



Original Research

Effects of Nutraceutical Supplementation on Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review

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Relevance

Acne is a prevalent dermatological condition that significantly impacts quality of life, particularly in individuals with polycystic ovary syndrome (PCOS). PCOS, a common endocrine disorder, is characterized by hyperandrogenism and insulin resistance, which exacerbate acne severity. While conventional treatments such as oral contraceptives and anti-androgen therapies are effective, increasing patient interest in nutraceuticals highlights a demand for integrative approaches to manage acne in this population.

Objective

This systematic review evaluates the efficacy and safety of nutraceutical supplementation in reducing acne severity among patients with PCOS.

Methods

A systematic review was conducted following PRISMA guidelines. Databases, including PubMed, Embase, and Cochrane, were searched for studies published through August 2024 using terms related to “acne,” “PCOS,” and “nutraceuticals.” Inclusion criteria were randomized controlled trials assessing oral nutraceuticals for acne outcomes in PCOS patients. Data on study design, population characteristics, interventions, outcomes, and adverse effects were extracted and analyzed.

Results

The review included 7 studies encompassing 498 participants. Nutraceuticals evaluated included chromium, berberine, selenium, magnesium, and antioxidant combinations. Chromium supplementation demonstrated significant reductions in acne severity ($P < 0.05$) and inflammatory markers such as C-reactive protein. Berberine showed improvements in Global Acne Grading System (GAGS) and Cardiff Acne Disability Index (CADI) scores, with additional benefits in metabolic and inflammatory parameters. Selenium supplementation resulted in a 46.9% reduction in acne lesions compared to placebo ($P = 0.003$). A combination of antioxidants (ALA, NAC, B6, SAME) showed acne improvement, but magnesium supplementation yielded no significant difference. A significant reduction in mean global acne score in the group taking metformin, MI, and DCI was also observed ($P=0.004$). No significant adverse effects were reported across studies.

A combination of antioxidants (ALA, NAC, B6, SAME) showed significant acne improvement, comparable to that seen in oral contraceptives. Selenium supplementation significantly reduced acne and inflammation ($P = 0.003$) and improved markers of inflammation and oxidative stress, while magnesium and a combination therapy of metformin with inositols did not affect acne in PCOS patients

Conclusion

This review suggests that certain nutraceuticals, particularly chromium, berberine, selenium, and a combination of antioxidants (ALA, NAC, B6, SAME), may offer complementary benefits in managing acne for PCOS patients through metabolic and anti-inflammatory effects. However, limitations such as small sample sizes, heterogeneity in study designs, and variable outcome measures warrant further

investigation. Clinicians may consider these nutraceuticals as adjunctive options while balancing evidence-based efficacy with patient-centered care.

1. INTRODUCTION

Acne is the most common skin condition in the United States. It affects about 85% of teenagers and can persist into and throughout adulthood.¹ There are four known mechanisms of acne pathogenesis: increased sebum production, inflammation, follicular hyperkeratinization, and colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*).² It is characterized by inflammatory lesions (papules and pustules) and non-inflammatory lesions (open and closed comedones). It is more likely to occur in areas with a high concentration of sebaceous glands. Sebum production promotes acne formation by providing a suitable environment for *C. acnes* to thrive. Hyperkeratinization, or the excessive production of keratin in the skin, blocks pores, further contributing to this cycle of inflammation and bacterial overgrowth. While acne is not life-threatening, it can significantly impact the daily quality of life in affected patients. Reported adverse psychological and physical effects include depression, anxiety, and emotional stress. Severe acne may also lead to permanent scarring, further impacting self-esteem and body image, making a comprehensive approach to management important.³

There is also growing research on the role of a comprehensive, holistic approach to managing skin conditions. For example, in addition to psychological stress, research indicates that several additional factors may contribute to the onset or aggravation of acne including high-glycemic diets, insufficient sleep, and hormonal imbalances.⁴ With regard to the role of hormones, it is well-documented that an increase in androgens is linked to sebum production, a component of acne pathogenesis. Moreover, androgens can also promote follicular hyperkeratosis in addition to their effect on the sebaceous glands.⁵ There is also research suggesting that acne in people with a polycystic ovarian syndrome (PCOS) diagnosis may be exacerbated by the excess androgen production associated with PCOS. It has also been found that there is an increase in androgen receptor sensitivity in those with PCOS relative to normal counterparts, potentially contributing to acne persistence or recurrence.^{5,6}

Current evidence-based acne treatments in PCOS patients include oral contraceptive pills (OCPs), and anti-androgen therapies such as spironolactone, cyproterone acetate, flutamide, and finasteride.⁶ These treatments target hormonal imbalances by either reducing androgen production or blocking androgen receptors, which helps lower sebum production and acne severity. While these treatments have proven effective in managing acne in PCOS, there is increasing patient interest in exploring nutraceutical vitamins, minerals, and plant-based compounds. These interventions often aim to address the root causes of acne by modulating hormones and reducing inflammation. With increasing research on their efficacy, nutraceuticals may offer an integrative and complementary approach to managing skin concerns. There is some research investigating the

use of nutraceuticals such as chromium, berberine, and selenium in PCOS individuals experiencing acne.⁷⁻¹⁰ Moreover, combinations of nutraceutical compounds along with metformin may also serve as an intervention to reduce acne in patients with PCOS.^{11,12} While this area of research is still gaining traction, the current state of evidence is limited. Other reviews have discussed the effects of nutraceuticals in metabolic syndromes seen in PCOS. However, to our knowledge, this is the first review to focus on acne reduction in PCOS patients. This systematic review aims to summarize the existing data on nutraceutical supplementation for acne in patients with PCOS.

2. MATERIALS AND METHODS

A search was conducted in PubMed, Embase, and Cochrane using the following keywords: “acne” AND (“PCOS” OR “hormones”) AND (“supplements” OR “nutrients” OR “herbs” OR “botanicals”) in August 2024. The PRISMA flow diagram depicting our search strategy and method of selecting articles is depicted in Figure 1.

Using Covidence, studies with relevant titles or abstracts were selected for full-text review. Randomized control trials on human subjects on oral supplementation and outcomes were included. Two authors independently reviewed the full texts, resolving any inclusion conflicts by consulting a third author. Two additional articles were obtained through manual searching. Data from each report were extracted collaboratively by two authors. Studies were categorized based on outcomes measured, and the discussion section included a qualitative comparison of study factors and populations to address heterogeneity and evidence quality. This review was not registered, and no protocol was prepared.

The following data were extracted from each included study: first author, year, study design, number of participants and their characteristics (including ethnicity, sex), intervention, control, dose per day (mg), duration of treatment, acne severity, and adverse side effects.

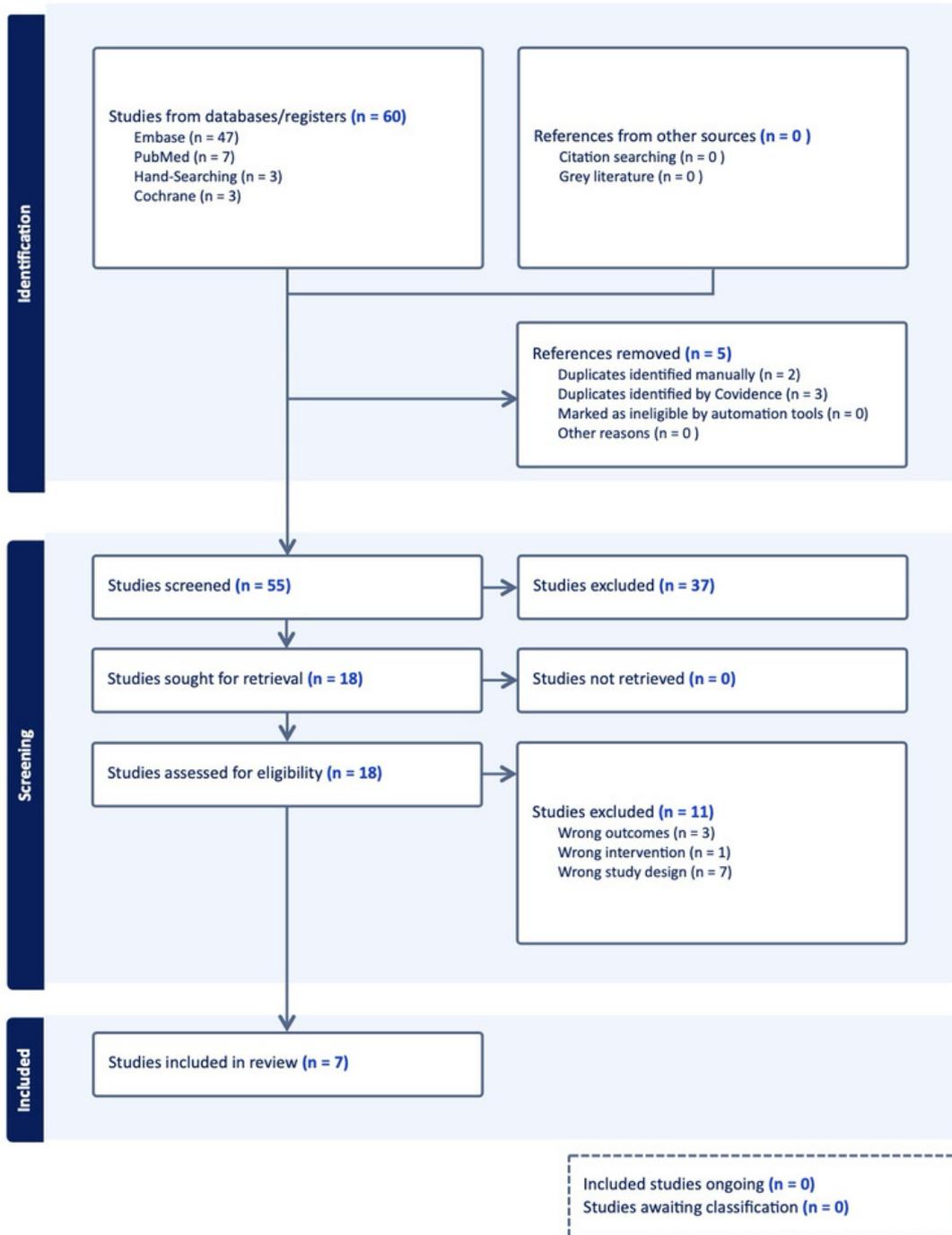
Institutional Review Board Statement: Not applicable as this is a review manuscript and did not involve primary research with human subjects.

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3. RESULTS

3.1. CHROMIUM

A randomized, double-blind, placebo-control trial assessed the effects of chromium supplementation on endocrine profiles, biomarkers of inflammation, and oxidative stress in 60 women with PCOS. Of the 60 participants, 30 women received 200 ug chromium supplements and 30 women received a placebo daily for 8 weeks. At the beginning and the end of the study, various outcome measures were assessed including endocrine profiles (such as prolactin, FSH,



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Figure 1. Flow chart of search strategy according to PRISMA.

LH, DHEA, free testosterone, etc), inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), biomarkers of oxidative stress such as total antioxidant capacity (TAC) and plasma malondialdehyde (MDA), and acne.¹³⁻¹⁵ Acne was evaluated following Kolodziejczyk et al's protocol, in four grades: 0 = no acne; 1 = minor acne on the face only; 2 = moderate acne on the face only; 3 = severe acne on the face and back or chest

Relative to placebo, the study found that chromium intake led to significant reductions in serum hs-CRP (-717.0 ± 1496.1 vs. $+227.1 \pm 1669.6$ ng/mL, $P = 0.02$), and plasma MDA (-0.1 ± 0.7 vs. $+1.1 \pm 1.5$ $\mu\text{mol/L}$, $P < 0.001$), and a significant rise in TAC concentrations ($+250.7 \pm 265.2$ vs. $+13.0 \pm 201.6$ mmol/L, $P < 0.001$). In addition, at 8 weeks, the prevalence of acne decreased with chromium treatment relative to placebo (20.0% vs. 3.3%, $P = 0.04$).⁷

However, this study did not find significant differences in endocrine outcomes, NO levels, or GSH levels after 8 weeks of chromium supplementation. During the study, no significant adverse effects were reported following chromium supplementation in PCOS patients.

3.2. BERBERINE

Berberine is a compound found in plants of the Berberidaceae family and has been found to have various actions, including anti-inflammatory, hypoglycemic, and antioxidant properties. One study evaluated the role of berberine on insulin resistance, inflammation, lipid metabolism, sex hormone profile, and symptoms correlated to hyperandrogenism, such as acne, in normal to overweight women with PCOS and normal menses. The study design was a pre-post intervention involving 12 participants who took two daily oral doses of 550 mg berberine supplement tablets for 60 days. The Global Acne Grading System (GAGS) and Cardiff Acne Disability Index (CADI) were used to measure acne before and after 60 days of berberine supplementation.

A significant decrease in acne symptoms was demonstrated by GAGS ($\beta = -8.17$, $P < 0.0001$) and CADI ($\beta = -8.158$, $P < 0.0001$) following 60 days of berberine supplementation.⁸ Rondanelli et al confirmed a prior study's results that two months of berberine supplementation in obese PCOS women significantly reduced CRP levels ($\beta = -0.14$, $P = 0.02$), in addition to being the first to report a statistically significant reduction in two other inflammatory markers after berberine supplementation: the pro-inflammatory cytokine TNF- α ($\beta = -6.17$, $P = 0.009$) and visceral adipose tissue ($\beta = -49.96$, $P = 0.003$). Following berberine supplementation, there was a significant reduction of glycemia levels ($\beta = -4.50$, $P = 0.0001$), insulin levels ($\beta = -2.83$, $P = 0.005$), and insulin resistance and function of pancreatic beta-cells (via Homeostasis Model Assessment (HOMA)) ($\beta = -0.69$, $P = 0.003$). Additionally, they reported decreases in testosterone ($\beta = -0.15$, $P = 0.007$) and free androgen index (FAI) (calculated by $FAI = \text{total testosterone} / \text{SHBG} \times 100$), while an increase was seen in sex hormone-binding globulin (SHBG) ($\beta = 9.04$, $P = 0.03$). Adverse effects were monitored through liver and kidney function studies in addition to self-report by subjects, and no adverse effects were found.

The effects of berberine on acne symptoms in PCOS were also studied in a controlled, randomized, multicenter, and open-labeled clinical trial in which 130 Pakistani women with a diagnosis of PCOS and fertility problems (defined by difficulty conceiving) due to menstrual and ovary abnormalities were enrolled. The experimental group ($n = 65$) received two daily doses of 180 mg berberine in a phytosome form (550 mg Berberine Phytosome®), while the control group ($n = 65$) did not receive any supplement or placebo pill. Fifty-one of the initial 65 experimental participants were analyzed after 14 were lost to follow-up, and 55 of the initial 65 control participants were analyzed after 10 were lost to follow-up.

A dermatologist determined acne severity based on acne type (comedones, papules, pustules, and nodules) and anatomic location (forehead, cheeks, nose, and chin), and

participants' acne was given a score to be compared in the study. Results demonstrated acne improvement in 50% of women compared to 16% in the control group ($P = 0.0409$).⁹ No adverse effects were reported in this study.

3.3. ANTIOXIDANT COMBINATION

Lipoic acid, *N*-acetylcysteine, vitamin B6, and *S*-adenosyl-L-methionine (**ALA + NAC + B6+SAME**)

A prospective, partially randomized, multicenter study was conducted to investigate the effects of an antioxidant supplement on metabolic, endocrine, and clinical parameters in comparison to an oral contraceptive in non-diabetic women newly diagnosed with PCOS. The antioxidant combination included lipoic acid, *N*-acetylcysteine, vitamin B6, and *S*-adenosyl-L-methionine. For 6 months, the 96 participants were either given the antioxidant combination administered as two tablets daily (each tablet included ALA 75 mg, NAC 100 mg, B6 0.65 mg, and SAME 200 mg (MetioNac®, Margan Biotech SL)) ($n = 41$), or an oral contraceptive (administered as ethinylestradiol 0.02 mg plus drospirenone 3 mg once daily or drospirenone 4 mg once daily (according to physician criteria)) ($n = 27$), or both the antioxidant combination and an oral contraceptive ($n = 28$). Although there were no statistically significant differences between the experimental groups, all three treatments demonstrated improvements in clinical parameters associated with PCOS (hirsutism and acne), quality of life score, and a significant reduction in androstenedione levels.¹¹ No serious adverse events were reported in this study.

3.4. SELENIUM

To investigate the effects of selenium supplementation on reproductive outcomes, inflammation, oxidative stress, and acne, a randomized, double-blind, placebo-controlled trial was conducted in women with PCOS.¹⁰ Sixty-four women were divided into two groups: one receiving 200 μg of selenium daily, and the other a placebo for eight weeks.

The study found that selenium supplementation had a statistically significant effect on reducing acne, reporting acne reduction by 46.9% in the selenium group while the placebo group showed a 12.5% reduction after the intervention (P value of 0.003). This reduction was accompanied by improvements in inflammatory and oxidative stress markers, which are closely associated with acne in PCOS patients. Specifically, the selenium group showed significant decreases in CRP (-3.02 mg/L vs. -1.2 mg/L, $P < 0.001$) and MDA (-0.33 $\mu\text{mol/L}$ vs. $+0.12$ $\mu\text{mol/L}$, $P < 0.001$), while antioxidant enzyme activity, such as glutathione peroxidase, increased significantly ($+142.8$ U/L vs. -25.2 U/L, $P < 0.001$).

Acne lesions were assessed using a 4-point scale: 0, no acne; 1, minor acne on the face; 2, moderate acne on the face only; and 3, severe acne, face, and back or chest. Additionally, there were no significant adverse effects reported related to selenium supplementation.

3.5. MAGNESIUM

A randomized clinical trial investigated the effects of magnesium supplementation on various measure outcomes in women with PCOS.¹⁶ In this study, 64 women were randomly assigned to receive either 250 mg of magnesium oxide tablet (n=32) or a placebo daily for 12 weeks (n=32). One of the outcome measures in the study was acne which was assessed with the Global Acne Grading System at the baseline and end of the study.

The authors found that magnesium supplementation had no significant effect on acne in patients with PCOS and that further studies are needed to determine its effects on these factors. In addition, no adverse events were reported in the study.

3.6. METFORMIN VERSUS COMBINED THERAPY OF METFORMIN WITH MYO-INOSITOL PLUS D-CHIRO-INOSITOL

Inositol is a naturally occurring compound that has been found to have insulin-sensitizing, anti-inflammatory, and antioxidant properties. Different forms of inositol can be found in supplements, including myo-inositol and D-chiro-inositol. One prospective, non-blinded randomized controlled trial, compared the effects of metformin as monotherapy to a combination therapy of metformin, myo-inositol (MI), and D-chiro-inositol (DCI) in women newly diagnosed with PCOS.¹² In this study, 72 female subjects with PCOS between the ages of 18 to 45 were randomized into two groups of 36. Group I was given metformin 500 mg twice daily for six months, while group II received the same metformin dosage in combination with 550 mg of MI and 150 mg of DCI twice daily for the same period. At the end of the 6-month study period, there was a significant reduction in mean global acne score from baseline to six months in group II compared to group I ($P = 0.004$).

4. DISCUSSION

The studies evaluated in this systematic review suggest that certain oral nutraceuticals, such as chromium, berberine, and selenium may improve acne in women with PCOS, through mechanisms of action related to metabolism, inflammation, and oxidative stress reductions.

One shared pathway in the pathophysiology of both PCOS and acne is glucose metabolism, which would offer insights into how some of these supplements confer their benefits. PCOS is a metabolic disorder linked to abnormal glucose metabolism with affected patients often demonstrating insulin resistance, high glucose levels, and an increased risk of type II diabetes. These disturbances in glucose metabolism accompanied by hyperinsulinemia contribute to increased androgen concentrations. These elevated levels of androgens are linked to acne development, making insulin resistance a pivotal factor in both conditions. A recent study showed that individuals with acne were more likely to exhibit insulin resistance than those without acne, highlighting the role of glucose dysregulation

in acne pathogenesis and its associated inflammatory responses.¹⁷ Additionally, insulin-like growth factor-1 (IGF-1), which is usually increased in insulin resistance, can stimulate sebaceous gland activity, worsening acne symptoms and indicating potential intervention points for nutraceuticals targeting insulin sensitivity and glucose control.¹⁸

Moreover, it is noteworthy to understand the roles of oxidative stress and inflammation and how nutraceuticals might benefit both conditions. The hormonal imbalances and insulin resistance seen in PCOS typically promote oxidative stress and low-grade chronic inflammation, both of which have been implicated in the pathogenesis of acne and metabolic syndrome.^{19,20} This link highlights the importance of anti-inflammatory and antioxidant measures in the management of PCOS and acne. Nutraceuticals with antioxidant and anti-inflammatory properties—such as inositol, N-acetylcysteine, and selenium—may address these oxidative and inflammatory states, potentially reducing androgen levels and improving insulin sensitivity.

Berberine is a naturally occurring compound found in a variety of plants. It has been found to affect glucose metabolism, with studies suggesting it may work to reduce blood glucose levels and support insulin sensitivity.²¹ In the two berberine studies included in this review, berberine supplementation alone improved acne via statistically significant reductions in GADS and CADI scores in normal or overweight women with PCOS and normal menses,²² and it has improved acne in women with PCOS who have irregular or absent menstrual cycles and fertility problems.²³ With berberine having been compared to metformin as an insulin sensitizer in women with PCOS, the improvement noted in acne may be related to improving glucose metabolism and in turn, modulating endocrine function in PCOS patients.¹¹

Further, berberine has shown antioxidant and anti-inflammatory effects in women with PCOS. Berberine's anti-inflammatory and antioxidant effects have been demonstrated through decreased levels of CRP, TNF- α , and VAT,⁸ and increased activity of superoxide dismutase and glutathione peroxidase.²⁴ This activity may contribute to the improvement in acne Di Pierro et al and Rondanelli et al showed. Berberine supplementation alone improved acne via statistically significant reductions in GADS and CADI scores in normal or overweight women with PCOS and normal menses.⁸ Similarly, testosterone and FAI decreased while SHBG increased significantly after two months of berberine supplementation. The mechanism by which berberine improves acne is unclear, but there are several hypotheses in addition to its antioxidant and anti-inflammatory effects. A study on rats with PCOS showed that berberine supplementation inhibited the inflammatory response and cell apoptosis.²⁵ Because berberine is a comparable insulin sensitizer to metformin in women with PCOS, some have postulated that berberine could reduce lipid synthesis by improving insulin resistance and lipid metabolism, modulating endocrine function in PCOS patients.²⁶ Despite not following a low-calorie diet, berberine additionally improved PCOS body composition by redistributing adipose tissue and reducing visceral fat mass.²⁶

Table 1. Summary of all studies included: design, sample size, intervention, outcomes, and mechanism of action, dosing, number of participants, dosing of intervention and control, and key outcomes.

Summary of Included Studies					
Author (Year)	Study Design	Sample Size	Intervention (Agent / Dose / Frequency)	Outcomes	Mechanism of Action
Acne and PCOS					
Jamillian et al (2016) ⁷	Randomized, double-blind, placebo-controlled trial	60	One tablet containing chromium 200 µg supplements (n = 30) or placebo daily (n = 30) for 8 weeks	Decreased acne and alopecia. Significant reductions in hirsutism, serum hs-CRP, and plasma MDA. Significant rise in TAC.	Decreases markers of inflammation and oxidative stress
Rondanelli et al (2021) ⁸	Pre-post intervention study	12	One tablet containing berberine 550 mg twice a day for 60 days No control group	Significant decrease in acne symptoms in normal to overweight women with PCOS. GAGS ($\beta = -8.17$, $P < 0.0001$) and CADI ($\beta = -8.158$ $P < 0.0001$)	Anti-inflammatory and antioxidant effects decreasing CRP, TNF- α , and VAT levels
Di Pierro et al (2023) ⁹	Controlled, randomized, multicentric, and open-labeled clinical trial	130	One tablet containing berberine 180 mg in a phytosome form (Berberine Phytosome® 550 mg) twice a day for 90 days (n = 65) No supplement in the control group (n = 65)	GAGs global score, improvement in 50% of women (vs. 16% in the control group; $P = 0.0409$)	Anti-inflammatory and antioxidant effects decreasing CRP, TNF- α , and VAT levels
Pingarrón Santofimia et al (2023) ¹¹	Prospective, partially randomized, multicenter study	96	One tablet containing ALA 75 mg, NAC 100 mg, B60.65 mg, and SAME 200 mg (MetioNac®, Margan Biotech SL) twice a day for 6 months (n = 41) OCP - ethinylestradiol 0.02 mg plus drospirenone 3 mg once daily or drospirenone 4 mg once daily (n = 27) MN + OC (n = 28)	No statistically significant differences between the experimental groups. However, the treatments demonstrated improvements in acne, hirsutism, irregular menstruation, and quality of life in non-diabetic women newly diagnosed with PCOS.	Hypothesized to be related to glutathione metabolism and metabolic syndrome
Razavi et al (2016) ¹⁰	Randomized, double-blind, placebo-controlled trial	64	200 µg selenium daily (n = 32) or placebo (n = 32) for 8 weeks	Acne was marked by a 4-point scale: 0, no acne; 1, minor acne on face; 2, moderate acne on face only; and 3, severe acne, face and back or chest. Acne decreased following the consumption of selenium supplements compared with placebo (46.9 vs. 12.5 %, $P = 0.003$) Significant reduction in acne, CRP, and malondialdehyde. Significant increase in glutathione peroxidase.	Neutralizes reactive oxygen and nitrogen species
Jaripur et al (2022) ¹⁶	Randomized clinical trial	64	Magnesium group (n = 32) or placebo group (n = 32) 250 mg magnesium	Via Global Acne Grading System. No significant effect on acne in women with PCOS.	Reduced oxidative stress, controls

Summary of Included Studies					
			oxide tablet (Magni One® produced by DonyaDarou, Tehran, Iran) per day was administered for 10 weeks. Place group received a placebo pill		inflammation, and stabilizes endothelium
Bahadur et al (2021) ¹	Prospective, non-blinded randomized controlled trial	72	Group I received metformin 500 mg twice a day orally for 6 months Group II received metformin 500 mg twice a day orally and MI 550 mg plus DCI 150 mg twice daily orally for 6 months	Via Global Acne Grading System. Significant reduction in mean global acne score in group taking metformin, MI, and DCI (group II). (P = 0.004). No significant acne reduction in group taking metformin only (group I).	Alters gut microbiota composition, increasing the Bacteroidetes-to-Firmicutes (B/F) ratio

Before Rondanelli et al's study, pure berberine supplementation was known to cause gastrointestinal discomfort, making berberine an unfavorable option for long-term treatment of chronic conditions.²⁷ Supplementation with berberine in phytosome form did not cause gastrointestinal discomfort, possibly due to improving bioavailability and reducing the dose needed. These findings suggest the phytosome form of berberine (with sunflower lecithin, pea protein, and grape seed extract) may be better tolerated. Limitations include the small sample size and lack of control. Additionally, the population studied was normal to overweight women with PCOS who experience normal menses, which may not be generalizable to all women with PCOS.

Di Pierro et al partially overcame the limitations of Rondanelli et al by increasing the number of participants in the study, using a randomized and controlled protocol, and including women with PCOS who have irregular or absent menstrual cycles and fertility problems. Their study demonstrated improvement in acne, reduction in hirsutism, resumption of normal menstruation, and normalization of ovarian anatomy following phytosome delivery of berberine supplementation. Though the study population is a larger group, it is important to note that the results may be specific to the demographic of the participants in the study: 130 Pakistani women with PCOS and infertility problems due to menstrual and ovarian abnormalities. It is also important to highlight that the results of this study cannot be fully attributed to berberine, as the phytosome formulation consists of other ingredients, which will need to be further studied for their effects on PCOS-related acne.

In addition, chromium is a naturally occurring essential trace mineral and according to a 2020 systematic review, various formulations of chromium supplements have been found to improve glycemic control at a wide range of doses.⁸ The Jamilian et al study demonstrated that chromium picolinate (200 µg) supplementation significantly decreased markers of inflammation and oxidative stress, reducing acne in those with PCOS. The underlying

mechanism of these findings may be related to chromium's effect on glucose metabolism. However, it is also important to note that there are different forms of chromium (chromium nicotinate, chromium histidine, chromium picolinate), and while this study found no changes in hormones with the picolinate form of chromium, further research in studies with larger sample sizes will be needed to understand the effect of other chromium formulations and their effect on hormones, inflammation, oxidative stress, and acne in those with PCOS.

The antioxidant combination of ALA + NAC + B6 + SAME has demonstrated benefit for acne in PCOS in one study. Supplementing with the antioxidant combination of ALA + NAC + B6 + SAME shows potential for people who desire fertility to treat PCOS-related acne.¹¹ Oral contraceptives are not an option for women who want to become pregnant. The results of this study offer a potential non-OCP option with similar efficacy for treating acne in women who want to conceive and encourage further research on the safety of nutraceutical use for acne in PCOS patients. The mechanism of this antioxidant combination's action is unknown but hypothesized to be related to glutathione metabolism and metabolic syndrome. Glutathione is decreased by 50% in PCOS patients.²⁸ The antioxidant combination of ALA + NAC + B6 + SAME induces de novo glutathione synthesis and possibly improves diabetes reactive oxygen species destruction of pancreatic beta cells via reactive oxygen species seen in diabetes.¹¹ Limitations of this study include a lack of negative control, a lack of randomization in the experimental group, and a lack of a central laboratory.

Selenium has demonstrated benefits for acne in PCOS in one RCT. As a trace element with potent antioxidant properties, selenium has garnered increasing attention for its role in nutrition and health. One of its critical functions is mediated by selenoprotein P (SeP), a liver-derived protein responsible for distributing selenium throughout the body, particularly to endocrine glands and insulin-responsive tissues. Research into selenium supplementation has revealed a significant impact on acne, particularly in PCOS

patients, by addressing systemic inflammation and oxidative stress—key components in acne pathogenesis. Selenium's antioxidant properties, particularly its ability to neutralize reactive oxygen and nitrogen species, are believed to drive these effects. A notable study demonstrated a 46.9% reduction in acne lesions in the selenium group compared to 12.5% in the placebo group ($P = 0.003$). However, the lack of standardized acne severity scales in this study limits the precision of its findings. A separate case-controlled study further emphasized selenium's role in regulating sebum production and its anti-inflammatory properties, strengthening its potential as a therapeutic agent for acne treatment.²⁹

Interestingly, lower blood selenium levels were observed in individuals with acne vulgaris, suggesting a potential protective role of selenium against skin conditions like acne.²⁹ A systematic review supported these findings, linking selenium deficiency to exacerbated acne lesions. Despite these promising results, caution is warranted with selenium supplementation.³⁰ Excessive selenium intake has been linked to potential risks, such as worsening insulin resistance and increasing the risk of type II diabetes by interfering with insulin signaling through Glutathione Peroxidase 1 and SeP.

While magnesium supplementation has shown no significant direct effect on acne lesion reduction in one RCT study, its critical role in glucose metabolism and insulin sensitivity makes it an essential factor to consider for PCOS patients. Hypomagnesemia has been associated with worsening insulin resistance, which could indirectly exacerbate acne. Magnesium's ability to reduce oxidative stress, control inflammation, and stabilize the endothelium suggests a potential benefit in metabolic and skin health.³¹ However, studies on magnesium's effects on acne are limited. One investigation highlighted the challenges of a small sample size, compounded by recruitment difficulties during the COVID-19 pandemic. Self-reported data in this study also introduced potential recall bias. Future research should focus on larger, well-controlled trials and explore various magnesium formulations to determine their specific roles in PCOS-related acne management.

Recent research has explored metformin's impact on the gut microbiome and its implications for acne management. A clinical trial demonstrated that metformin significantly altered gut microbiota composition, notably increasing the Bacteroidetes-to-Firmicutes (B/F) ratio, initially lower in acne patients. This change, observed after 12 weeks of met-

formin treatment ($P = 0.006$), is particularly relevant. A reduced B/F ratio has been linked to inflammatory diseases, obesity, and metabolic disorders—all common in PCOS patients.³² Inositols, another promising intervention, have shown favorable outcomes for metabolic and hormonal imbalances in PCOS. Supplementation with d-chiro-inositol (DCI) increased SHBG levels and reduced free testosterone and LH levels while improving estradiol levels. Over three months, therapies combining myoinositol (MI) plus folic acid or the combination of MI, DCI, and folic acid significantly improved insulin resistance, glycosylated hemoglobin, lipid profiles, and blood pressure.³³ These findings suggest a potential role for inositols in acne management through hormonal and metabolic modulation. Metformin and inositols have synergistic effects, enhancing both metabolic and dermatologic outcomes for PCOS patients. Importantly, no adverse effects were reported in the studies investigating these therapies. However, small sample sizes remain a limitation, underscoring the need for larger trials to confirm efficacy and safety. These findings highlight the importance of integrating metformin with nutraceuticals such as inositols for comprehensive PCOS management.

Overall, the studies in this systematic review suggest that oral supplementation with ingredients, such as chromium, berberine, and selenium may play a role in managing PCOS-related acne. However, due to limitations such as small sample sizes, lack of control groups, and variability in study design and measure outcomes, further research will be necessary to better understand the efficacy and safety of these supplements and their mechanisms of action in the treatment of acne in women with PCOS.

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CONFLICTS OF INTERESTS

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