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REVIEW ARTICLE

Effect of astaxanthin supplementation on oxidative stress in adult women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

BACKGROUND
Polycystic ovary syndrome (PCOS) can cause significant morbidity through fertility disorders and most often found in the productive age. Recent research suggests that oxidative stress plays an important role in the pathogenesis of PCOS. Astaxanthin (AST) has broad protective effects, particularly in the regulation of antioxidant and anti-inflammatory activity. The objective of this systematic review and meta-analysis was to evaluate the efficacy of AST supplementation on PCOS management.

METHODS
A systematic literature search was conducted in PubMed, Scopus, Science Direct, and Cochrane Library from January 2020 to March 2025. Randomized controlled trials (RCTs) assessing astaxanthin supplementation in adult women with PCOS were included. Outcomes of interest were malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC). Data were analyzed using Review Manager (RevMan) version 5.4.1. Pooled effects were calculated as mean differences (MDs) with 95% confidence intervals (CIs).

RESULTS
Four RCTs involving 194 participants were included. Astaxanthin supplementation significantly reduced MDA levels (MD −0.670; 95% CI −1.070 to −0.270; p = 0.001; I^2 = 93%) and significantly increased TAC levels (MD 0.030; 95% CI 0.000 to 0.060; p = 0.030; I^2 = 76%). No significant effect was observed on SOD levels (MD 0.025; 95% CI −0.850 to 1.350; p = 0.660; I^2 = 57%). The overall risk of bias across included studies was low.

CONCLUSION
This systematic review shows that AST supplementation significantly reduced lipid peroxidation in women with PCOS. These findings suggest that AST may serve as potential adjuvant antioxidant therapy in PCOS management.

Keywords: Polycystic ovary syndrome, astaxanthin supplement, antioxidant, placebo, oxidative stress, adult women

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a collection of symptoms related to reproductive hormones in women with low grade inflammation.[1,2] Polycystic ovarian syndrome can cause significant morbidity, such as fertility disorders, hormone-induced acne, and menstrual disorders.[3-5] This condition affects about 5–15% of women worldwide, accounts for about 70% of ovulatory infertility cases, and is most often found in the reproductive age, between 20-30 years.[6-8] According to previous studies, obesity has a statistical link to fat mass and obesity-associated (FTO) gene, but its link to PCOS is not entirely clear.[9,10] Many studies have examined the relationship of genetic and epigenetic factors with the occurrence of PCOS.[11-15] Recent research suggests that oxidative stress plays an important role in the pathogenesis of polycystic ovary syndrome, including effects on follicular development, insulin resistance, and hyperandrogenemia.[16-18] Astaxanthin (AST) is believed to penetrate the phospholipid bilayer in biological membranes.[19,20] This is supported by observations showing that AST can scavenge reactive oxygen species (ROS), reactive nitrogen species (RNS), and free radicals, both in the inner and surface layers of lipid membranes.[21-24] Overall, research over the past two decades has shown that AST has broad protective effects, particularly in the regulation of antioxidant and anti-inflammatory activity, enhancement of immune responses, and protection of DNA from damage.[25-27] Although the detrimental impact of oxidative stress on female fertility is recognized, and the potential benefits of AST as a powerful antioxidant have been explored, there remains a significant gap in the literature. This systematic review study was conducted to synthesize data from human clinical trials to determine the potential therapeutic benefits of AST as a complementary treatment for managing the complications associated with PCOS, while also highlighting the need for further high-quality research in this area.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines.[28] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number **CRD420251005588** and the link: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251005588

Search strategy

A comprehensive literature search was performed in PubMed, Scopus, ScienceDirect, and the Cochrane Library to identify relevant studies published in Indonesian and English between January 2020 and March 2025. The search strategy combined keywords and Medical Subject Headings (MeSH) related to "astaxanthin", "polycystic ovary syndrome", and "oxidative stress".[29] Reference lists of relevant articles, systematic reviews, and meta-analyses were also manually screened to ensure completeness.

Inclusion and exclusion criteria

The investigators conducted the data search process using electronic devices, followed by an initial screening of research data. A thorough review of the article texts was then performed based on the inclusion and exclusion criteria. Articles meeting these criteria were included in the systematic review and meta-analysis. The selection process was based on the title and abstract, with any inconsistencies re-checked by researchers. The inclusion criteria encompassed studies in Indonesian and English, involving human subjects, and focusing on randomized controlled trials (RCTs) with astaxanthin intervention in adult women with PCOS across various countries based on population, intervention, comparison and outcome (PICO) (Table 1).[30, 31] Exclusion criteria included animal studies, non-RCT studies, no astaxanthin intervention, and outcomes unrelated to oxidative stress.

Table 1. Description of PICO elements

PICO element	Description
Population (P)	Adult women diagnosed with PCOS
Intervention (I)	Astaxanthin supplementation
Comparison (C)	Placebo
Outcome (O)	Changes in oxidative stress markers (MDA, SOD, TAC)

Eligibility criteria

The population included in this analysis were adult women with a diagnosis of PCOS. This study examined the impact of AST and placebo interventions on this population in various countries. Pregnant women, incomplete articles, and inappropriate and irrelevant data were excluded.

Data extraction

The researchers independently collected relevant information, including study variables such as the main author, publication year, research method, sample size, and the presence of a control group. Additionally, they evaluated genetic factors, the method used to assess AST intervention, and key findings. The data were organized into a table containing the author's name, publication year, country of origin, study design, sample size, intervention vs. placebo comparison, and results.

Risk of bias assessment

The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2). This tool evaluates bias across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.[32] Each domain was rated as low risk, some concerns, or high risk of bias. The overall risk of bias for each study was determined according to the Cochrane Handbook guidelines. Any disagreements between reviewers were resolved by consensus.

Outcomes of interest

The primary outcomes of this review were changes in oxidative stress biomarkers, including malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC). These biomarkers were selected because they represent lipid peroxidation status, enzymatic antioxidant defense, and overall antioxidant capacity, respectively. Secondary outcomes, when available, included inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and catalase (CAT).

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.4.1. Continuous outcomes were summarized using **mean differences (MDs)** with corresponding **95% confidence intervals (CIs).** Statistical heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. A random-effects model was applied when significant heterogeneity was present; otherwise, a fixed-effects model was used. Forest plots were generated to illustrate pooled effect estimates, and funnel plots were constructed to explore potential publication bias.

RESULTS

Study selection and characteristics

From 168 identified records, 112 were screened after removing duplicates. Eight full-text articles were assessed for eligibility, with four RCTs included in the final analysis involving 194 participants. The study selection process is illustrated in the PRISMA flow diagram (Figure 1). All included studies were RCTs conducted in Iran. Astaxanthin dosage ranged from 6 to 12 mg/day, with intervention durations between 40 to 84 days. Outcome measures included malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC). Details and the characteristic of studies included are summarized in Table 2.

This study processed 4 studies that determined the impact of AST on oxidative stress in women with PCOS, with a total sample size of 194 individuals. The research method included in this study was the randomized controlled trial (RCT). Among the data resulting from the 4 RCTs, the investigators determined which data were to be included in the present study, in accordance with the inclusion and exclusion criteria. The overall diagram of the selection process can be seen in Figure 1 and the PRISMA checklist in the Supplementary material.

Risk of bias

The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2). This tool evaluates bias across five domains: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, and (v) bias in selection of the reported result. Each domain was judged as low risk, some concerns, or high risk of bias. Overall risk of bias was determined

according to the Cochrane Handbook recommendations. Overall, all four studies demonstrated a low risk of bias. However, minor concerns were noted in selective reporting and outcome measurement in some studies, though these did not substantially impact the overall quality or validity of the evidence. The risk of bias summary is presented in Figure 2, indicating a generally robust methodological quality across the included trials.

Table 2. Characteristics of included studies

Authors	Country	Research methods	Population		Intervention	Post intervention results		Conclusion
			Intervention	Control		Astaxanthin	Placebo	
Gharaei et al.[33]	Iran	RCT	20	20	The intervention group received 8 mg AST, and the control group received the placebo daily for 40 days.	MDA: 103.1 ± 79.44 SOD: 23.96 ± 3.7 TAC: 0.398 ± 0.20 CAT: 3.91 ± 2.61	MDA : 93.66 ± 43.47 SOD : 24.01 ± 4.7 TAC : 0.599 ± 0.21 CAT: 8.22 ± 2.38	Astaxanthin supplementation in women with PCOS was associated with increased serum antioxidant parameters.
Jabarpour et al.[21]	Iran	RCT	27	26	The intervention group receiving 12 mg/day for 60 days	MDA: 2.18 ± 0.89 SOD: 177.5 ± 19.85 TAC: 0.32 ± 0.04	MDA: 2.55 ± 0.82 SOD: 173.4 ± 27.32 TAC: 0.28 ± 0.06	The molecular pathways of endoplasmic reticulum (ER) stress can be modified by AST as a natural supplement through antioxidant activity.
Rostami et al. [34]	Iran	RCT	28	29	Intervention group received 12 weeks of AST treatment 6 mg per day and control group received placebo	MDA: 14.619420 ±2.505294 SOD: 13.458493 ±7.276019 TAC: 398.661250 ±57.686710 CAT: 11.338269 ±4.778701 IL-1β: 4.5152±0.9078 IL-6: 5.0543±0.7099 TNF-α: 2.5200±0.5255	MDA : 21.392248 ±4.035089 SOD: 9.077471 ±4.587139 TAC : 406.175507 ±64.271907 CAT: 13.272669 ±8.355258 IL-1β: 6.4580±0.9847 IL-6: 5.5208±0.5218 TNF-α: 3.0102±0.7495	AST administration could be a promising approach to reduce oxidative stress and inflammatory responses in female reproductive disorders.
Shafie et al.[35]	Iran	RCT	26	25	Intervention group received 12 mg/day Astaxanthin and control group received placebo for eight weeks	MDA: 12.94 ± 1.16 SOD : 14.49 ± 2.12 TAC: 816.18± 126.06 Il-6: 2.05± 0.60 Il-8: 24.52 ± 3.68	MDA: 13.32 ± 2.05 SOD: 14.83 ± 2.60 TAC: 835.71 ± 149.95 Il-6: 2.98 ± 1.02 Il-8 : 28.66 ± 8.74	AST demonstrates promise as an adjuvant therapy in COS for patients with POR. The findings suggest that AST supplementation may improve ART outcomes, including increased numbers of retrieved oocytes, MII oocytes, frozen embryos, and high-quality embryos.

Note: First row: Ref 33 - Gharaei et al.; second row: Ref 21 – Jabarpour et al.
Third row: Ref 34 – Rostami et al.; fourth row: Ref 35 – Shafie et al.

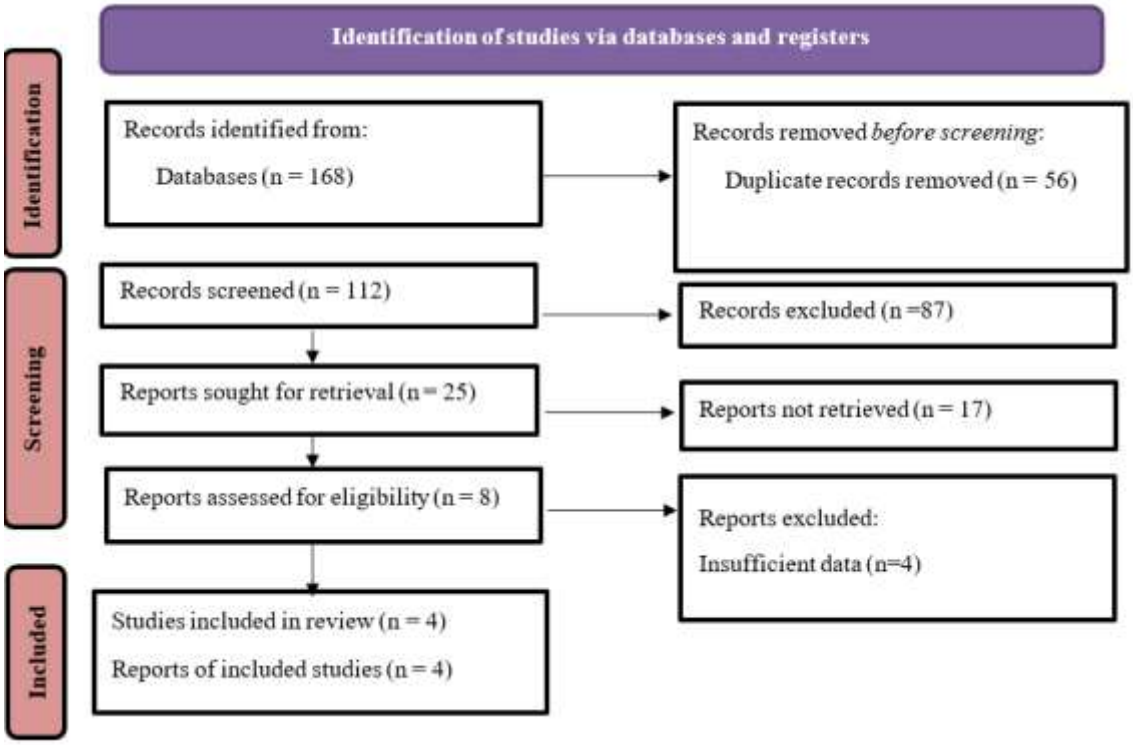

Figure 1. Flow diagram of the study selection procedure

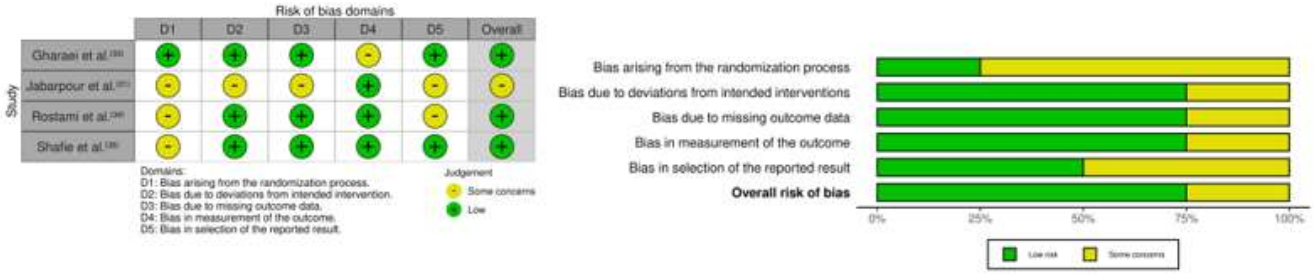

Figure 2. Risk of bias by RoB 2

Meta-analysis of malondialdehyde and superoxide dismutase

The analysis of oxidative stress malondialdehyde (MDA) found a mean difference of 95%CI -0.670 [-1.070, -0.270]; p=0.001; I^2 = 93%. The second analysis was on superoxide dismutase (SOD), resulting in a mean difference of 95%CI 0.025 [-0.850,1.350]; p=0.660; I^2 = 57%. The result of the last analysis on total antioxidant capacity (TAC), showed a mean difference of 95%CI 0.03 [0.000,0.060]; p=0.030; I^2 = 76%. The forest plots are illustrated in Figure 3 panels a-c below.

Publication Bias

To evaluate potential publication bias, funnel plots were generated for each oxidative stress marker analyzed (MDA, SOD, and TAC). A visual inspection of the plots revealed some asymmetry, particularly in the MDA funnel plot, suggesting the possibility of small-study effects or selective publication. The funnel plot for SOD appeared relatively symmetric, indicating minimal publication bias for this outcome. Meanwhile, the TAC funnel plot showed moderate asymmetry, which could reflect either true heterogeneity among studies or unpublished negative findings. Although funnel plot asymmetry alone cannot definitively confirm publication bias, these findings highlight the importance of cautious interpretation of results, especially given the limited number of studies included (n=4). Further studies with larger sample sizes and rigorous design are needed to enhance the strength and generalizability of these findings. The funnel plots are illustrated in Figure 4 (Panels a–c) for each respective marker.

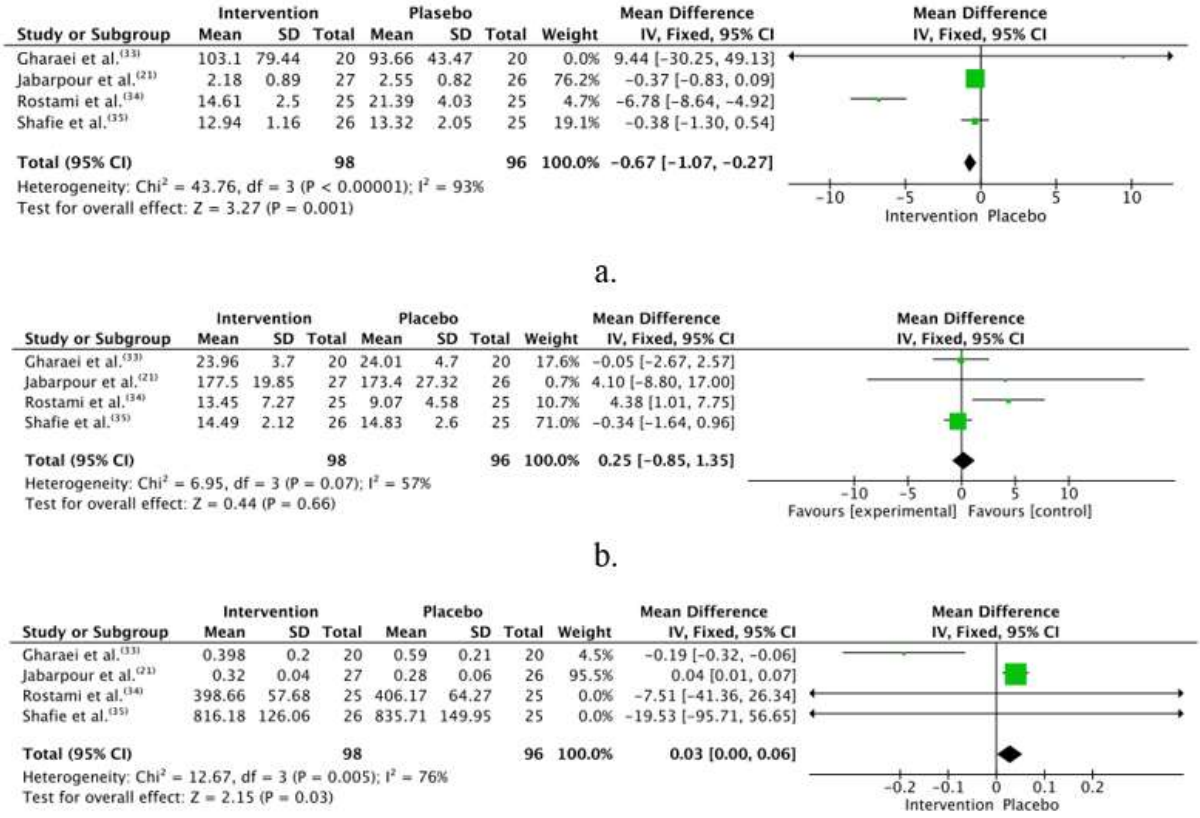

Figure 3. Forest plots, the statistical results of the studies on: a. malondialdehyde (MDA); b. superoxide dismutase (SOD); c. total antioxidant capacity (TAC)

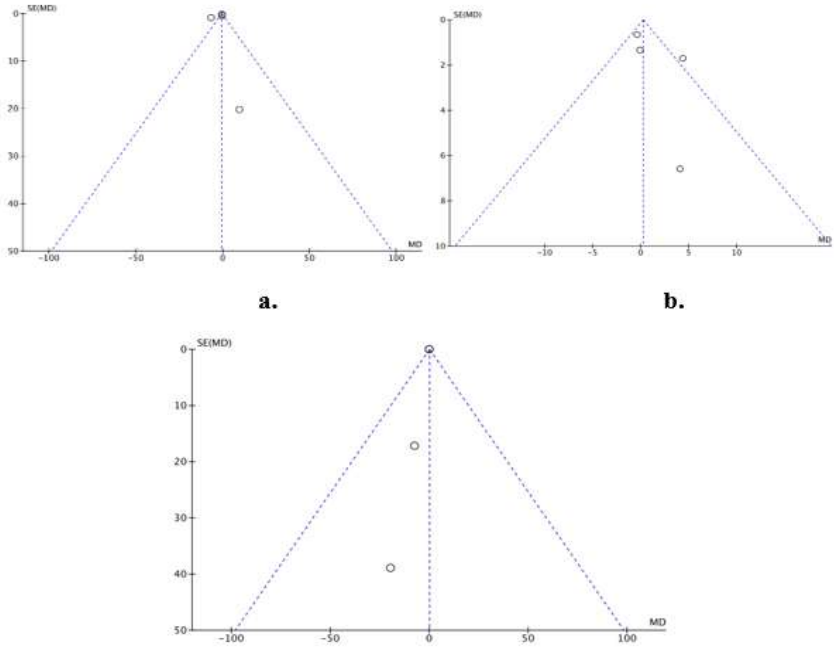

Figure 4. Funnel plots: **a**. malondialdehyde (MDA); **b.** superoxide dismutase (SOD); **c.** total antioxidant capacity (TAC)

DISCUSSION

Astaxanthin functions as an antioxidant with high free radical scavenging capacity.[26] Astaxanthin is well known for its strong ability to inhibit the accumulation of lipid peroxides resulting from lipid peroxidation chain reactions.[36,37] In biological environments, astaxanthin has been found in lipid droplets, cell membranes, or bound to proteins due to its highly lipophilic nature.[38-40] Additionally, similar to several other xanthophylls, astaxanthin is believed to span across phospholipid bilayers in biological membranes.[20,41,42] This assumption is supported by observations showing that astaxanthin can quench or scavenge ROS, RNS, and free radicals in both the interior and surface layers of lipid membranes.[4,7]

Malondialdehyde (MDA) is a key biomarker of lipid peroxidation and oxidative stress.[6,43,44] Elevated MDA levels indicate increased oxidative damage, which is associated with conditions such as PCOS.[16,45,46] From the results of the study on MDA, we can see that astaxanthin interventions resulted in significant MDA levels (mean difference -0.670; 95% CI: -1.070- -0.270; p=0.001), but that there was a high degree of heterogeneity, as seen from the results of $I^2 = 93\%$. It was seen that AST had a specific effect in lowering the MDA levels.

Superoxide dismutase (SOD) is an important antioxidant enzyme that helps neutralize oxidative stress.[10,35,47] In PCOS, oxidative stress is elevated, but based on the meta-analysis results, astaxanthin supplementation did not significantly impact SOD levels (mean difference 0.025,95% CI: -0.850-1.350; p=0.660). This suggests that while AST may reduce lipid peroxidation (as seen with MDA reduction), its effect on enzymatic antioxidants such as SOD remains unclear.

Total antioxidant capacity reflects the body's overall ability to neutralize oxidative stress. In women with PCOS, oxidative stress is often elevated due to insulin resistance, inflammation, and metabolic imbalances.[48-50] This meta-analysis found that AST supplementation led to a slight but significant increase in TAC levels (mean difference 0.030, 95% CI: 0.000- 0.060; p=0.030; I^2=76%), suggesting a potential antioxidant benefit. However, the moderate degree of heterogeneity indicates variability in study results, highlighting the need for further research to confirm its clinical relevance in PCOS management. The presence of asymmetry in any funnel diagram indicates the possibility of small study effects or missing studies, potentially affecting the overall conclusions.

CONCLUSION

Astaxanthin supplementation significantly reduces MDA but not SOD levels. Total antioxidant capacity level showed a slight but significant increase, indicating potential antioxidant benefits. Further research is needed, considering the heterogeneous results of this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Authors' Contributions

DP: Conceptualization, data curation, formal analysis, investigation, interpretation of data, and drafting of the manuscript. IWAH: Supervision, validation, interpretation of data, and critical revision of the manuscript for important intellectual content. IWW: Methodological design, data validation, and critical intellectual revision of the manuscript. NKS: Data interpretation and critical revision of the manuscript. SAA: Clinical interpretation, methodological refinement, supervision, and critical revision of the manuscript. IWGS: Statistical analysis, interpretation of results, and critical revision of the manuscript. All authors met the ICMJE criteria for authorship, contributed substantially to this work, and approved the final version of the manuscript.

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Data Availability Statement

All data supporting the findings of this study are included in the manuscript and supplementary materials. Any additional data or analysis files can be made available upon reasonable request to the corresponding author.

Declaration of AI Usage in Scientific Writing

Nothing to declare

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