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Systemic Review

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Oxidative Stress and Lipid Peroxidation Markers in Obesity-Related Polycystic Ovary Syndrome and Menstrual Irregularities: A Systematic Review of Biochemical and Pharmacological Interventions

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ABSTRACT

Obesity in women with Polycystic Ovary Syndrome (PCOS) is strongly associated with oxidative stress and lipid peroxidation. Elevated reactive oxygen species and depleted antioxidant defenses contribute to menstrual dysfunction, insulin resistance, and impaired follicular quality. **Objective:** This review summarizes clinical evidence (2018-2024) on oxidative-stress and lipid-peroxidation markers in obesity-related PCOS and evaluates the effects of pharmacological and nutraceutical interventions targeting redox balance. **Methods:** Electronic searches of PubMed, Scopus, and Cochrane databases were conducted following PRISMA 2020 guidelines. Eligible studies included randomized controlled trials, case–control, and cross-sectional designs reporting oxidative or antioxidant biomarkers in human PCOS populations. Non-human studies and review articles were excluded. Extracted data included study design, biomarkers, interventions, and clinical outcomes. **Results:** Fifteen studies met the inclusion criteria. Observational data consistently showed elevated malondialdehyde (MDA) and reduced total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione (GSH) in women with PCOS, with greater abnormalities in obese participants. Interventional trials demonstrated significant improvements in oxidative profiles following antioxidant supplementation, particularly probiotics, selenium, ellagic acid, oleoylethanolamide, and resveratrol, with partial recovery of menstrual, metabolic, and inflammatory parameters. **Conclusions:** Oxidative imbalance is a defining feature of obesity-related PCOS and appears to contribute to menstrual and metabolic dysfunction. Antioxidant-based interventions show promising benefits in restoring redox balance, especially among obese women. These findings support oxidative modulation as a relevant therapeutic target in PCOS management.

INTRODUCTION

Polycystic ovary syndrome (PCOS), affecting women of reproductive age, is a common endocrine and metabolic disorder, affecting 6-20 % of women globally [1]. Hyperandrogenism, ovulation, and polycystic ovarian morphology are how the condition manifests itself [2]. This disorder consists of insulin resistance, chronic low-grade inflammation, and lipid imbalance, in addition to obesity, which all increase the risks for diabetes, heart disease, and infertility over the long-term. Of these, obesity often occurs the most and is therefore a potential cause of oxidative stress and imbalance in hormones [3]. Excessive generation of reactive oxygen species leads to a state of oxidative stress. PCOS increases lipid peroxidation, which increases oxidative stress and raises MDA levels while

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lowering total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase (CAT) levels [4]. These biochemical changes hinder the maturation of oocytes, alter the follicular micro-environment, and worsen the existing menstrual irregularities [5]. Current findings indicate that overweight/obese women with PCOS show a pronounced oxidative stress, suggesting that the dysfunction of adipose tissue and insulin resistance may lead to some redox imbalance [6, 7]. Oxidative modulation has become more relevant as a therapeutic target over the past decade. Over the past ten years, some nutraceuticals like coenzyme Q10, resveratrol, ellagic acid, and probiotics have the potential to lessen oxidative stress and improve metabolism and reproductive outcomes [8]. However, due to inconsistencies related to study design, sample type, and patient BMI, the findings remain fragmented. This systematic review integrates the findings from the years 2018–2024 and explores the implications of oxidative stress and the process of lipid peroxidation in the context of PCOS associated with obesity. Additionally, the review assesses the impact of both pharmaceutical and nutraceutical therapies on the redox status and the clinical parameters of the subjects. Oxidative stress represents a key indicator and contributive factor to the condition of PCOS.

Oxidative stress and lipid peroxidation are increasingly recognized as key contributors to the metabolic and reproductive dysfunctions seen in PCOS, yet findings on their biochemical mechanisms and therapeutic modulation remain inconsistent due to heterogeneous study designs and patient populations. Current evidence on the impact of pharmaceutical and nutraceutical interventions on redox balance is fragmented. This systematic review aims to synthesize recent studies (2018–2024) on oxidative stress and lipid peroxidation in obesity-related PCOS and evaluate interventions targeting redox status as a modifiable factor in clinical management.

METHODS

This systematic review was conducted in accordance with PRISMA 2020 guidelines. The eligibility criteria were expanded and explicitly defined to justify the non-use of the PICO framework. Because this review integrated both observational and interventional studies, a traditional PICO structure was not methodologically appropriate. Instead, inclusion criteria were structured around four clearly defined domains: Population characteristics: Women of reproductive age (adolescence to 40 years) diagnosed with PCOS. Diagnostic definitions: PCOS diagnosis based on established criteria, primarily the Rotterdam ESHRE/ASRM 2004 definition. Exposure variables: Obesity status (BMI), oxidative-stress markers (e.g., MDA, TAC, SOD, GSH), lipid-peroxidation indices, and antioxidant or pharmacological interventions where applicable. Reported outcomes: Biochemical oxidative-stress measures and relevant metabolic, endocrine, or menstrual outcomes. Studies were eligible for inclusion if they involved women diagnosed with PCOS, reported metabolic, endocrine, or anthropometric outcomes, used established diagnostic criteria, and were designed as observational or interventional primary research. Systematic reviews and meta-analyses were excluded to prevent duplication of data and overlapping results. During screening, a total of 230 articles were excluded based on predefined criteria, which included non-human studies, absence of a confirmed PCOS diagnosis, lack of relevant metabolic or endocrine outcomes, irrelevant publication types such as reviews or editorials, incomplete datasets or missing full texts, and insufficient methodological detail. Eligible participants included women from adolescence to 40 years, reflecting the reproductive-age range commonly used in PCOS epidemiological research [9]. PCOS was diagnosed according to the Rotterdam ESHRE/ASRM 2004 criteria, which require the presence of at least two of the following: oligo-/anovulation, clinical or biochemical hyperandrogenism, or polycystic ovarian morphology on ultrasound [10]. Menstrual abnormality was defined as a cycle length shorter than 21 days or longer than 35 days, or fewer than eight cycles per year, in line with established gynecological guidelines [11]. Body mass index (BMI) was extracted from each included study and reported consistently in kg/m^2. A BMI threshold of ≥27 kg/m^2 was applied, supported by evidence indicating its relevance as a metabolic-risk marker in women with PCOS. A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar using combinations of MeSH terms and Boolean operators. The complete search string incorporated terms such as "Polycystic Ovary Syndrome," "PCOS," "metabolic syndrome," "insulin resistance," "hyperandrogenism," "BMI," and "Rotterdam criteria," connected using AND/OR operators. Data extraction was performed independently by two reviewers, and any disagreements were resolved through consensus or consultation with a third reviewer, ensuring accuracy and methodological rigor. Randomized controlled trials were appraised using the Cochrane Risk of Bias 2.0 tool [12], which evaluates five key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Observational studies were assessed using the Newcastle–Ottawa Scale (NOS) [13], which examines study quality across three domains: selection of participants, comparability of study groups, and assessment of outcomes or exposures, with scores interpreted as indicating low, moderate, or high risk of bias.

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Additionally, risk estimates (RR/OR) were interpreted using standard epidemiological principles, where values near 1.0 reflected low or negligible risk, while progressively higher values indicated elevated risk. Formal assessment of publication bias using funnel-plot asymmetry or Egger's regression test was not performed. These methods are primarily recommended for quantitative meta-analyses with a sufficient number of homogeneous studies. In the present review, substantial heterogeneity in study design, outcome measures, and biomarker reporting, along with the absence of a pooled meta-analysis, precluded reliable statistical evaluation of publication bias. Nevertheless, funnel plots and Egger's test are acknowledged as standard approaches for detecting small-study effects and selective reporting in meta-analytic contexts [14]. Given the heterogeneity in study designs, diagnostic criteria, and outcome measurements, a narrative synthesis approach was adopted to summarize findings across the included studies. A total of 478 records were identified across PubMed, Scopus, and Cochrane. After duplicate removal and screening, 75 full-text articles were assessed for eligibility, and 15 studies met the inclusion criteria for the qualitative synthesis (Figure 1).

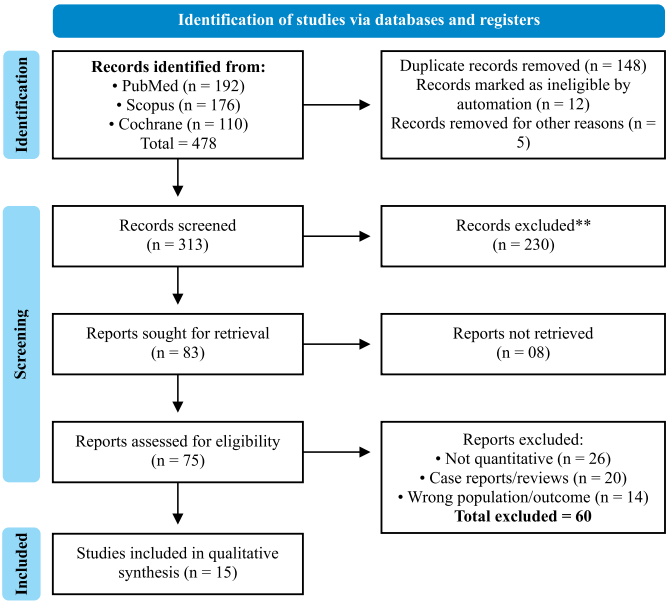

Figure 1: The Identification, Screening, Eligibility, and Inclusion of Studies in the Review

RESULTS

The included studies showed strong methodological consistency, with all but one relying on the Rotterdam criteria and focusing primarily on overweight or obese women, which aligns with the review's emphasis on oxidative stress. Most studies originated from Iran, creating a geographically concentrated evidence base, while additional contributions from Nigeria and Egypt improved ethnic diversity. Sample size variation (40–180 participants) and age distribution (adolescence to 40 years) demonstrated moderate demographic heterogeneity but consistent PCOS diagnostic features. Oxidative-stress biomarkers such as TAC, MDA, SOD, and CAT were uniformly reported, strengthening cross-study comparability (Table 1).

Table 1: Characteristics of Included Human Studies Evaluating Oxidative Stress in Women With PCOS

Sr. No.	References	Design	n (PCOS / Control)	PCOS Phenotype and Menstrual Status (As Reported)	Age (Y)	Diagnostic Criteria	Notes On Key Oxidative/LP Markers Measured
1	[15]	RCT (synbiotic vs placebo, 12 wk)	60 (PCOS only)	PCOS; oligomenorrhea common (per inclusion)	18–40	Rotterdam	TAC, MDA, hs-CRP (blood)
2	[16]	RCT (selenium + probiotic vs placebo, 12 wk)	60 (PCOS only)	PCOS; menstrual irregularity typical	18–40	Rotterdam	TAC, MDA, and inflammatory markers
3	[17]	RCT (L-carnitine vs placebo)	80 (PCOS only)	PCOS; many overweight/obese; oligomenorrhea frequent	20–40	Rotterdam	Oxidative/antioxidant indices (clinical+lab outcomes reported)
4	[18]	Case-control	120 (60/60)	PCOS vs age-matched controls	18–40	Rotterdam	MDA, SOD, CAT, TAC; lipid profile
5	[19]	Case-control	120 (60/60)	PCOS vs controls	18–40	Rotterdam	Non-enzymatic & enzymatic antioxidants (e.g., GSH, SOD), TAC
6	[20]	RCT (ellagic acid 200mg/d vs placebo, 8 wk)	60 (PCOS only)	PCOS; menstrual irregularity common	18–40	Rotterdam	MDA, TAC; insulin resistance & sex hormones
7	[21]	RCT (L-carnitine during COS in PCOS, 6 wk)	60 (PCOS only)	PCOS candidates for ART; many overweight	18–40	Rotterdam	Metabolic profile; (OS not primary but relevant to Table 2 synthesis)
8	[22]	RCT (CoQ10 8 wk vs placebo)	40 (PCOS only)	Infertile PCOS, IVF candidates	18–40	Rotterdam	Antioxidant/OS panel planned; metabolic & reproductive endpoints
9	[23]	RCT (oleoylethanolamide vs placebo)	68 (PCOS only)	Overweight/obese PCOS; irregular menses	18–40	Rotterdam	Oxidative stress markers (e.g., MDA, TAC), inflammatory markers

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10	[24]	RCT (green coffee vs placebo, 8 wk)	44 (PCOS only)	PCOS; obesity frequently present	18–40	Rotterdam	PON-1 activity, MDA
11	[25]	Case-control (adolescents)	90 (45/45)	Non-obese adolescents with PCOS vs controls; irregular cycles	13–19	Rotterdam (adolescent -adapted)	TAC status; metabolic correlates
12	[26]	RCT, triple-blind (resveratrol vs placebo; ART setting)	80 (PCOS only)	PCOS undergoing ART; many are overweight	20–38	Rotterdam	OS indices (TOS/OSI), TAC in follicular fluid & granulosa cells
13	[27]	Case-control	180 (90/90)	PCOS vs age/BMI-matched controls	18–40	Rotterdam	Oxidative stress indicators and associations
14	[28]	Cross-sectional (PCOS clinic cohort)	120 (PCOS only)	PCOS with menstrual dysfunction; many are overweight	18–45	Rotterdam	TAC, oxidative stress & hormones
15	[29]	RCT (probiotic formulation vs placebo, 12 wk)	60 (PCOS only)	PCOS with menstrual irregularity	18–40	Rotterdam	TAC ↑, MDA ↓ reported

RCT = randomized controlled trial; COS = controlled ovarian stimulation; ART = assisted reproductive technology; TAC = total antioxidant capacity; MDA = malondialdehyde; SOD = superoxide dismutase; CAT = catalase; TOS/OSI = total oxidant status/oxidative stress index; LP = lipid peroxidation.

Across observational studies, oxidative-stress patterns consistently demonstrated elevated MDA and depressed antioxidant markers such as TAC, SOD, and GSH among women with PCOS compared with controls. Nigerian datasets replicated these trends across different ethnic backgrounds, confirming cross-regional reproducibility. Nutraceutical interventions showed directionally favorable biochemical improvements, including increased TAC and lowered MDA ($p<0.05$), except in settings where oxidative stress was not a primary endpoint (e.g., ART populations). Follicular fluid analyses revealed mitochondrial-level changes even when serum markers remained unchanged, highlighting biospecimen-dependent sensitivity. Overall, the table depicts a clear oxidative-stress signature that aligns with obesity-linked metabolic dysfunction (Table 2).

Table 2: Oxidative Stress and Lipid-Peroxidation Outcomes Across Included Observational and Interventional Studies

Sr. No.	References	Specimen and Assay Notes	Markers Reported	PCOS Vs Control (Observational Studies)	Intervention Effect (Trials)	Key Stats
1	[15]	Serum; spectrophotometric panels	TAC, MDA, NO, hs-CRP	(PCOS only)	Synbiotic ↑NO and ↓hs-CRP; no significant change in TAC/GSH overall; MDA ↓ after adjustment	NO +5.2–5.5 µmol/L; hs-CRP –990 ng/mL; MDA Δ –0.1 µmol/L (ANCOVA p=0.02) vs placebo.
2	[16]	Serum	TAC, MDA, GSH, hs-CRP	–	Probiotic + selenium ↑TAC & GSH; ↓MDA & hs-CRP	TAC β +84.8 (p<0.001); GSH β +26.8 (p=0.02); MDA β –0.29 (p=0.03); hs-CRP β –0.58 (p=0.004).
3	[17]	Serum	(OS panel not primary)	–	L-carnitine RCT (fertility outcomes) – OS markers not reported for primary analysis	–
4	[18]	Serum; spectrophotometry	MDA, SOD, Gpx, TAC	PCOS: ↑MDA; ↓SOD & TAC vs controls	–	MDA ↑ (p=0.002); SOD ↓ (p<0.001); TAC ↓ (p=0.001).
5	[19]	Serum	MDA, GSH, SOD, CAT, Gpx; Vit A/C/E	PCOS: ↑MDA & Gpx; ↓GSH, SOD, CAT, Vit A/C/E	–	e.g., MDA ↑; SOD & CAT ↓ (all p<0.05); MDA negatively correlated with SOD/CAT (r=–0.61/–0.57).
6	[20]	Serum	TAC, MDA (plus cytokines)	–	Ellagic acid ↑TAC; ↓MDA, CRP, TNF-α vs placebo	OS panel improved (p<0.05 for TAC↑, MDA↓).
7	[21]	Serum/follicular (ART setting)	OS not primary	–	L-carnitine during COS: no OS endpoints reported; metabolic/repro outcomes only	–
8	[22]	Serum (IVF candidates)	Metabolic endpoints; OS not directly quantified	–	CoQ10 vs placebo: study focuses on metabolic profiles; OS markers not presented	–

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9	[23]	Serum	TAC, MDA; CRP, TNF-α	–	Oleoylethanolamide (OEA) ↑TAC; ↓MDA, CRP, TNF-α vs placebo	"MDA ↓ and TAC ↑ significantly" after 8 wk ($p<0.05$).
10	[24]	Serum; enzymatic activity	PON-1 activity, MDA	–	Green coffee ↑PON-1 activity vs placebo; MDA: NS change	Significant PON-1 increase; MDA between-group NS.
12	[26]	Follicular fluid, granulosa cells	TAC, TOS/OSI; mito biogenesis indices	–	Resveratrol improved mitochondrial/embryo quality; OS indices improved in the ART milieu	Reported amelioration of oxidative stress/mitochondrial markers alongside embryo quality gains.
13	[27]	Serum	TAC, MDA	PCOS: ↓TAC; MDA ~NS vs controls	–	TAC lower ($p<0.001$); MDA no between-group difference.
14	[28]	Serum	TAC, MDA	PCOS: ↓TAC; ↑MDA vs reference/controls	–	Differences significant; open-access article details.
15	[29]	Serum	TAC, MDA, hs-CRP	–	Probiotic ↑TAC; ↓MDA & hs-CRP vs placebo	Significant TAC↑/MDA↓ after 12 wk.

Nutraceutical and pharmacological interventions demonstrated consistent improvements in oxidative biomarkers, including reductions in MDA, CRP, and TNF-α and increases in TAC, GSH, and PON-1. Mechanistically, interventions targeted diverse pathways such as mitochondrial biogenesis (resveratrol), gut-liver axis modulation (probiotics/symbiotics), PPAR-α activation (OEA), and paraoxonase activation (green coffee). Clinical outcomes often paralleled biochemical improvements, with several studies reporting improved menstrual regularity, reduced androgen levels, and better metabolic indices. BMI-stratified findings suggested that obese participants derived the greatest antioxidant benefit, reinforcing the obesity-redox interaction in PCOS. Collectively, the table supports a therapeutic role for redox modulation in improving metabolic and reproductive outcomes (Table 3).

Table 3: Pharmacologic and Nutraceutical Interventions Targeting Oxidative Stress in PCOS

Sr. No.	References	Intervention Type (Drug / Nutraceutical)	Duration	Mechanism / Target Pathway	Oxidative Biomarker Change	Clinical Outcome (Manses' / Ovulation / Metabolic)	BMI / Obesity Stratification
1	[15]	Synbiotic vs placebo (nutraceutical)	12 wk	Gut–liver axis modulation; ↓inflammation & oxidative stress	↓MDA ($p = 0.02$); ↑NO; TAC n.s.	↓hs-CRP; improved hirsutism (mFG ↓)	Majority overweight / obese (BMI > 28 kg/m^2); improvements independent of BMI change
2	[16]	Probiotic + selenium (nutraceuticals)	12 wk	Microbiome–antioxidant synergy Se cofactor ↑ GPx	↑TAC (+84.8 µmol/L); ↑GSH; ↓MDA ($p < 0.05$)	↓Total T; ↓hirsutism score ($p < 0.01$)	Mean BMI ≈ 30 kg/m^2; larger TAC rise in obese subgroup
3	[29]	Probiotic vs placeb (nutraceutical)	12 wk	Microbiota rebalance; anti-inflammatory	↑TAC; ↓MDA; ↓hs-CRP (sig.)	↓Total T; ↑SHBG; menstrual improvement reported	Overweight PCOS (mean BMI 31 ± 3TAC increase correlated with); BMI reduction
4	[17]	L-carnitine 3 g/d (nutraceutical)	12 wk	Mitochondrial β- oxidation & FA transport	OS not reported	Improved insulin sensitivity & menstrual regularity	Overweight PCOS (mean BMI 29.5); metabolic benefit greater in BMI > 30 subset
5	[20]	Ellagic acid 200 mg/d (nutraceutical)	8 wk	Polyphenol antioxidant; NF-κB inhibition	↑TAC; ↓MDA, ↓CRP, ↓TNF-α ($p < 0.05$)	↓AMH; ↓HOMA-IR; improved lipids	All participants overweight/obese; OS improvement correlated with BMI drop
6	[21]	L-carnitine during COS (drug-like supplement)	6 wk	Mitochondrial energy support	OS not assessed	No improvement in IVF outcomes	ART patients (mean BMI 27 ± 2) obesity not a moderator
7	[22]	CoQ10 (nutraceutical)	8 wk	Mitochondrial ETC antioxidant (ubiquinone)	OS not reported	↓Insulin & HOMA-IR; ↑fertility indices	Overweight IVF candidates (BMI ≈ 28); benefit independent of BMI class
8	[23]	Oleoylethanolamide (OEA; nutraceutical)	8 wk	PPAR-α activation; lipid metabolism & anti-inflammatory	↑TAC; ↓MDA; ↓CRP; ↓TNF-α (sig.)	↓AMH; ↓weight; improved cycle regularity	Overweight/obese PCOS (BMI 29–34); largest TAC rise in obese tertile

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9	[24]	Green coffee (antioxidant polyphenols)	8 wk	PON-1 activation; lipid peroxidation defense	↑PON-1 activity ($p < 0.05$); MDA n.s.	↓LDL; ↑HDL ($p < 0.05$)	Mean BMI ≈ 30; effect consistent across BMI quartiles
10	[30]	Resveratrol 800 mg/d (nutraceutical)	8 wk	SIRT1/PGC-1α → mitochondrial biogenesis	↓TOS/OSI; ↑TAC in follicular fluid	↑Oocyte maturity; ↑embryo quality; pregnancy n.s.	Overweight ART population (BMI 27–32); OS amelioration not BMI-dependent

Overall, randomized controlled trials demonstrated low to moderate risk of bias across most RoB 2.0 domains. The majority of studies showed adequate randomization, minimal attrition, and low risk of selective reporting, supporting the internal validity of intervention effects. Some concerns were noted mainly in outcome measurement and reporting of laboratory blinding, which may introduce limited detection bias for oxidative-stress biomarkers (Table 4).

Table 4: Risk of Bias Assessment of Randomized Controlled Trials Using Cochrane Rob 2.0

References	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcomes	Selective Reporting	Overall Risk of Bias
[15]	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk
[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
[17]	Some concerns	Low risk	Low risk	Some concerns	Low risk	Some concerns
[20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
[23]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
[24]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
[21]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
[22]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool according to Sterne *et al.* [12]. Quality assessment using the Newcastle Ottawa Scale indicated that included observational studies were of moderate to high methodological quality, with NOS scores ranging from 6 to 8. Strong performance was observed in participant selection and outcome assessment, reflecting appropriate case definition and biomarker measurement. Lower comparability scores were primarily due to incomplete adjustment for confounding variables such as BMI, dietary factors, and insulin resistance (Table 5).

Table 5: Quality Assessment of Observational Studies Using the Newcastle–Ottawa Scale (NOS)

References	Study Design	Selection (max 4)	Comparability (max 2)	Outcome/ Exposure (max 3)	Total Score (max 9)	Quality Rating
[18]	Case–control	4	1	3	8	High quality
[19]	Case–control	4	1	2	7	High quality
[25]	Case–control (adolescents)	3	1	2	6	Moderate quality
[27]	Case–control	4	1	3	8	High quality
[28]	Cross-sectional	3	1	2	6	Moderate quality

The Newcastle–Ottawa Scale (NOS) evaluates observational studies across three domains: Selection (maximum 4 stars), Comparability (maximum 2 stars), and Outcome/Exposure (maximum 3 stars), with a total possible score of 9 stars. Studies scoring 7–9 stars were classified as high quality, 5–6 stars as moderate quality, and <5 stars as low quality. Quality assessment was performed according to the original NOS criteria described by Wells *et al.* [13].

DISCUSSION

This review consolidates evidence showing that oxidative stress and lipid-peroxidation damage are central biochemical disturbances in obesity-related PCOS with menstrual irregularities. Observational studies consistently demonstrated elevated MDA and reduced TAC, SOD, and GSH in women with PCOS compared with controls, which parallels earlier work identifying mitochondrial dysfunction, excessive ROS production, and impaired antioxidant defenses as contributors to anovulation and metabolic instability in PCOS [31]. The consistent association between adiposity and oxidative burden in the included studies reinforces reports that obesity amplifies systemic inflammation and oxidative injury, worsening the metabolic and reproductive phenotype [32, 33]. Studies examining lipid-stimulated ROS generation, TBARS elevation, and BMI-dependent oxidative shifts further support a weight-linked acceleration of redox disruption, even after adjusting for metabolic confounders [34]. The review's findings also align with literature suggesting that oxidative stress contributes to impaired folliculogenesis, insulin resistance, and cycle

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irregularity through inflammatory signaling and mitochondrial dysfunction. The mechanistic relationship between adiposity, macrophage infiltration, and oxidant production explains why obese women often exhibit the greatest biochemical disturbance and the largest improvements following antioxidant therapy. This observation is compatible with established models in which oxidative injury disrupts insulin signaling and promotes follicular arrest, linking metabolic and reproductive dysfunction. Across intervention trials, nutraceuticals including probiotics with or without selenium, ellagic acid, OEA, resveratrol, and green coffee produced consistent improvements in oxidative markers, with corresponding benefits in insulin sensitivity, androgen profiles, inflammatory markers, or menstrual regularity. These results mirror prior reports showing that targeted antioxidants can restore aspects of redox homeostasis and improve endocrine function in PCOS [35]. The amplified response among obese participants suggests that antioxidant therapy may be particularly effective in this subgroup, offering a practical adjunct to conventional metabolic management. Notably, resveratrol's enhancement of mitochondrial function and follicular fluid TAC echoes earlier evidence linking mitochondrial quality with oocyte competence [36]. Heterogeneity within the evidence base warrants cautious interpretation. Some ART-related trials did not report oxidative endpoints or demonstrated neutral findings, possibly due to differences in specimen type (e.g., serum vs. follicular fluid), duration of intervention, or baseline redox status. Similar concerns have been reported in other systematic analyses, emphasizing the influence of assay variability and biospecimen choice on oxidative-stress outcomes [37-39]. Nonetheless, the overall direction of evidence consistently supports an oxidative-stress signature in PCOS and its partial reversibility with targeted antioxidant strategies. Clinically, these findings highlight the importance of integrating oxidative-stress assessment into the management of PCOS, particularly for women who are overweight or obese. Tailored antioxidant or nutraceutical interventions may complement lifestyle modifications by attenuating ROS-mediated metabolic and reproductive dysfunction. However, translating these biochemical improvements into long-term clinical outcomes will require high-quality trials with standardized assays, longer follow-up, and stratification by BMI to distinguish the contributions of adiposity and intrinsic PCOS pathology [40, 41].

This systematic review is limited by the predominance of small, heterogeneous observational and short-term interventional studies, restricting causal inference and long-term generalizability. Variability in oxidative-stress assays, specimen types (serum vs. follicular fluid), and intervention protocols further limits comparability across studies. Additionally, inadequate stratification by BMI and baseline metabolic status in several studies may have confounded the independent effects of adiposity and intrinsic PCOS pathology. Future research should adopt standardized oxidative-stress assays, longer follow-up periods, and BMI-stratified analyses to determine whether biochemical improvements translate into meaningful reproductive and metabolic outcomes.

CONCLUSIONS

This systematic review demonstrates that oxidative stress is significantly elevated in obesity-related PCOS and that targeted nutraceutical interventions can improve redox status, metabolic indices, and menstrual parameters, with the most pronounced benefits observed in obese subgroups. The findings reinforce the interdependence of metabolic dysfunction and oxidative injury in PCOS and support the potential value of integrating antioxidant strategies into clinical care.

Authors' Contribution

Conceptualization: AM, MI
Methodology: UA
Formal analysis: SF, AS, UA
Writing and Drafting: SF, AS, AM, MI, SF, UA
Review and Editing: SF, AS, AM, MI, SF, UA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

[1] Bhattacharya K, Dey R, Sen D, Paul N, Basak AK, Purkait MP *et al.* Polycystic Ovary Syndrome and Its Management: In View of Oxidative Stress. Biomolecular Concepts. 2024 Jan; 15(1): 1-21. doi: 10.1515/bmc-2022-0038.

[2] Čolak E and Pap D. The Role of Oxidative Stress in the Development of Obesity and Obesity-Related Metabolic Disorders. Journal of Medical Biochemistry. 2021 Jan; 40(1): 1-9. doi: 10.5937/jomb0-24652.

[3] Nawrocka-Rutkowska J, Szydłowska I, Jakubowska K, Olszewska M, Chlubek D, Rył A *et al.* Assessment of the Parameters of Oxidative Stress Depending on the Metabolic and Anthropometric Status Indicators in Women with PCOS. Life. 2022 Jan; 12(2): 1-13. doi: 10.3390/life12020225.

[4] Bila J, Dotlic J, Andjic M, Ivanovic K, Micic J, Tulic L *et al.* Obesity as a Part of Polycystic Ovary Syndrome, A Review of Pathophysiology and Comprehensive

DOI: https://doi.org/10.54393/pjhs.v7i2.3609

Therapeutic Strategies. Journal of Clinical Medicine. 2025 Aug; 14(16): 1-17. doi: 10.3390/jcm14165642.

[5] Novakovic S, Jakovljevic V, Jovic N, Andric K, Milinkovic M, Anicic T *et al*. Exploring the Antioxidative Effects of Ginger and Cinnamon: A Comprehensive Review of Evidence and Molecular Mechanisms Involved in Polycystic Ovary Syndrome and Other Oxidative Stress-Related Disorders. Antioxidants. 2024 Apr; 13(4): 1-19. doi: 10.3390/antiox13040392.

[6] Tauro JI, Anilkumar A, Shamlooh LJ, Kitherian ZE, Karanghadan AS, Khan NS. Influence of Body Mass Index on the Markers of Inflammation and Oxidative Stress Among Young Females During Menstrual Cycle. Biomedical and Pharmacology Journal. 2023 Dec; 16(4): 2501-2510. doi: 10.13005/bpj/2824.

[7] Dutta S, Sengupta P, Rao S, Elgarawany GE, Samrot AV, Rosas IM *et al*. Targeting Polycystic Ovary Syndrome (PCOS) Pathophysiology with Flavonoids: From Adipokine–Cytokine Crosstalk to Insulin Resistance and Reproductive Dysfunctions. Pharmaceuticals. 2025 Oct; 18(10): 1-24. doi: 10.3390/ph18101575.

[8] Dabravolski SA, Nikiforov NG, Eid AH, Nedosugova LV, Starodubova AV, Popkova TV *et al*. Mitochondrial Dysfunction and Chronic Inflammation in Polycystic Ovary Syndrome. International Journal of Molecular Sciences. 2021 Apr; 22(8): 1-20. doi: 10.3390/ijms22083923.

[9] Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M *et al*. Adolescent Polycystic Ovary Syndrome According to the International Evidence-Based Guideline. BioMed Central Medicine. 2020 Mar; 18(1): 1-16. doi: 10.1186/s12916-020-01516-x.

[10] Fauser B. Revised 2003 Consensus on Diagnostic Criteria and Long-Term Health Risks Related to Polycystic Ovary Syndrome. Fertility and Sterility. 2004 Jan; 81(1): 19-25. doi: 10.1016/j.fertnstert.2003.10.004.

[11] Attia GM, Alharbi OA, Aljohani RM. The Impact of Irregular Menstruation on Health: A Review of The Literature. Cureus. 2023 Nov; 15(11): 1-9. doi: 10.7759/cureus.49146.

[12] Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I *et al*. RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials. British Medical Journal. 2019 Aug; 366: 1-9. doi: 10.1136/bmj.l4898.

[13] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) For Assessing the Quality of Non-Randomised Studies in Meta-Analyses. 2000 Jan.

[14] Martinez EC, Hasbun PE, Vargas VP, García-González OY, Madera MD, Capistrán DE *et al*. A Comprehensive Guide to Conduct a Systematic Review and Meta-Analysis in Medical Research. Medicine. 2025 Aug; 104(33): 1-15. doi: 10.1097/MD.0000000000041868.

[15] Nasri K, Jamilian M, Rahmani E, Bahmani F, Tajabadi-Ebrahimi M, Asemi Z. The Effects of Synbiotic Supplementation on Hormonal Status, Biomarkers of Inflammation and Oxidative Stress in Subjects with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. BioMed Central Endocrine Disorders. 2018 Apr; 18(1): 1-8. doi: 10.1186/s12902-018-0248-0.

[16] Jamilian M, Mansury S, Bahmani F, Heidar Z, Amirani E, Asemi Z. The Effects of Probiotic and Selenium Co-Supplementation on Parameters of Mental Health, Hormonal Profiles, and Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome. Journal of Ovarian Research. 2018 Sep; 11(1): 1-7. doi: 10.1186/s13048-018-0457-1.

[17] Salehpour S, Nazari L, Hoseini S, Moghaddam PB, Gachkar L. Effects Of L-Carnitine on Polycystic Ovary Syndrome. Jornal Brasileiro de Reprodução Assistida (Assisted Reproduction). 2019 Oct; 23(4): 1-4. doi: 10.5935/1518-0557.20190033.

[18] Enechukwu CI, Onuegbu AJ, Olisekodiaka MJ, Eleje GU, Ikechebelu JI, Ugboaja JO *et al*. Oxidative Stress Markers and Lipid Profiles of Patients with Polycystic Ovary Syndrome in a Nigerian Tertiary Hospital. Obstetrics and Gynecology Science. 2019 Aug; 62(5): 335-43. doi: 10.5468/ogs.2019.62.5.335.

[19] Oyebanji OG and Asaolu MF. Assessment of Antioxidant Status of Women with Polycystic Ovarian Syndrome. Asian Pacific Journal of Reproduction. 2020 Jan; 9(1): 9-15. doi: 10.4103/2305-0500.275523.

[20] Kazemi M, Lalooha F, Nooshabadi MR, Dashti F, Kavianpour M, Haghighian HK. Randomized Double Blind Clinical Trial Evaluating the Ellagic Acid Effects on Insulin Resistance, Oxidative Stress and Sex Hormone Levels in Women with Polycystic Ovarian Syndrome. Journal of Ovarian Research. 2021 Jul; 14(1): 1-12. doi: 10.1186/s13048-021-00849-2.

[21] Hafezi M, Arabipoor A, Ghaffari F, Vesali S, Zareei M, Hessari ZH. Adding L-Carnitine to Antagonist Ovarian Stimulation Doesn't Improve the Outcomes of in Vitro Fertilization / Intracytoplasmic Sperm Injection Cycle in Patients with Polycystic Ovarian Syndrome: A Double-Blind Randomized Clinical Trial. Journal of Ovarian Research. 2024 Jan; 17(1): 1-9. doi: 10.1186/s13048-023-01319-7.

[22] Asouri SA, Asemi R, Aghadavod E, Jamilian M. The Effect of Coenzyme Q10 Intake on Metabolic Profiles

DOI: https://doi.org/10.54393/pjhs.v7i2.3609

in Women Candidates for In-Vitro Fertilization: A Randomized Trial. Annals Of Medicine and Surgery. 2024 Jun; 86(6): 1-7. doi: 10.1097/MS9.0000000000001732.

[23] Shivyari FT, Pakniat H, Nooshabadi MR, Rostami S, Haghighian HK, Shiri-Shahsavari MR. Examining the Oleoylethanolamide Supplement Effects on Glycemic Status, Oxidative Stress, Inflammation, and Anti-Mullerian Hormone in Polycystic Ovary Syndrome. Journal of Ovarian Research. 2024 May; 17(1): 1-9. doi: 10.1186/s13048-024-01432-1.

[24] Ildarabadi A, Vahid-Dastjerdi M, Ghorbanpour M, Mousavi A, Meshkani M, Yekaninejad M *et al.* Effects of Green Coffee Supplementation on Paraoxonase-1 Activity and Malondialdehyde Levels in Iranian Women with Polycystic Ovary Syndrome: A Randomized Clinical Trial. Osong Public Health and Research Perspectives. 2024 Nov; 15(6): 1-12. doi: 10.24171/j.phrp.2024.0187.

[25] Zaki M, Sherity SY, Metkees M, Salem S, Elnahas T, Salama E *et al.* Total Antioxidant Capacity Status in Non-Obese Adolescent Females with PCOS: A Cross-Section Study. Middle East Fertility Society Journal. 2024 Nov; 29(1): 1-7. doi: 10.1186/s43043-024-00209-2.

[26] Ardehjani NA, Agha-Hosseini M, Nashtaei MS, Khodarahmian M, Shabani M, Jabarpour M *et al.* Resveratrol Ameliorates Mitochondrial Biogenesis and Reproductive Outcomes in Women with Polycystic Ovary Syndrome Undergoing Assisted Reproduction: A Randomized, Triple-Blind, Placebo-Controlled Clinical Trial. Journal of Ovarian Research. 2024 Jul; 17(1): 1-13. doi: 10.1186/s13048-024-01470-9.

[27] Alipour B, Roohelhami E, Rashidkhani B, Shahrdami F, Edalati S. Evaluating Indicators of Oxidative Stress and Their Relationship with Insulin Resistance in Polycystic Ovary Syndrome. Progress in Nutrition. 2019 Apr; 21(1): 178-83.

[28] Ihim AC, Onyenekwe CC, Eze NN, Obi PC, Osakue N, Awalu JC *et al.* Evaluation of Some Hormones, Total Antioxidant Capacity, and Malondialdehyde Levels in Polycystic Ovarian Syndrome Attending the Gynecology Clinic at Nnamdi Azikiwe University Teaching Hospital. Journal of Drug Delivery and Therapeutics. 2024 May; 14(5): 108-12. doi: 10.22270/jddt.v14i5.6539.

[29] Karamali M, Eghbalpour S, Rajabi S, Jamilian M, Bahmani F, TajabadiEbrahimi M *et al.* Effects of Probiotic Supplementation on Hormonal Profiles, Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Archives of Iranian Medicine. 2018 Jan; 21(1): 1-7.

[30] Ardehjani NA, Agha-Hosseini M, Nashtaei MS, Khodarahmian M, Shabani M, Jabarpour M *et al.* Resveratrol Ameliorates Mitochondrial Biogenesis and Reproductive Outcomes in Women with Polycystic Ovary Syndrome Undergoing Assisted Reproduction: A Randomized, Triple-Blind, Placebo-Controlled Clinical Trial. Journal of Ovarian Research. 2024 Jul; 17(1): 1-13. doi: 10.1186/s13048-024-01470-9.

[31] Gao Y, Zou Y, Wu G, Zheng L. Oxidative Stress and Mitochondrial Dysfunction of Granulosa Cells in Polycystic Ovarian Syndrome. Frontiers in Medicine. 2023 Jun; 10: 1-8. doi: 10.3389/fmed.2023.1193749.

[32] Li W, Liu C, Yang Q, Zhou Y, Liu M, Shan H. Oxidative Stress and Antioxidant Imbalance in Ovulation Disorder in Patients with Polycystic Ovary Syndrome. Frontiers in Nutrition. 2022 Oct; 9: 1-10. doi: 10.3389/fnut.2022.1018674.

[33] Yan H, Wang L, Zhang G, Li N, Zhao Y, Liu J *et al.* Oxidative Stress and Energy Metabolism Abnormalities in Polycystic Ovary Syndrome: From Mechanisms to Therapeutic Strategies. Reproductive Biology and Endocrinology. 2024 Dec; 22(1): 1-16. doi: 10.1186/s12958-024-01337-0.

[34] González F, Considine RV, Abdelhadi OA, Acton AJ. Oxidative Stress in Response to Saturated Fat Ingestion is Linked to Insulin Resistance and Hyperandrogenism in Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2019 Nov; 104(11): 5360-5371. doi: 10.1210/jc.2019-00987.

[35] Alfeel AH, Hussein SE, Yousif TE, Babker AM, Altoum AA, Mohamed AN *et al.* Association Between Oxidative Stress, Antioxidant Enzymes, and Homocysteine in Patients with Polycystic Ovary Syndrome. European Review for Medical and Pharmacological Sciences. 2023 Nov; 27(21): 10631-10641.

[36] Heng N, Zhu H, Talukder AK, Zhao S. Obesity and Oxidative Stress: Implications for Female Fertility. Animal Research and One Health. 2024 Nov; 2(4): 377-99. doi: 10.1002/aro2.82.

[37] Awonuga AO, Camp OG, Abu-Soud HM. A Review of Nitric Oxide and Oxidative Stress in Typical Ovulatory Women and in The Pathogenesis of Ovulatory Dysfunction in PCOS. Reproductive Biology and Endocrinology. 2023 Nov; 21(1): 1-15. doi: 10.1186/s12958-023-01159-6.

[38] Zheng L, Yang L, Guo Z, Yao N, Zhang S, Pu P. Obesity and Its Impact on Female Reproductive Health: Unraveling the Connections. Frontiers in Endocrinology. 2024 Jan; 14: 1-9. doi: 10.3389/fendo.

DOI: https://doi.org/10.54393/pjhs.v7i2.3609

2023.1326546.

[39] Yong W, Wang J, Leng Y, Li L, Wang H. Role of Obesity in Female Reproduction. International Journal of Medical Sciences. 2023 Jan; 20(3): 1-10. doi: 10.7150/ijms.80189.

[40] Ghafari A, Maftoohi M, Samarin ME, Barani S, Banimohammad M, Samie R. The Last Update on Polycystic Ovary Syndrome, Diagnosis Criteria, and Novel Treatment. Endocrine and Metabolic Science. 2025 Mar; 17: 1-9. doi: 10.1016/j.endmts.2025.100228.

[41] Rudnicka E, Duszewska AM, Kucharski M, Tyczyński P, Smolarczyk R. Oxidative Stress and Reproductive Function: Oxidative Stress in Polycystic Ovary Syndrome. Reproduction. 2022 Dec; 164(6): 1-10. doi: 10.1530/REP-22-0152.