



## Systematic Review



# Association of Oxidative Stress Biomarkers with Polycystic Ovary Syndrome (PCOS) and Its Metabolic Outcomes, Including Insulin Resistance and Dyslipidemia: A Systematic Review

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## ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, and insulin resistance. Increasing evidence suggests that oxidative stress (OS) contributes to its metabolic and reproductive complications. **Objectives:** To systematically review primary studies evaluating oxidative stress biomarkers in PCOS and their associations with metabolic outcomes. **Methods:** A comprehensive search was conducted in PubMed, Scopus, and Cochrane Library up to April 2024, following PRISMA 2020 guidelines. Eligible studies included case-control and cross-sectional designs reporting quantitative OS biomarker data in PCOS versus controls. Quality and risk of bias were assessed using the Newcastle Ottawa Scale (NOS). **Results:** Fifteen studies (2014–2024) involving over 1,000 participants were included. Malondialdehyde (MDA) was elevated in nearly all studies, indicating enhanced lipid peroxidation. Total antioxidant capacity (TAC/FRAP) and enzymatic antioxidants (SOD, CAT) were consistently reduced, while non-enzymatic antioxidants (GSH, vitamins A/C/E) were also lower. PON1 activity and sRAGE levels decreased, and 8-isoprostane in follicular fluid correlated with poorer oocyte quality. OS markers were positively associated with BMI, insulin resistance, and dyslipidemia. Five studies were rated low risk and ten moderate risk by NOS criteria. **Conclusions:** PCOS is characterized by increased oxidative stress and reduced antioxidant defense, closely linked to metabolic severity. Incorporating OS biomarkers into clinical evaluation and exploring phenotype-specific antioxidant interventions may improve metabolic and reproductive outcomes. Future longitudinal studies should standardize biomarker measurement to strengthen clinical applicability.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders among women of reproductive age, affecting 8–13% globally and up to 20% in South Asian populations [1]. Beyond menstrual irregularities and hyperandrogenic features, PCOS is

strongly linked with a cluster of metabolic abnormalities, including obesity, insulin resistance, dyslipidemia, and an increased lifetime risk of type 2 diabetes and cardiovascular disease, making it a major public health concern [2, 3]. Increasing evidence suggests that oxidative



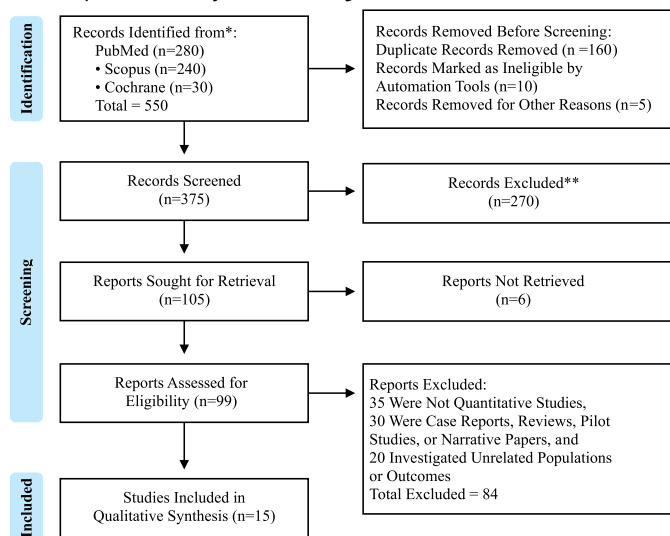
stress(OS) plays a central role in the pathogenesis of PCOS, contributing to both metabolic dysregulation and impaired folliculogenesis [4]. Oxidative stress is known to influence key metabolic pathways involved in insulin signaling, lipid metabolism, and adipocyte function. Reactive oxygen species (ROS) can impair insulin receptor activity, promote lipid peroxidation, and trigger chronic low-grade inflammation, all of which exacerbate insulin resistance, obesity, and dyslipidemia in women with PCOS [5]. Recent international studies have highlighted that PCOS is characterized by elevated reactive oxygen species, higher malondialdehyde (MDA) levels, and reduced antioxidant defenses, even in non-obese phenotypes [6]. Studies like Yan *et al.* demonstrated that women with PCOS exhibit energy metabolism abnormalities with heightened OS independent of body mass index [7], while Padder *et al.* reported significantly reduced superoxide dismutase (SOD) and catalase (CAT) activity in hyperinsulinemic, hyperandrogenic PCOS phenotypes [8]. Granulosa-cell studies confirm that mitochondrial dysfunction parallels OS burden and negatively affects oocyte quality [9]. Similarly, Santander *et al.* observed downregulation of Nrf2-regulated antioxidant genes in PCOS, implying impaired cellular defense [10]. Furthermore, several interventional studies have demonstrated that reducing oxidative stress can improve metabolic profiles in PCOS. Interventional research supports these findings, showing that lifestyle measures such as yoga [10] and structured exercise [11] and structured exercise [12] can significantly lower OS indices and improve metabolic profiles. Locally, oxidative imbalance in PCOS remains underexplored despite the high prevalence of obesity and metabolic syndrome among South Asian women. Azim *et al.* reported significantly higher MDA and lower paraoxonase-1 (PON1) activity among Pakistani women with PCOS [13], and Zaki *et al.* documented reduced total antioxidant capacity in adolescents with PCOS, suggesting that OS is present early in the disease course [14].

However, heterogeneity in biomarker selection, assay methods, and reporting makes it difficult to compare results across populations and to establish clear links with metabolic severity. Taken together, these findings indicate that oxidative stress not only contributes to reproductive dysfunction in PCOS but also underlies its major metabolic manifestations, including insulin resistance, dyslipidemia, and obesity. This systematic review was therefore conducted to synthesize global and regional evidence on oxidative stress biomarkers in PCOS and explore their associations with insulin resistance, dyslipidemia, obesity, and reproductive outcomes. The study aimed to generate a consolidated understanding of the redox imbalance in PCOS and highlight its potential as a target for therapeutic intervention and risk stratification.

## METHODS

This systematic review was conducted between 2014 and 2024, and in June 2024, following the PRISMA 2020 guidelines. The primary objective was to synthesize available evidence on oxidative stress biomarkers in women with polycystic ovary syndrome (PCOS) and their association with metabolic manifestations such as obesity, insulin resistance, and dyslipidemia. The review protocol was prospectively planned; however, it was not pre-registered in a public database but developed in advance to ensure methodological transparency, specifying the search strategy, eligibility criteria, and data extraction approach. A comprehensive electronic literature search was carried out in PubMed, Scopus, and Cochrane Library from database inception until April 2024. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords including "polycystic ovary syndrome" OR "PCOS" AND "oxidative stress" OR "malondialdehyde" OR "MDA" OR "superoxide dismutase" OR "SOD" OR "glutathione peroxidase" OR "GPx" OR "catalase" OR "total antioxidant capacity" OR "paraoxonase" OR "8-isoprostane" OR "sRAGE". Boolean operators (AND/OR) were used to maximize sensitivity. Reference lists of all eligible articles were also screened manually to capture additional studies not indexed in the databases. Studies were selected based on the following inclusion criteria: Population: Women of reproductive age diagnosed with PCOS (any diagnostic criteria acceptable, preferably Rotterdam), Design: Original primary research limited to cross-sectional and case-control designs, as no cohort or interventional studies meeting the inclusion criteria were available, Outcomes: Assessment of at least one oxidative stress marker (MDA, TAC, SOD, CAT, GPx, GSH, PON1, oxLDL, 8-isoprostane, sRAGE, or antioxidant vitamins) with or without metabolic parameter correlations and Language: Published in English and available as full text. Exclusion criteria included review articles, systematic reviews, meta-analyses, pilot or narrative studies, case reports, animal studies, and studies not reporting quantitative biomarker data or involving non-PCOS populations. All retrieved records were exported to EndNote and duplicates were removed. Two reviewers independently screened titles and abstracts for relevance, followed by full-text review of potentially eligible articles. Discrepancies were resolved by consensus. A total of 550 records were identified through database searching, of which 175 were removed before screening (duplicates and ineligible records). After screening 375 titles and abstracts, 270 records were excluded as irrelevant. Full texts of 105 articles were assessed for eligibility, leading to the exclusion of 84 studies (35 non-quantitative, 30 reviews/case reports, 20 with unrelated outcomes). Finally, 15 studies were included

in the qualitative synthesis (Figure 1).



**Figure 1:** Selection of Studies for the Systematic Review

Data were extracted using a standardized data extraction sheet. Extracted variables included first author, year of publication, country, study design, sample size (PCOS vs controls), mean age, mean BMI, diagnostic criteria, biomarkers measured, and key findings (direction of change, correlations with metabolic parameters). Where available, information on assay type, sample type (serum, plasma, follicular fluid), and cycle phase was also recorded. Risk of bias for included studies was evaluated independently by two reviewers using the Newcastle-

Ottawa Scale (NOS) for case-control and cross-sectional studies. Each study was scored across three domains: selection (0-4), comparability (0-2), and exposure/outcome assessment (0-3). Studies scoring  $\geq 8$  were rated low risk, scores of 6-7 were considered moderate risk, and scores  $\leq 5$  were considered high risk. Disagreements were resolved through discussion.

## RESULTS

This systematic review included 15 primary studies published between 2014 and 2024, collectively representing a wide geographic distribution across Asia, Africa, and Europe. Most were case-control studies, with one cross-sectional study in adolescents. Sample sizes ranged from 19 to over 300 participants. Where reported, mean age typically fell between 24-32 years, aligning with the reproductive age group, and most PCOS cohorts were in the overweight or obese range (e.g., Azim *et al.* reported mean BMI 28.5 kg/m<sup>2</sup> vs. 25.7 kg/m<sup>2</sup> in controls)[13]. All but two studies used the Rotterdam criteria for PCOS diagnosis. The most common biomarkers evaluated were malondialdehyde (MDA) and total antioxidant capacity (TAC/FRAP), with several studies measuring enzymatic antioxidants (SOD, CAT, GPx), non-enzymatic antioxidants (GSH, vitamins A/C/E), and advanced markers (PON1, oxLDL, 8-isoprostane, sRAGE). Together. This study highlighted the moderately heterogeneous but methodologically comparable evidence base (Table 1).

**Table 1:** Characteristics of Included Primary Studies on Oxidative-Stress Biomarkers in PCOS

Sr. No.	References	Country	Design	n (PCOS/ Control)	Mean Age (y) (PCOS / CTL)	BMI (kg/m <sup>2</sup> ) (PCOS / CTL)	PCOS Criteria	Biomarkers Measured	Main Findings (PCOS vs Control)
1	[5]	Poland	Case-control	63 / 53	NR	NR	NR	oxLDL-C, FRAP	Pro/antioxidant imbalance; subgroup patterns.
2	[13]	Pakistan	Case-control	70 Total (split per paper)	NR	28.5 ± 4.6 / 25.7 ± 4.5	Rotterdam	MDA, PON1	↑MDA; ↓PON1 in PCOS.
3	[14]	Egypt	Cross-sectional	50 / 50	17.15 ± 2.6 / 16.09 ± 1.6	20.50 ± 1.74 / 20.75 ± 1.50 (non-obese)	Rotterdam	TAC/FRAP + hormones	↓TAC; negative correlation with LH/FSH.
4	[15]	Nigeria	Case-control	50 / 50	28.18 ± 5.06 / 27.80 ± 5.11	26.58 ± 5.16 / 24.40 ± 2.86	Rotterdam	MDA, SOD, TAC, lipids	↑MDA; ↓SOD & TAC; adverse lipids.
5	[16]	Poland	Case-control	26 / 21	28.09 ± 6.68 / 32.84 ± 9.92	26.57 ± 6.68 / 24.53 ± 4.37	Rotterdam (in PCOS)	MDA, SOD, CAT, GPx	Group differences; patterns vs IR/obesity.
6	[17]	Turkey	Case-control (infertility clinic)	44 / 44	24.8 ± 4.8 / 31.3 ± 5.6	28.4 ± 6.7 / 25.9 ± 4.6	Rotterdam	PON1, Fetuin-A	↓PON1 more evident with higher BMI.
7	[18]	Oman	Case-control	100 / 100	29.9 ± 6.2 / 32.2 ± 6.3	NR (reported by obesity categories, not mean)	Rotterdam	Multiple OS indices (e.g., TOS/TAS, MDA)	PCOS linked to increased oxidative stress.
8	[19]	Sudan	Case-control	153 / 152	NR	NR	NR	GSH, SOD, LPO/MDA, Homocysteine	↑Lipid peroxidation, SOD, TG; associations with BMI /age.
9	[20]	India	Case-control (ART; follicular fluid)	90 / 90	NR	NR	Rotterdam	8-isoprostane (FF)	↑8-iso in PCOS FF; possible impact on ART outcomes.

10	[21]	Saudi Arabia	Case-control	NR	NR	NR	NR	SOD, GSH, metals	↓SOD & GSH; heavy-metal exposure links with OS.
11	[22]	Turkey	Case-control	51 / 50	NR(18-45 y)	NR	NR	TOS/TAS, inflammatory markers	OS and inflammation elevated in PCOS.
12	[23]	Iran	Case-control (IVF)	19 / 26	29.3 ± 5.54 / 37.4 ± 5.97	27.3 ± 4.40 / 24.9 ± 3.38	Rotterdam	sRAGE (serum & FF)	Altered sRAGE profile vs covariates; BMI influences FF sRAGE.
13	[24]	Turkey	Case-control (FF)	40 / 40	NR	NR	NR	TAC, TOC, 8-OHdG (FF)	Redox imbalance & DNA damage markers differ by PCOS phenotype.
15	[26]	Bangladesh	Case-control (pregnant PCOS vs controls)	NR	NR	NR	NR	MDA, vitamins A/C	↑MDA; ↓vitamins A/C in pregnant PCOS.

Among the 14 studies, MDA/LPO was the most consistently reported biomarker, appearing in nine studies and showing elevated levels in nearly all PCOS cohorts, strongly indicating increased lipid peroxidation. TAC/FRAP/TAS was assessed in five studies, with four reporting significant reductions, pointing to impaired antioxidant defenses. SOD activity was lower in four of four studies, whereas GPx findings were mixed, reflecting possible compensatory upregulation in select phenotypes. Non-enzymatic antioxidants (GSH, vitamins A/C/E) were uniformly decreased in all reporting studies, reinforcing the presence of systemic redox imbalance. Both studies measuring PON1 reported significantly reduced activity, while follicular fluid 8-isoprostane levels were consistently elevated. Overall, oxidative stress in PCOS was not isolated to one pathway but represents a broad imbalance between oxidants and antioxidants (Table 2).

**Table 2:** Oxidative-Stress Biomarkers with Number of Studies and References

Biomarkers	No. of Studies	Studies Reporting	Direction of Change in PCOS vs Control	Consistency of Evidence
MDA / LPO	9	[24-26]	↑ Significantly higher in nearly all studies	High
TAC / FRAP / TAS	5	[21, 22]	↓ Lower in PCOS in 4/5 studies	Moderate-High
SOD	4	[19, 24]	↓ Lower activity in most (4/4)	Moderate
GPx	2	[16, 24]	Mixed (1 ↑, 1 ↓)	Low
CAT	2	[16, 24]	↓ in both	High
GSH	2	[19, 24]	↓ in all	High
PON1	2	[13, 17]	↓ Lower activity across both studies	High
oxLDL-C	1	[21]	↑ Elevated vs controls	Single-study evidence
8-Isoprostane (FF)	2	[20, 24]	↑ Elevated in follicular fluid	High
sRAGE	1	[23]	↓ Lower serum & FF levels	Single-study evidence
TOC / TOS	2	[22, 24]	↑ Higher in PCOS	Consistent (2/2)
Antioxidant Vitamins (A, C, E)	2	[24, 26]	↓ Lower levels in both	High

↑ for increased, ↓ for decreased, and "mixed" where studies disagreed. Consistency is rated qualitatively High = ≥80 % of studies agree on direction, Moderate = 50-79 % agree, and Low = <50 % or highly mixed results.

Associations between oxidative markers and metabolic outcomes were evident in several studies. MDA showed positive correlations with BMI, HOMA-IR, fasting insulin, and dyslipidemia, indicating that oxidative stress burden parallels metabolic risk severity. TAC/FRAP and SOD were inversely associated with BMI and HOMA-IR, suggesting that lower antioxidant defense accompanies worsening insulin resistance. Markers such as GSH and PON1 consistently displayed negative correlations with BMI and HOMA-IR, indicating their depletion may contribute to cardiometabolic risk. Follicular fluid biomarkers (8-isoprostane, TOC) were linked to poorer oocyte quality and reduced fertilization rates, supporting the hypothesis that oxidative stress directly compromises reproductive potential in PCOS (Table 3).

**Table 3:** Association of Oxidative-Stress Biomarkers with Metabolic and Endocrine Parameters in PCOS

Biomarkers	Metabolic / Endocrine Parameter	No. of Studies	Direction / Key Findings	Studies Reporting
MDA / LPO	BMI / Obesity	4	Positive correlation – higher MDA in overweight/obese PCOS and rises with BMI category.	[21, 25]
	HOMA-IR / Fasting Insulin	5	↑MDA strongly associated with higher HOMA-IR, fasting insulin and IR prevalence.	[22, 26]
	Lipid Profile (TG, LDL, HDL)	3	↑MDA correlates with ↑TG, ↑LDL, ↓HDL (atherogenic pattern).	[18, 19]

TAC / FRAP / TAS	BMI / Obesity	3	↓TAC more pronounced in obese PCOS women.	[18, 21]
	HOMA-IR / Insulin	2	Inverse correlation lower TAC associated with worse insulin sensitivity.	[18, 22]
SOD	BMI / WC	3	Negative association lower SOD activity with higher BMI and WC.	[18, 19]
	HOMA-IR / Insulin	2	Lower SOD linked to higher IR indices.	[15, 19]
GPx	BMI / HOMA-IR	2	Mixed evidence ↑GPx in one study, ↓ in another; may depend on obesity status.	[16, 18]
CAT	BMI / WC	2	↓Catalase correlated with higher waist circumference.	[16, 18]
GSH	BMI / HOMA-IR	3	↓GSH consistently associated with obesity and IR severity.	[18, 21]
PON1	BMI / IR markers	2	↓PON1 activity inversely correlated with BMI and HOMA-IR.	[13, 17]
8-Isoprostane (FF)	Ovarian response / ART outcomes	2	↑8-iso associated with poorer oocyte quality, reduced fertilization rates.	[20, 24]
sRAGE	HOMA-IR / AMH	1	↓sRAGE associated with higher IR and altered ovarian reserve (AMH).	[23]
TOC / TOS	HOMA-IR / TG	2	↑TOS positively correlated with TG and IR markers.	[22, 24]
Vitamins A/C/E	BMI / HOMA-IR	2	↓Vitamin levels inversely related to BMI and IR indices.	[18, 26]

Quality assessment rated five studies as low risk (NOS score  $\geq 8$ ) and nine as moderate risk (NOS score 6–7). No study was considered high risk. Lower scores were mainly due to smaller control groups, incomplete reporting of BMI/age, or single-center design. Importantly, most studies used validated diagnostic criteria and standardized assays, lending confidence to the overall findings. These results suggest the evidence base is reasonably strong but would benefit from larger multicenter cohorts, standardized sample timing (fasting state, cycle phase), and consistent reporting of anthropometrics to enhance comparability (Table 4).

**Table 4:** Risk of Bias Assessment of Included Studies Using Newcastle-Ottawa Scale (NOS)

References	Selection (0–4)	Comparability (0–2)	Outcome/Exposure (0–3)	Total (0–9)	Risk Category
[5]	4	1	3	8	Low
[13]	4	1	3	8	Low
[14]	3	1	3	7	Moderate (adolescents only – generalizability limited)
[15]	4	1	3	8	Low
[16]	3	1	3	7	Moderate (control group smaller, single-center)
[17]	3	2	3	8	Low
[18]	3	1	3	7	Moderate (BMI data categorical only)
[19]	3	1	2	6	Moderate
[20]	3	1	2	6	Moderate
[21]	3	1	2	6	Moderate
[22]	4	2	3	9	Low
[23]	3	2	3	8	Low
[24]	3	1	2	6	Moderate
[25]	3	1	2	6	Moderate
[26]	3	1	2	6	Moderate

## DISCUSSION

This systematic review of 15 primary studies provides strong evidence that women with polycystic ovary syndrome (PCOS) have significantly elevated oxidative stress (OS) and impaired antioxidant capacity. Lipid peroxidation markers such as malondialdehyde (MDA) were consistently elevated in nine studies, while total

antioxidant capacity (TAC/FRAP) was reduced in most studies. Enzymatic antioxidants, including superoxide dismutase (SOD) and catalase (CAT), were significantly lower in PCOS cohorts, whereas glutathione peroxidase (GPx) showed mixed results. Non-enzymatic antioxidants such as glutathione (GSH) and vitamins A, C, and E were universally reduced, indicating a systemic redox imbalance. These findings corroborate previous evidence that OS plays a central role in the pathophysiology of PCOS, influencing both metabolic and reproductive outcomes. Recent studies reinforce these observations. Sharma *et al.* reported significantly higher total oxidant status (TOS) and lower TAC in PCOS, confirming a pronounced redox shift [27]. Similarly, Sen *et al.* demonstrated elevated OSI and inflammatory markers, suggesting that OS and inflammation act synergistically in PCOS progression [22]. In non-obese adolescents, Zaki *et al.* observed reduced TAC with significant correlations to LH and FSH, indicating that OS is present early and independent of obesity [14]. These findings highlight that metabolic factors exacerbate oxidative stress but do not solely determine its presence, suggesting underlying genetic, hormonal, and environmental influences. The variability in GPx results observed across studies may reflect differences in PCOS phenotypes, body composition, ethnicity, and environmental exposures. Obese and hyperandrogenic PCOS phenotypes tend to display greater oxidative burden, while lean phenotypes may show compensatory increases in GPx activity. These differences underscore that oxidative stress is a heterogeneous process influenced by both intrinsic metabolic status and external factors such as diet, pollutants, and micronutrient intake. Understanding this variability is essential for interpreting biomarker data

and developing phenotype-specific interventions. Markers of lipid peroxidation also appear to be closely tied to metabolic dysfunction. MDA showed positive associations with BMI, HOMA-IR, and dyslipidemia in our synthesis, which was consistent with Nawrocka-Rutkowska *et al.* who reported that MDA and GPx were significantly higher in PCOS and correlated with triglycerides and insulin resistance [16]. Heavy-metal exposure has also been implicated in aggravating OS. Abudawood *et al.* found higher cadmium and lead levels with lower SOD and GSH in PCOS women, supporting the role of environmental triggers [28]. These environmental and metabolic modifiers highlight the multifactorial nature of oxidative imbalance in PCOS and its complex interplay with systemic inflammation and insulin resistance. The ovarian microenvironment is particularly vulnerable to oxidative damage. Our review showed that follicular fluid (FF) 8-isoprostane levels were elevated and associated with poorer oocyte quality. Similar results were reported by Ardehjani *et al.* where resveratrol supplementation significantly reduced TOS and OSI in FF and improved ART outcomes [29]. Growth hormone co-treatment has also been shown to attenuate FF oxidative stress and improve fertilization rates in PCOS undergoing IVF [30]. Proteomic studies by Pereira *et al.* revealed altered HDL-related proteins and antioxidant pathways in FF, further supporting that OS contributes to compromised folliculogenesis [31]. Therapeutic interventions targeting OS appear promising. Ildarabadi *et al.* demonstrated that green coffee supplementation increased PON1 activity without significantly lowering MDA [32], indicating selective improvement of antioxidant defense. Melatonin supplementation has consistently raised TAC and improved menstrual cyclicity [33]. Vitamin D replacement has been shown to improve TAC and reduce hs-CRP in infertile PCOS women, highlighting a potential adjunctive role for antioxidant-oriented therapy [34]. These findings suggest that individualized antioxidant interventions could be integrated into PCOS management, with treatment tailored according to metabolic phenotype, BMI, and oxidative biomarker profile. Phenotype-specific analyses reveal that obese and hyperandrogenic PCOS phenotypes exhibit the greatest OS burden. Mizgier *et al.* reported that MDA and CRP were significantly higher in obese PCOS women than lean counterparts [35]. Lifestyle factors also play a role, as Song *et al.* found that lower dietary TAC was associated with increased odds of PCOS [36], indicating that diet modification may help restore redox balance. Collectively, these insights reinforce the need for precision-based approaches that consider both phenotype and metabolic background when addressing oxidative stress in PCOS.

This review is limited by significant heterogeneity in study

design, PCOS diagnostic criteria, oxidative stress biomarkers, and participant characteristics, which may reduce comparability and limit quantitative synthesis. Additionally, most included studies were cross-sectional with relatively small sample sizes, restricting causal inference and generalizability of the findings. Future research should focus on longitudinal, phenotype-specific studies with standardized biomarker protocols to enhance comparability and clinical translation. Recognizing oxidative stress as both a diagnostic and therapeutic target may pave the way toward more personalized and effective management strategies for women with PCOS.

## CONCLUSIONS

This review underscores oxidative stress as a central mechanism linking metabolic, endocrine, and reproductive abnormalities in PCOS. The consistent elevation of MDA and reduction of antioxidant capacity across diverse populations support the inclusion of oxidative biomarkers in risk assessment and clinical monitoring. Targeted antioxidant interventions, including melatonin, vitamin D, polyphenols, and lifestyle modification, hold promise for improving metabolic health, insulin sensitivity, and fertility outcomes.

## Authors' Contribution

Conceptualization: HZ

Methodology: BI, AA, SK

Formal analysis: BI, AA

Writing and Drafting: HZ, SS, BI, AM, AA

Review and Editing: HZ, SS, BI, AM, AA, SK

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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