly reduces hirsutism, CRP-as, MDA, and TAC; however, it did not influence the plasma concentrations of NO and GSH²⁴. The exact mechanism by which chromium influences CRP levels is not precisely known, but it is suggested that its inhibitory effect on pro-inflammatory cytokines is related to the reduction of oxidative stress, which decreases CRP²⁴. Chromium has an insulinotropic impact inhibiting epinephrine, which could be related to the decrease in oxidative stress biomarkers²⁴. The intake of chromium supplements has been shown to improve insulin metabolism in

PCOS patients, decreasing serum insulin levels, HOMA IR, HOMA B, and significantly increasing QUICKI, but it does not affect glucose levels ²⁵.

SELENIUM

It is an essential trace element with antioxidant properties, fundamental for selenoproteins that regulate the function of endothelial cells and protect against oxidative damage ²⁶. A randomized, double-blind, placebo-controlled trial conducted by Razavi et al. ²⁷ found that supplementation with 200 µg of selenium for 8 weeks significantly increased pregnancy rates and reduced levels of alopecia, acne, DHEA, hirsutism, CRP, and MDA compared to placebo. It is said that antioxidants can influence female reproduction by eliminating or suppressing the formation of ROS, free radicals, and lipid hydroperoxides ²⁷. The effect of the decrease in serum levels of dehydroepiandrosterone (DHEA) and hirsutism occurs by improving insulin metabolism markers ²⁷. Similarly, selenium supplementation reduces serum levels of CRP by inhibiting the activation of NF-kappa B through the modulation of selenoprotein gene expression and the increase in its biosynthesis, resulting in a suppressed production of CRP ²⁷. A study conducted by Jamilian et al. ²⁸ reported that 200 µg of selenium for 8 weeks of intervention in women with PCOS had significantly reduced levels of insulin, HOMA-IR, HOMA-B, triglycerides, VLDL, and a significant increase in QUICK compared to placebo. Also, Jamilian et al. suggest that the improvement in insulin parameters could be due to the inhibition of COX-2 expression, P-selectin, or inflammatory cytokines such as TNF-α and IL-1. Other studies have shown that selenium stimulates the expression of the pancreatic beta cell gene and improves islet function in cell cultures, suggesting its antidiabetic potential due to its insulin-like properties ²⁸.

ZINC

It is an essential trace element in prominent sources of both animal and plant origin ²⁹. Zinc (Zn) is required to maintain homeostasis, serving as a catalytic, structural, or regulatory ion for approximately 3000 proteins in the body ²⁹. It has antioxidant properties and protective actions against ROS in collaboration with other antioxidants, such as vitamin E ²⁹. A study conducted by Jamilian et al. ³⁰ demonstrated that the administration of 50 mg/day of zinc in patients with PCOS for 8 weeks significantly reduced hirsutism, alopecia, MDA, and CRP; however, it did not affect hormonal profiles, inflammatory cytokines, or other oxidation biomarkers. The intervention with 220 mg of zinc sulfate (containing 50 mg of zinc) for 8 weeks reduced fasting serum glucose and insulin levels and improved HOMA-IR, HOMA-B, and QUICK ³¹.

Additionally, a decrease in the concentration of triglycerides and VLDL cholesterol was observed in subjects with PCOS ³¹. Zinc is an insulin mimetic as it stimulates lipogenesis and glucose uptake in isolated adipocytes; this effect occurs through the modulation of protein tyrosine phosphatase activity in IGF-1 signaling ¹⁷. It performs a regulatory action on insulin phosphorylation and its impact on oxidative stress ²⁹. Regarding triglyceride and VLDL cholesterol levels, it has been suggested that Zn affects the enzymes involved in lipid metabolism ³¹.

L-CARNITINE

Carnitine (LC) is a quaternary amine synthesized endogenously from lysine and methionine. Among its multiple functions, LC is a mandatory cofactor in transporting long-chain fatty acids across the mitochondrial membrane, facilitating beta-oxidation ³². LC can regulate androgen levels and, in turn, contribute to the decrease of testosterone. Just as it improves insulin sensitivity, thus affecting androgen levels and ovarian hormones ³². A study reports that a daily dose of 250 mg of carnitine supplement for 12 weeks among women with PCOS resulted in a significant reduction in body weight, BMI, fasting glucose, serum insulin, HOMA-IR, and DHEA but did not affect lipid profiles or free testosterone ³³. The improvement in insulin metabolism parameters is associated with L-carnitine potentially modulating the expression of glycolytic and gluconeogenic enzymes involved in mitochondrial glucose oxidation and facilitating the transport of free fatty acids or their action as acetyl group donors in high-energy metabolism situations ³³.

OMEGA-3

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) in dietary supplements such as fish oil. The three main omega-3 fatty acids are alpha-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)¹⁷. They are attributed to anti-inflammatory, antioxidant, and antihypertensive properties and regulate the abnormal expression of some genes in polycystic ovary syndrome¹⁷. It is under debate whether there is a relationship between PCOS, omega-3 fatty acids, and insulin resistance³⁴. Several studies suggest that omega-3 supplementation improves glucose parameters, possibly due to the potential of fatty acids to increase adiponectin production³⁴. Adiponectin is a hormone that enhances cell sensitivity to insulin and has anti-inflammatory and anti-atherogenic effects³⁴.

Melo et al.³⁴ reported that supplementation with 1000 mg/day of omega-3 from flaxseed oil for 12 weeks showed effective results, even more so than in similar studies. The consumption of omega-3 based on flaxseed oil favored the reduction of insulin, HOMA-IR, CRP, and the increase in QUICKI³⁵. There was also a reduction in triglycerides and VLDL cholesterol. However, I do not observe any significant effect on hormonal profiles, other lipid profiles, and nitric oxide levels³⁵. Regarding the improvement of insulin sensitivity, omega-3 fatty acids inhibit the activation of nuclear factor kappa B (NF-κB), which reduces the production of pro-inflammatory cytokines and helps reverse insulin resistance³⁵. Omega-3 supplementation seems to be an option that can be effective in improving the lipid profile and reducing cardiovascular risk, as metabolic nuclear receptors like PPAR and SREBP-1 (sterol regulatory element-binding protein 1) are activated by the binding of natural lipid-derived ligands such as fatty acids, allowing the inhibition of protein-coding that stimulates lipid synthesis and genes that increase lipid oxidation in the liver and muscle³⁴. Moreover, the consumption of omega-3 is associated with activating the AMPK (AMP-activated protein kinase) pathway, which acts as a sensor of the cellular energy state that regulates energy homeostasis between lipid oxidation and lipogenesis³⁴. A randomized, parallel-arm, double-blind study was conducted on 51 women with PCOS, showing a significant improvement in the triglyceride lipid profile and the high-density lipoprotein (HDL) ratio³⁴. The effects of n-3 PUFAs on lipid metabolism may be class-specific, as fish oil and flaxseed oil decrease triglyceride concentration³⁶. In 6 months of intervention with a supplemental dose of 2 g/day of omega-3 in women with PCOS, they showed a reduction in total cholesterol, LDL, and triglycerides and a significant increase in HDL cholesterol^{34,37}.

MAGNESIUM

It is an intracellular ion and a cofactor for hundreds of enzymes involved in regulating the effects of insulin¹⁷. Due to its mechanisms of regulating glycemic and neurological functions, magnesium is associated with insulin resistance and depression, including polycystic ovary syndrome, as well as some cardiovascular diseases and diabetes¹⁷. A systematic review found that high magnesium levels were associated with a general decrease in insulin resistance (IR), based on four epidemiological studies in women with polycystic ovary syndrome (PCOS). However, when analyzing the results of three randomized clinical trials (RCTs), the effects of magnesium supplementation on IR in these women were variable. However, when analyzing the results of three randomized clinical trials (RCTs), the impact of magnesium supplementation on IR in these women was variable¹⁷.

VITAMIN E

It is a fat-soluble nutrient with anticoagulant and antioxidant properties that help protect cells from damage caused by free radicals¹⁷. A study reported that supplementation with vitamin E alone for 8 weeks significantly decreased serum triglyceride². However, there was no effect on HDL or LDL levels³⁸. The exact mechanism of action of vitamin E on the lipid profile is unknown³⁸. One of the hypotheses attempting to explain this is that alterations in oxidative stress mediate these effects. Consequently, chronic exposure to oxidants conditions cellular metabolism by oxidizing lipids³⁸. It is claimed that vitamin E has antioxidant, anti-inflammatory, and anti-obesity properties³⁸.

Supplement	Doses	Time	Analyte	Base Value	Final value	P value	Ref.
Oleoylethanolamide	125mg	8 weeks	Glucose (mg/dl)	106.08± 22.54	92.14 ± 20.32	0.032	5
			Insulin (μU/ml)	15.19± 2.51	9.13 ± 2.22	0.03	
			TAC (mg/dL)	1.06± 0.034	1.98 ± 0.061	0.017	
			MDA (mg/dL)	1.59 ± 0.055	0.71 ±0.026	0.028	
			TNF-α (pg/ml)	16.78 ± 4.19	12.31 ±3.36	0.036	
			PCR (ng/mL)	10.14±2.62	6.9 ±1.59	0.031	
			AMH (ng/mL)	12.0 ± 3.25	7.59 ±2.13	0.041	
Q10 Coenzyme	100 mg	12 weeks	Glucose (mmol/L)	4.97 ± 0.54	4.73 ± 0.57	0.04	9
			Insulin (pmol/L)	74.4 ± 14.4	66.6 ± 16.2	<0.001	
			HOMA IR	2.8 ± 0.7	2.5 ± 0.7	0.001	
			HOMA-B	46.8 ± 9.4	41.4 ±11.2	<0.001	
Curcumin	1,500 mg	12 weeks	Glucose (mg/dl)	105.26± 13.15	100.17 ± 13.91	NSD	11
			DHEA (micro gr/dl)	138.57 ± 96.92	149.14 ± 78.75	NSD	
	1 g	6 weeks	Insulin (uU/mL)	15.42 ± 8.09	12.35 ± 6.79	0.020	12
			QUICKI	0.32 ± 0.02	0.33 ± 0.03	0.003	
Vitamina D	50,000 UI	12 weeks	Glucosa (mg/dl)	91.0± 6.1	87.8 ± 7.6	0.02	15
			Insulina (μUI/ml)	9.6 ± 4.5	8.2 ± 2.8	0.004	
			HOMA-IR	2.2±1.1	1.8±0.6	0.003	
			PCR (μg/ml)	2.6 ± 2.8	1.9 ± 1.7	0.009	
			MDA (μmol/l)	2.2±0.4	2.1±0.4	0.01	
Vitamin k	90 μg of menaquinona-7	8 weeks	Insulin (μIU/ml)	8.05 (7–9)	7.4 (6.4–8.6)	0.001	18
			HOMA-IR	1.71 (1.55– 2.03)	1.47 (1.23– 1.75)	<0.001	
			HOMA-β	6 (4.8– 6.83)	5.59 (4.61– 6.59)	0.003	
			QUICKI	0.35 (0.34– 0.35)	0.35 (0.34– 0.36)	0.002	
Myo-inositol	2 g	12 weeks	Glucose (mg/dl)	97.5 ± 6.6	89.8 ± 8.5	0.001	22
			Insulin (μUI/ml)	13.0 ± 3.4	10.8 ± 3.0	<0.001	
			HOMA IR	3.1 ± 0.9	2.6 ± 0.8	<0.001	
			QUICK	0.32 ± 0.01	0.33 ± 0.01	0.006	
Chromium	200 μg	8 weeks	Insulin (μUI/mL)	13.3 ± 8.4	9.7 ± 7.5	<0.001	25
			HOMA-IR	2.8 ±1.8	2.0 ± 1.6	<0.001	
			HOMA-B	53.1 ± 36.0	37.6 ± 31.1	<0.001	
			QUICKI	0.34±0.03	0.36±0.04	0.001	
	200 μg	8 weeks	PCR-as (ng/mL)	2757.6 ±2887. 7	2040. 6 ± 2397. 2	0.01	24
MDA (μmol/L)			3.2 ± 1.1	3.1 ± 1.1	0.25		

			TAC (mmol/L)	683.1 ± 128.4	933.8 ± 281.1	<0.001	
Selenium	200 µg	8 seman as	DHEAS (µg/ml)	2.01 ± 0.80	1.65 ± 0.85	0.02	27
			PCR-as (ng/ml)	2 184.06 ± 2 693.84	1 472.7 0 ± 1444.4 3	0.02	
			MDA (µmol/l)	4.95 ± 1.25	4.81 ± 1.36	0.01	
	200 µg	8 weeks	Insulin (µmol/l)	80.69±42.28	50.86±32.83	0.013	28
		HOMA-IR	3.00±1. 69	1.85± 1.22	0.011		
		HOMA-B	50.36± 26.67	31.30 ±22.2 6	0.017		
		QUICKI	0.33±0. 03	0.36± 0.03	0.032		
Zinc	220 mg zinc sulphat	8 seman as	MDA (µmol/L)	4.37 ± 1.04	4.28 ± 0.65	0.04	30
			PCR-as (ng/mL)	2088.3 1 ± 1733.3 7	1865. 68 ± 1469. 46	0.06	
	220 mg zinc sulphate	8 weeks	Glucose (mg/dL)	99.8±10.3	95.5±8.0	0.03	31
			Insulin (µUI/mL)	10.4±3.7	7.4±2.0	0.01	
			HOMA-IR	2.6±1.2	1.8±0. 8	0.006	
			HOMA-B	33.7±1 1.4	23.1± 7.4	0.02	
			QUICKI	0.33±0. 02	0.35± 0.02	0.03	
L-carnitine	250 mg car-nitine	12 weeks	Glucose (mmol/l)	5.26± 0.57	4.88± 0.56	0.01	33
			Insulin (pmol/l)	66.00± 31.82	51.61 ± 24.05	0.04	
			HOMA-IR	2.62 ± 1.34	2.01 ± 1.04	0.04	
			DHEAS (Imol/l)	11.18± 6.21	7.54 ±7.14	0.03	
Omega-3	1000 mg omega-3	12 weeks	Insulin (µIU/mL)	13.3 ± 8.7	10.7 ± 6.2	0.01	35
			PCR-as (mg/L)	4.9 ± 3.1	3.2 ± 3.9	0.004	
			HOMA-IR	3.1 ± 2.1	2.4 ± 1.5	0.01	
			QUICK	0.33 ± 0.02	0.34 ± 0.02	0.01	

*N/A: Not available

Table 1. Summary of supplements for glycemic control, oxidative stress, and insulin resistance

Supple-ment	Doses	Time	Analyte	Base value	Final value	P value	Ref.
Vitamin D	2000 UI/day	12 weeks	Insulin (mIU/L) fast, 1 h, 2 h y 3 h After OGTT	27.7 ± 5.8	N/A	0.046	7
				312.5 ± 56.4	N/A	0.029	
				206.8 ± 44.3	N/A	0.035	
				61.5 ± 10.4	N/A	0.041	
			HOMA-IR fast, 1 h, 2 h y 3 h after OGTT	5.0 ± 0.6	N/A	0.048	
				127.8 ± 19.7	N/A	0.021	
				61.2 ± 15.2	NA	0.033	
				11.8 ± 3.9	N/A	0.047	

			Triglycerides(mmol/L)	1.9 ± 0.3	N/A	0.031	
			Cholesterol (mmol/L)	5.6 ± 1.4	N/A	0.027	
Vitamin E	400 IU	8 weeks	Triglycerides(mg/dL)	111.68 ± 44.41	105.18 ± 8.22	< 0.001	38
Omega-3	Group 1: 3,5 g/day fish oil	6 weeks	Triglycerides (mmol/L)	1.5 ± 0.6	-0.3 ± 0.4	< 0.05	36
	Group 2: 3,5 g/day linseed oil		Triglycerides(mmol/L)	1.6 ± 1.0	-0.3 ± 0.5	< 0.05	
	2 g/day, each with 180 mg of EPA and 120 mg of DHA)	6 months	Triglycerides(mg/dL)	125.16±2.66	116.02±3.12	0.0001	37
			Cholesterol (mg/dL)	189.97±6.23	180.34±6.33	0.0001	
			LDL (mg/dL)	117.34±1.66	107.79±1.68	0.0001	
			HDL (mg/dL)	41.44±1.11	47.2±1.37	0.0001	

*N/A: Not Available

Table 2. Summary of supplements used in the control of dyslipidemia

Probiotics And Symbiotic Supplementation

Various authors have linked the gut microbiome and PCOS, as a deficient microbiome can influence the progression of this syndrome due to hyperandrogenism, impaired signaling through epithelial receptors, disorders in the gut-brain axis, and increased secretion of inflammatory cytokines³⁹. Recently, probiotics and prebiotics have been studied as treatments for dysbiosis³⁹.

Symbiotics, a combination of probiotics and prebiotics, develop a stimulating function that is selective for the growth and activation of beneficial intestinal bacteria³⁹. It has been shown that administering probiotics, prebiotics, and synbiotics to women with PCOS benefits glycemic status, insulin resistance, and lipid profile³⁹. As part of the studies recorded to date, microorganisms such as *Bacillus coagulans* (GBI-30), *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and fructooligosaccharides have been used, which have managed to improve the quality of life concerning health, total testosterone, SHBG, hs-CRP, TAC, and MDA³⁹.

Table 3. Summary of hormonal, inflammatory, and oxidative stress biomarkers following 12-week supplementation with a symbiotic combination (*L. acidophilus*, *L. casei*, *B. bifidum*, and inulin) in women with PCOS. The table presents changes in serum levels of testosterone, SHBG, DHEAS, hs-CRP, nitric oxide (NO), total antioxidant capacity (TAC), glutamine, and malondialdehyde (MDA) before and after treatment. All values are expressed as mean ± standard deviation. N/A: P-values were not reported in the original study. Data adapted from reference³⁹.

Symbiotic (<i>L. acidophilus</i>, <i>L. casei</i>, <i>B. bifidum</i>, <i>inulin</i>) Doses: 2×10⁹ CFU/g – Time: 12 weeks ³⁹			
Analyte	Base Value	Final Value	P value
Testosterone (ng/mL)	2.8 ± 1.3	2.4 ± 0.9	N/A
SHBG (nmol/L)	37.3 ± 13.1	57.1 ± 48.6	N/A
DHEAS (µg/ml)	2.6 ± 1.5	2.2 ± 0.8	N/A
hs-CRP (ng/mL)	2920.0 ± 2251.2	1970.0 ± 1442.0	N/A
NO (µmol/L)	39.0 ± 3.1	44.5 ± 5.0	N/A
TAC (mmol/L)	773.1 ± 38.7	818.2 ± 57.5	N/A
Glutamine (µmol/L)	498.9 ± 56.8	523.5 ± 53.4	N/A
MDA (µmol/L)	2.3 ± 0.4	2.1 ± 0.4	N/A

Table 3. Summary of probiotics and symbiotics.

This literature review defined and compared thirteen supplements to treat and manage PCOS as an alternative to traditional drugs, identifying their main effects, the most appropriate doses for each, and the most favorable time periods to achieve significant results. Among the main findings of the research, we highlight that the supplements of greatest clinical relevance in the treatment of PCOS are characterized by being aimed at the progressive improvement of the most frequent clinical manifestations in patients, thus encompassing four important parameters to achieve an efficient result: glycemic control, dyslipidemia control, reduction of oxidative stress, and hormonal control (Figure 1). Although there is significant evidence regarding the contribution of different supplements to these parameters, it seems that there is no "ideal" supplementation that improves all these elements of PCOS at once. However, Omega 3 is the most promising as it demonstrates modulatory effects on the lipid profile (TGC, LDL-C, VLDL-C, and HDL-C) and insulin resistance (HOMA-IR). The limitation of Omega 3 is that it appears to have no significant effect on glycemia. No adverse effects have been reported from using Omega 3, being considered relatively safe, although authors like Melo et al.³⁴ y Xia et al.⁴⁰ recommend larger-scale studies with long-term follow-up to evaluate possible adverse effects. However, it is recommended to use this supplementation in women with PCOS who present both insulin resistance and dyslipidemia⁴¹.

On the other hand, OEA and CoQ10 have a positive effect on glucose control by increasing insulin sensitivity. It has been evidenced that administering 125 mg of OEA or ingesting 100 to 200 mg of CoQ10 for 8 to 12 weeks significantly reduces serum glucose and insulin levels in patients with PCOS⁵. Establishing the dose of Co Q10 has been a topic of discussion; authors identify a greater beneficial effect on total cholesterol when doses below 400 mg/day are used⁴². CoQ10 supplementation has proven to be safe and well-tolerated even at high doses, but rare adverse effects such as nausea, vomiting, loss of appetite, and dyspepsia have been reported⁴³.

For its part, Inositol has proven to be one of the supplements with the best effect in treating PCOS, being comparable in most parameters to metformin²⁰. Both isoforms, Myo-Inositol and D-chiro Inositol, have shown effectiveness in glycemic metabolism and ovarian function. Myo-inositol shows improvement in glycemic/metabolic profile at the ovarian level by modulating glucose metabolism and FSH signaling, while D-chiro shows improvement in signs of hyperandrogenism⁴⁴. Therefore, a combined dose of Myo-Inositol and D-chiro inositol (40:1) is recommended to improve both aspects of PCOS. Regarding adverse effects, Inositol has proven to be a safe treatment; evidence shows that there may be a higher risk of adverse effects in women using metformin compared to those using inositol⁴⁵.

On the other hand, in our bibliographic research, we have found evidence of a beneficial effect of certain supplements on dyslipidemia or insulin resistance but not directly on PCOS, so these could be the subject of future studies. These are vitamin K, melatonin, chromium, selenium, magnesium, and vitamin E. Regarding vitamin K, we could say that there are few studies on the effect of this vitamin on PCOS, as studies are often designed using co-supplementation with vitamin D and calcium, showing that this co-supplementation improves hyperandrogenism and antioxidant status⁴⁶ and has a positive effect on insulin resistance in women with PCOS⁴⁷. On the other hand, the improvement of depressive state in women with PCOS has been reported when supplemented with vitamin K2⁴⁸. Lastly, another supplement with interesting evidence is selenium. As we explained earlier, selenium supplementation improves the state of hyperandrogenism, hirsutism, oxidative status, and insulin resistance in women with PCOS. Also, it seems promising as an antidiabetic treatment for enhancing the function of pancreatic beta cells^{49,50}.

Critical Analysis of the Evidence

Despite the valuable information provided by the current review, it is necessary to consider the variability and limitations of the scientific evidence supporting the use of supplements to treat and manage PCOS. One of the major challenges encountered is the heterogeneity in study design, sample size, population characteristics, and dosage and duration of supplementation. For instance, while some trials use standardized doses over controlled periods, others vary considerably in their protocols, making it difficult to compare their outcomes⁵¹ directly.

In addition, many studies do not control for confounding variables such as diet, lifestyle, and baseline hormonal levels, which may significantly influence the effectiveness of supplementation⁵². This issue is particularly relevant in cases of co-supplementation or the simultaneous use of pharmacological treatment, which often obscures the isolated effect of the supplement under investigation⁵³.

Another important factor is the lack of long-term data. Most studies reviewed are short-term (typically 6 to 12 weeks) and do not provide information on the sustainability of the clinical benefits or potential adverse effects of prolonged use. For example, while selenium and vitamin D have shown promising results in short-term trials, their long-term impact on endocrine and metabolic parameters in PCOS remains unclear⁵⁴.

It is also notable that some supplements show inconsistent results across studies. A clear example is melatonin, which presents mixed findings regarding its impact on glucose and lipid profiles⁵⁵. These inconsistencies may reflect the differences in study methodologies and the need for more rigorous clinical trials with standardized endpoints and larger sample sizes.

Lastly, while several supplements show strong potential (such as Inositol and omega-3 fatty acids), only a few have sufficient evidence from randomized controlled trials to support their clinical recommendation. This underscores the importance of continuing high-quality research that can clarify which supplements are most beneficial, under what circumstances, and for which subgroups of PCOS patients.

To better understand the reliability of the reviewed studies, we conducted a methodological quality assessment based on key design features, including randomization, blinding, use of control groups, and sample size. The table below summarizes the quality grading for the main trials considered in this review. Studies with complete reporting and rigorous design were rated as "High," while others with some limitations or missing methodological details were rated as "Medium" or "Low."

To evaluate the reliability and scientific rigor of the evidence presented in this review, we conducted a methodological quality assessment of the primary clinical trials included. The evaluation focused on essential design elements such as sample size, randomization procedures, blinding, presence of a control group, and overall risk of bias. The table below summarizes the core methodological features and provides a quality rating for each study, helping to contextualize their contribution to clinical recommendations.

Study (Ref.)	Supplement	Study Design	Sample Size	Randomization	Blinding	Control Group	Quality Rating
Samimi et al. ⁹	CoQ10	RCT	60	Yes	Double	Placebo	High
Heshmati et al. ¹¹	Curcumin	RCT	67	Yes	Single	Placebo	Medium
Jamilian et al. ²⁸	Selenium	RCT	70	Yes	Double	Placebo	High
Tarkesh et al. ¹⁸	Vitamin K	RCT	84	Yes	Not Reported	Placebo	Medium
Sohaie et al. ¹²	Curcumin	RCT	80	Yes	Single	Placebo	Medium
Razavi et al. ²⁷	Selenium	RCT	80	Yes	Double	Placebo	High
Melo et al. ³⁴	Omega-3	RCT	51	Yes	Double	Placebo	High
Shahmoradi et al. ³⁶	Magnesium	RCT	66	Yes	Not Reported	Placebo	Medium
Wen et al. ⁷	Vitamin D	RCT	90	Yes	Double	Placebo	High
Jamilian et al. ³⁰	Zinc	RCT	60	Yes	Double	Placebo	High
Jamilian et al. ⁶⁵	Melatonin	RCT (Double-Blind)	56	yes	Double	Placebo	High

Table 4. A methodological quality assessment of the clinical trials is included in this review. The table presents the characteristics of eleven randomized controlled trials evaluating the efficacy of nutritional supplements in women with PCOS. Quality was graded based on the presence of randomization, blinding, control groups, and completeness of reporting. Studies were classified as High, Medium, or Low quality. Data extracted from sources referenced in the review.

Practical Recommendations for Supplement Use in PCOS

Based on the evidence reviewed, we developed a set of practical recommendations to guide the potential use of dietary supplements in clinical settings. These recommendations consider the main clinical targets in PCOS (insulin resistance, lipid imbalance, hormonal dysfunction), the most effective dosages and durations, and the current level of supporting evidence. The table below is intended to help clinicians make decisions while acknowledging the need for individualized treatment plans.

Based on the reviewed evidence, a practical summary was developed to guide clinicians in selecting dietary supplements tailored to specific clinical presentations of PCOS. This table compiles the most commonly studied supplements, their suggested dosages and durations, clinical focus, and strength of supporting evidence. It is intended as a quick reference tool to aid in formulating personalized and evidence-based treatment strategies.

Supplement	Clinical Focus	Suggested Dose / Duration	Evidence Strength	Comment
Myo-Inositol	Insulin resistance, ovulatory function	2 g twice daily / 12 weeks	High ²²	Effective alternative to metformin in non-obese women.
Vitamin D	Glucose metabolism, lipid profile	≥4000 IU/day / 12 weeks	High ^{15, 54}	It is especially effective in women with baseline deficiency.
Omega-3 Fatty Acids	Lipid metabolism, inflammation	1–2 g/day / 12–24 weeks	High ^{34, 35}	Shown to improve triglycerides and reduce CRP.
Coenzyme Q10	Glycemic control, oxidative stress	100–200 mg/day / 12 weeks	Medium ^{9, 10}	It may reduce LDL and improve insulin sensitivity.
Selenium	Androgen profile, antioxidant effect	200 µg/day / 8 weeks	High ^{27, 28}	It improves hirsutism and reduces DHEAS and CRP.
Zinc	Oxidative stress, insulin metabolism	50 mg/day / 8 weeks	Medium ^{30, 31}	Aids glucose uptake; effects on hormones are mixed.
Curcumin	Glucose homeostasis	1–1.5 g/day / 6–12 weeks	Medium ^{11, 12}	Variable results are better when combined with lifestyle changes.
Vitamin K2	Insulin sensitivity, lipid profile	90 µg/day / 8 weeks	Low-Medium ¹⁸	It is promising, but more studies are needed.
Melatonin	Inflammation, antioxidant role	3–10 mg/day / 3–12 weeks	Low ⁵⁵	Mixed results; lacks consistent evidence.
Magnesium	Metabolic profile, BMI, HOMA-IR	250–350 mg/day / 8–12 weeks	Medium ³⁶	It is especially useful if dietary magnesium is deficient.

Table 5. Practical recommendations for the clinical use of nutritional supplements in PCOS. This table summarizes key supplements by clinical indication, recommended dosage, duration, and available evidence's strength. The strength of evidence was rated as High, Medium, or Low, based on trial design and reproducibility of results.

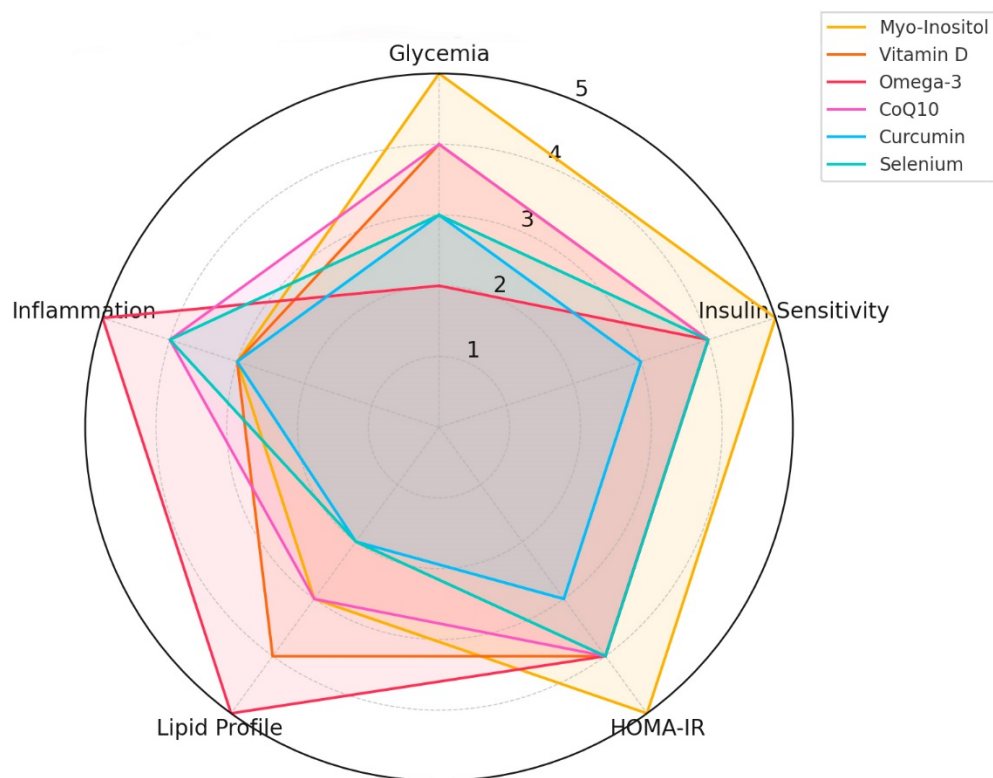


Figure 3. Comparative radar chart of the clinical efficacy of selected supplements in PCOS management. The graph illustrates the relative performance of six key supplements—Myo-Inositol, Vitamin D, Omega-3, Coenzyme Q10, Curcumin, and Selenium—across five critical outcome domains: glycemic control, insulin sensitivity, HOMA-IR, lipid profile improvement, and reduction of inflammation. Data are synthesized from clinical trials and categorized on a scale from 0 (no effect) to 5 (strong effect). This visualization supports quick clinical comparison and decision-making.

Clinical Limitations and Safety Considerations of Supplement Use

While nutritional supplements offer promising benefits for the management of PCOS, several limitations and potential risks must be acknowledged to provide a balanced interpretation of the evidence.

Firstly, the safety profiles of many supplements are not fully established, especially for long-term use. Although short-term trials show minimal adverse effects, the prolonged intake of agents such as selenium, vitamin D, and zinc can lead to toxicity if not monitored adequately⁵⁸. For instance, high doses of selenium have been associated with selenosis, which manifests with gastrointestinal disturbances, hair loss, and neurological symptoms⁵⁹. Similarly, hypervitaminosis D may lead to hypercalcemia, nephrocalcinosis, and vascular calcifications⁶⁰.

Secondly, potential drug-supplement interactions must be considered, especially in women undergoing pharmacological treatments for PCOS or comorbidities. For example, supplements like omega-3 fatty acids and vitamin E have anticoagulant properties that might interact with medications such as oral contraceptives or metformin⁶¹.

Another critical aspect is the variability in supplement formulations. Different brands and preparations can vary widely in purity, bioavailability, and actual content compared to what is declared on the label⁶². This inconsistency may affect clinical outcomes and raise concerns about study results' reproducibility.

Moreover, individual variability among patients can influence supplement efficacy. Factors such as baseline nutritional status, gut microbiome composition, genetic polymorphisms, and severity of PCOS symptoms may alter the response to supplementation⁶³. This emphasizes the necessity of a personalized approach rather than a one-size-fits-all recommendation.

Finally, the lack of regulatory oversight in many countries regarding dietary supplements compared to pharmaceutical drugs increases the risk of contamination or mislabeling⁶⁴, further highlighting the importance of selecting supplements from reputable manufacturers.

CONCLUSIONS

This literature review highlights the growing interest in dietary supplements as a complementary approach to treating and managing Polycystic Ovary Syndrome (PCOS). By synthesizing data from clinical trials and reviews, we categorized the most clinically relevant supplements according to their primary effects—glycemic control, lipid regulation, oxidative stress reduction, and hormonal balance—while also detailing their recommended doses and treatment durations.

The evidence suggests that Inositol, vitamin D, omega-3 fatty acids, coenzyme Q10, curcumin, and oleoyl ethanolamide benefit insulin sensitivity, glucose metabolism, and inflammatory markers. Other supplements like selenium, zinc, L-carnitine, probiotics, and vitamin K show potential in improving endocrine-metabolic profiles, though more high-quality research is needed to confirm their efficacy and safety.

However, researchers have conducted many studies with small sample sizes, short intervention periods, and frequent use of co-supplementation, which limits the ability to isolate the effects of individual compounds. Most studies fail to include direct statistical comparisons between supplements or report long-term safety outcomes. Moreover, inconsistent study designs further complicate the clinical translation of findings.

Despite these challenges, nutritional supplementation remains promising, particularly for patients seeking personalized or alternative therapies. For optimal results, clinicians should consider individualized approaches, monitor for possible adverse effects, and ensure supplementation is integrated into a broader treatment plan grounded in evidence-based practice.

Future research should focus on:

- Conducting large-scale, randomized controlled trials with rigorous methodological quality.
- Investigating long-term outcomes and safety profiles.
- Clarifying mechanisms of action for each supplement.
- Exploring potential interactions with conventional pharmacotherapy.

By addressing these gaps, the scientific community can better define the role of dietary supplements in PCOS and contribute to improved quality of life and clinical outcomes for women affected by this complex syndrome.

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