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EFFICACY AND SAFETY OF ANTIOXIDANT SUPPLEMENTATION IN WOMEN WITH ENDOMETRIOSIS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Background: Endometriosis affects ~10% of reproductive-age women, causing pain and infertility. Limitations of conventional therapies have driven interest in targeting oxidative stress, though clinical evidence on antioxidant efficacy and safety remains inconsistent.
Aim: To evaluate the efficacy, safety, and biomarker impact of antioxidant supplementation in women with endometriosis based on randomized controlled trials (RCTs).
Materials and Methods: Following PRISMA guidelines, a systematic PubMed search identified 119 unique records, screened via Rayyan based on PICOS criteria. Eligible studies were RCTs evaluating antioxidant supplementation versus control in adult women with confirmed endometriosis. Ultimately, 26 RCTs met all inclusion criteria.
Results: Selected antioxidants significantly attenuated oxidative and inflammatory markers (e.g., reduced hs-CRP with vitamin D; lower IL-1β, TNF-α, and MDA with astaxanthin/nanocurcumin; suppressed MMP-2/9 and VEGF with resveratrol). Clinically, vitamins C/E, nanocurcumin, selenium, and vitamin D reduced pelvic pain, whereas melatonin, fish oil, and resveratrol showed mixed or no benefit. Quality of life (EHP-30) did not improve vs. placebo, though adjunctive curcumin enhanced generic quality of life and sexual function. Astaxanthin and nanocurcumin increased mature oocyte yield and embryo quality during ART, but without significant improvements in clinical pregnancy rates.
Conclusions: Antioxidants effectively modulate oxidative, inflammatory, and angiogenic pathways in endometriosis. However, biochemical improvements do not consistently translate into clinical benefits regarding pain, quality of life, or pregnancy rates. Due to high study heterogeneity and inconsistent safety data, antioxidants should be considered investigational adjunctive options rather than routine treatment.

KEYWORDS

Endometriosis, Antioxidant Supplementation, Oxidative Stress, Randomized Controlled Trials

CITATION

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1. Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity and affecting approximately 10% of women of reproductive age worldwide. The disease is commonly associated with dysmenorrhea, chronic pelvic pain, dyspareunia, infertility, and substantial impairment of quality of life. Despite advances in diagnostic and therapeutic strategies, the management of endometriosis remains challenging, particularly in women with persistent symptoms or reproductive difficulties. Current treatment options include hormonal therapies, analgesics, and surgical intervention, with assisted reproductive techniques frequently required in women experiencing infertility. However, hormonal treatment may be associated with adverse effects and is not suitable for all patients, while surgical treatment may be followed by disease recurrence and may adversely affect ovarian reserve. These limitations have stimulated increasing interest in complementary and non-hormonal therapeutic strategies that could target the underlying biological mechanisms of endometriosis rather than only its clinical manifestations [1].

Oxidative stress has emerged as an important component of the pathophysiology of endometriosis. It is defined as an imbalance between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant systems to neutralize them. Excessive ROS generation may promote lipid, protein, and DNA damage and contribute to inflammatory signaling, cellular proliferation, angiogenesis, tissue remodeling, and persistence of ectopic endometrial lesions. The peritoneal cavity in women with endometriosis may be particularly susceptible to oxidative injury because retrograde menstruation introduces erythrocytes, hemoglobin, and iron into the pelvic environment, while activated macrophages and other inflammatory cells may further increase ROS production. Consequently, oxidative stress may act as an important link between retrograde menstruation, chronic inflammation, and the establishment and progression of endometriotic lesions [2,3].

Clinical and experimental evidence supports an association between endometriosis and impaired redox homeostasis. Increased concentrations of oxidative stress markers and altered antioxidant capacity have been reported in the peritoneal fluid and systemic circulation of women with endometriosis. Oxidative damage may additionally interact with inflammatory pathways and immune dysfunction, thereby creating a self-perpetuating microenvironment favorable to lesion survival and disease progression [2,3]. Importantly, the relationship between oxidative stress and endometriosis may extend beyond local pelvic inflammation. Oxidative injury has been associated with reproductive dysfunction and may influence oocyte quality, follicular development, fertilization, and implantation, providing a potential biological explanation for the association between endometriosis and reduced fertility.

Iron metabolism may represent an additional mechanism linking endometriosis with oxidative stress. Repeated episodes of bleeding within endometriotic lesions and the peritoneal cavity may result in local iron accumulation. A systematic review demonstrated that iron excess occurs in endometriotic lesions, peritoneal fluid, and other tissues affected by the disease and is associated with oxidative stress, inflammation, and cellular damage. Iron-mediated oxidative stress has also been linked to symptom severity and subfertility, suggesting that iron dysregulation may contribute to both the local and systemic consequences of endometriosis [4]. More recently, increasing attention has been directed toward ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation. Evidence suggests that endometriotic cells may exhibit resistance to ferroptosis despite an environment characterized by iron excess and oxidative stress, potentially facilitating the survival of ectopic endometrial tissue. These findings further support the importance of redox mechanisms in endometriosis and provide a biological rationale for investigating antioxidant-based therapeutic approaches [5].

Antioxidant supplementation has consequently been proposed as a potential adjunctive strategy in women with endometriosis. Antioxidant compounds may counteract excessive ROS production, restore redox balance, reduce lipid and cellular damage, and potentially attenuate downstream inflammatory processes. A variety of antioxidant and antioxidant-related interventions have been investigated in clinical studies, including vitamins, melatonin, polyphenolic compounds, omega-3 fatty acids, and other bioactive substances. However, these interventions differ substantially in their biological properties, dosage, duration of treatment, and potential clinical effects [2,5]. The heterogeneity of available interventions makes it difficult to determine whether the potential benefits observed in individual trials can be attributed to a general antioxidant effect or to specific compounds and treatment regimens.

The clinical evidence has expanded considerably in recent years, and several systematic reviews and meta-analyses have attempted to synthesize the available randomized evidence. A recent meta-analysis including 21 randomized controlled trials and 1,626 participants reported potential benefits of antioxidant supplementation for pelvic pain, dysmenorrhea, dyspareunia, and peripheral malondialdehyde concentrations, while no significant improvement was observed in overall pain or clinical pregnancy rate. Importantly, substantial heterogeneity was observed across antioxidant types, disease stages, treatment durations, and clinical outcomes, highlighting the complexity of interpreting the available evidence [6]. Another recent systematic review and meta-analysis focused specifically on endometriosis-related pain and similarly emphasized the potential efficacy of antioxidant supplementation while demonstrating considerable methodological and clinical heterogeneity among the included trials [7]. These findings suggest that although antioxidant supplementation may provide clinically relevant benefits for selected outcomes, the certainty and generalizability of the evidence remain limited. Furthermore, the substantial clinical and methodological heterogeneity across studies limits the extent to which pooled findings can be generalized to individual antioxidant interventions or specific patient populations.

In addition to efficacy, the safety of antioxidant supplementation represents an important clinical consideration. Women with endometriosis may use dietary supplements for prolonged periods, frequently alongside hormonal treatment, analgesics, or fertility-directed interventions. Nevertheless, adverse events, treatment discontinuation, tolerability, and potential differences in safety profiles between individual antioxidant compounds have received less systematic attention than efficacy outcomes. Safety reporting may also be inconsistent across randomized trials, with substantial variation in the reporting of adverse events, treatment discontinuation, and treatment tolerability. Furthermore, the assumption that antioxidant supplementation is inherently safe may be inappropriate, as biological effects are dependent on the specific compound, dose, duration of exposure, and characteristics of the treated population. A balanced assessment of both potential benefits and harms is therefore essential before antioxidant supplementation can be considered an evidence-based adjunct to conventional endometriosis management.

Although the existing literature provides increasing support for a potential role of antioxidant supplementation in endometriosis, important uncertainties remain regarding the consistency of clinical benefits across different interventions and outcomes, as well as the safety and tolerability of these treatments. Previous reviews have differed in their inclusion criteria, evaluated outcomes, antioxidant classifications, and methodological approaches, with several analyses concentrating primarily on pain or selected reproductive outcomes [6,7]. Moreover, statistical significance does not necessarily translate into clinically meaningful improvement, and the magnitude of symptom reduction and responder rates may vary substantially across interventions. Therefore, an updated synthesis specifically integrating both efficacy and safety outcomes across randomized controlled trials is warranted, with particular attention to the magnitude of changes in symptom severity and, where available, clinically meaningful improvement or responder rates.

The aim of this systematic review was to evaluate the efficacy and safety of antioxidant and antioxidant-related supplementation in women with endometriosis based on randomized controlled trials. We sought to assess the effects of these interventions on endometriosis-associated pain, quality of life, reproductive outcomes, and biochemical markers of oxidative stress and inflammation, while also systematically evaluating adverse events, tolerability, and treatment discontinuation. Particular attention was given to the magnitude of symptom changes and, where available, clinically meaningful improvement or responder rates, in addition to statistical significance. By integrating clinical and biochemical outcomes with available safety data, this review aims to provide a comprehensive assessment of the potential role of antioxidant supplementation as an adjunctive therapeutic strategy in women with endometriosis and to identify important gaps requiring further investigation in future randomized clinical trials.

2. Materials and Methods

To investigate the efficacy and safety of antioxidant supplementation in women with endometriosis, a systematic literature search was conducted on August, 10th, 2026, in the PubMed electronic database.

The following search query was applied.

("Endometriosis"[Mesh] OR endometriosis[tiab] OR endometriotic[tiab] OR endometrioma*[tiab]) AND ("Antioxidants"[Mesh] OR antioxidant*[tiab] OR anti-oxidant*[tiab] OR acetylcysteine[tiab] OR "N-acetylcysteine"[tiab] OR "vitamin C"[tiab] OR "ascorbic acid"[tiab] OR "vitamin E"[tiab] OR tocopherol*[tiab] OR "vitamin D"[tiab] OR cholecalciferol[tiab] OR melatonin[tiab] OR resveratrol[tiab] OR curcumin[tiab] OR "alpha-lipoic acid"[tiab] OR "lipoic acid"[tiab] OR selenium[tiab] OR zinc[tiab] OR "omega-3"[tiab] OR "omega 3"[tiab] OR polyphenol*[tiab]) AND (random*[tiab] OR placebo[tiab] OR trial[tiab] OR "Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt]) NOT (animals[mh] NOT humans[mh])

As a result of applying this strategy, 125 records were identified. The results were exported to the Rayyan platform, which is dedicated to literature review management and analyses. Using this platform, six duplicates were identified and removed after manual verification by our team. This process identified 119 unique articles that qualified for the next selection stage.

2.1. Inclusion Criteria

The research inclusion criteria were structured based on the PICOS framework (Population, Intervention, Comparison, Outcome, Study design), in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The selected articles aimed to answer the following research question: "What are the efficacy and safety of antioxidant supplementation in women with endometriosis?"

The main inclusion criteria were: (1) randomized controlled trials (RCTs), including placebo-controlled, active-controlled, or trials comparing the intervention with standard medical treatment or no intervention; (2) a population of adult female participants (≥18 years of age) with a documented diagnosis of endometriosis, irrespective of anatomical location, phenotype, disease stage, or the co-occurrence of infertility; (3) supplementation with substances possessing explicitly defined antioxidant activity (e.g., N-acetylcysteine [NAC], vitamins C, E, and D, melatonin, resveratrol, curcumin, alpha-lipoic acid, zinc, selenium, omega-3 polyunsaturated fatty acids [PUFAs], polyphenols, or flavonoids), administered either as monotherapy or as an adjunct to standard treatment, regardless of dosage, formulation, or duration of therapy; (4) the presence of an appropriate comparison group (placebo, no intervention, standard care, a different dose or formulation of the supplement, or another active control); (5) evaluation of relevant effectiveness or safety outcomes, including primary clinical endpoints (endometriosis-associated pain such as chronic pelvic pain, dysmenorrhea, and dyspareunia; health-related quality of life; analgesic consumption; and reproductive outcomes or fertility parameters) or secondary endpoints (circulating or local biomarkers of oxidative stress and inflammation, hormonal or metabolic parameters, oocyte and embryo quality, adverse events, treatment discontinuation rates, and therapy tolerability).

Exclusion criteria included: (1) literature reviews, systematic reviews, meta-analyses, editorials, commentaries, study protocols, and individual case reports or case series; (2) preclinical in vitro experiments, animal studies, non-randomized observational designs, or research conducted exclusively in pediatric populations (<18 years of age); (3) studies evaluating general dietary patterns, pharmaceuticals, or other interventions without a distinct, standalone assessment of an antioxidant supplement; (4) purely descriptive studies or trials lacking an appropriate comparison group or failing to report quantitative data on clinical, reproductive, or biological outcomes.

2.2. Data collection and analysis

The literature selection process was performed in multiple stages, strictly following the PRISMA guidelines. Initially, a five-member team of independent reviewers assessed the titles and abstracts of 119 articles, examining their compliance with the main objective of the study. To ensure maximum objectivity and minimize systematic errors, this stage was conducted independently on the Rayyan platform. Studies that did not meet the basic assumptions of the PICOS protocol were excluded. The next step involved an independent full-text assessment of the remaining publications by all five authors based on detailed inclusion and exclusion criteria. Potential disagreements and conflicting assessments were subjected to joint analysis and discussion until a final consensus was reached. Twenty six studies were included in this systematic review. All of them were RCTs.

2.3. Data Extraction

The following data were extracted from the qualified publications: study characteristics (first author, publication year, DOI, and specific trial design); participant demographics and sample sizes (total number of randomized patients, group allocations, age, and treatment and follow-up durations); patient clinical profiles and diagnostic criteria (presence of chronic pelvic pain, dysmenorrhea, dyspareunia, or co-occurring infertility, diagnostic confirmation method, and rASRM disease stage); intervention parameters (supplement or antioxidant type, dosage, frequency, and treatment duration); and details regarding control groups and co-administered therapies (placebo, standard care, or concomitant medical and surgical treatments). Primary clinical outcomes included pain intensity scores evaluated via Visual Analog Scale (VAS) or Numerical Rating Scale (NRS) across various pelvic pain domains, fertility and assisted reproductive technology (ART) outcomes (including oocyte yield, MII oocytes, fertilization and cleavage rates, high-quality embryo counts, clinical pregnancy, live birth rates, and endometrioma size changes), and health-related quality of life or functional scores (EHP-30, WHOQOL-BREF, FSFI, PSQI). Baseline values, post-intervention mean changes, responder rates, and clinically meaningful improvement thresholds were also collected. Finally, secondary endpoints covered biological parameters—including systemic and local oxidative stress markers (e.g., MDA, ROS, TAC, SOD, CAT, 8-OHdG), inflammatory cytokines (e.g., IL-1β, IL-6, IL-8, IL-10, TNF-α, hs-CRP, RANTES, MCP-1, fecal calprotectin), and tissue or gene expression profiles (β-catenin, MMP-2, MMP-9, VEGF)—alongside safety and tolerability outcomes (adverse events, side effects, and study dropouts) and overall study conclusions.

3. Research results

3.1.1. Inflammatory and inflammation-related biomarkers

Several randomized controlled trials investigated the effects of antioxidant and antioxidant-related supplementation on inflammatory and inflammation-related biomarkers in women with endometriosis. Overall, the findings suggest that selected interventions may modulate inflammatory pathways, although substantial heterogeneity was observed with respect to the biomarkers assessed, biological compartments, intervention characteristics, and study populations.

3.1.2. Systemic inflammatory biomarkers

Systemic inflammatory markers were evaluated in several trials. Vitamin D supplementation was associated with a significant reduction in serum high-sensitivity C-reactive protein (hs-CRP), with an adjusted between group difference of 0.64 mg/L (95% CI −0.97 to 0.30; $p<0.001$). This effect was accompanied by a significant increase in total antioxidant capacity (TAC) (β=47.54 mmol/L; 95% CI 19.98–75.11; p=0.001), suggesting a potential improvement in systemic inflammatory and redox status [9]. In contrast, the study evaluating vitamin D or omega-3 fatty acid supplementation in adolescents and young women primarily assessed clinical symptoms and biochemical status and did not demonstrate a consistent effect on inflammatory biomarkers [10].

A more pronounced effect on systemic proinflammatory cytokines was reported in a randomized, triple-blind trial of astaxanthin in women with advanced endometriosis undergoing assisted reproductive treatment. Astaxanthin supplementation significantly reduced serum IL-1β ($p<0.001$) and TNF-α (p=0.038), while a significant between group difference was also reported for IL-6 (p=0.024). In follicular fluid, IL-6 and TNF-α concentrations were also lower in the astaxanthin group. These changes occurred alongside an increase in TAC and SOD activity and a reduction in MDA concentrations, suggesting simultaneous modulation of oxidative and inflammatory pathways [11].

Fish derived lipid supplementation produced a different and more heterogeneous inflammatory response. In the randomized trial concentrations of several proinflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, did not demonstrate consistent significant between group differences. In contrast, the concentration of the anti-inflammatory cytokine IL-10 increased significantly in the intervention group, from 32.5±51.5 to 265±508 pg/mL (p=0.024), with a significant adjusted between-group effect (ANCOVA: 5.07; 95% CI 1.32–19.48; p=0.019) [21]. Fecal calprotectin, assessed as an additional inflammation related marker, did not change significantly following the intervention [21]. These findings may indicate a selective immunomodulatory effect rather than broad suppression of proinflammatory cytokines.

3.1.3. Local inflammatory mediators

The effects of antioxidant supplementation on local inflammatory mediators were assessed in peritoneal or follicular fluid in several studies. Combined vitamin C and vitamin E supplementation was associated with a significant reduction in the chemokines RANTES (CCL5) ($p \leq 0.002$) and MCP-1 (CCL2) ($p \leq 0.016$) in peritoneal fluid. IL-6 also decreased following supplementation, although the reported reduction did not reach conventional statistical significance ($p \leq 0.056$) [14]. As RANTES and MCP-1 are involved in the recruitment and activation of inflammatory cells, their reduction may indicate attenuation of local inflammatory signaling within the peritoneal environment.

Similarly, astaxanthin supplementation was associated with lower concentrations of IL-6 and TNF-α in follicular fluid [11]. This finding is of particular interest because the follicular microenvironment may influence oocyte competence and reproductive outcomes in women with endometriosis. The reduction in follicular inflammatory cytokines was accompanied by improved oxidative stress parameters and a higher number of mature oocytes and high-quality embryos in the astaxanthin group [11].

Nanomicelle curcumin was also associated with modulation of local inflammatory signaling. In women with endometriosis undergoing assisted reproductive treatment, curcumin supplementation resulted in lower concentrations of IL-8 and TNF-α in follicular fluid [16]. These changes occurred together with improvements in oxidative stress parameters and selected embryological outcomes, suggesting a potential interaction between oxidative stress, local inflammation, and reproductive function. However, because inflammatory biomarkers were assessed in only a limited number of studies, the consistency of this effect across curcumin preparations and patient populations remains uncertain.

3.1.4. Inflammation-related markers of tissue remodeling and angiogenesis

In addition to classical inflammatory cytokines and chemokines, several studies assessed biomarkers involved in tissue remodeling and angiogenesis, which are closely related to the pathophysiology and persistence of endometriotic lesions.

Resveratrol demonstrated particularly consistent effects on matrix metalloproteinases. In a randomized exploratory trial, resveratrol significantly reduced both mRNA and protein expression of MMP-2 and MMP-9 in eutopic endometrial tissue [23]. These molecular changes were accompanied by significant reductions in MMP concentrations in both endometrial fluid and serum. Serum MMP-2 decreased from 485.0±92.4 to 394.0±87.9 ng/mL ($p<0.001$), while MMP-9 decreased from 739.4±114.2 to 591.2±70.1 ng/mL ($p<0.001$). Significant reductions were also observed in endometrial fluid, with MMP-2 decreasing from 896.9±127.8 to 722.2±102.3 ng/mL ($p<0.001$) and MMP-9 from 429.2±36.8 to 347.5±43.0 ng/mL ($p<0.001$). Post-intervention concentrations were significantly lower than those in the control group for both MMP-2 and MMP-9 ($p<0.001$) [23]. These findings suggest that resveratrol may inhibit extracellular matrix remodeling, a process that contributes to tissue invasion, lesion establishment, and progression in endometriosis.

Further evidence for the modulation of inflammation related and angiogenic pathways was provided by another randomized exploratory trial of resveratrol. Following supplementation, both mRNA and protein expression of TNF-α and vascular endothelial growth factor (VEGF) in eutopic endometrium were significantly reduced [32]. TNF-α is a key proinflammatory cytokine, whereas VEGF is an important mediator of angiogenesis; therefore, simultaneous reductions in these markers suggest that resveratrol may affect both inflammatory and angiogenic mechanisms involved in endometriotic lesion persistence.

CA-125, another inflammation associated biomarker frequently used in the clinical assessment of endometriosis, was also investigated in a randomized trial of resveratrol combined with a monophasic combined oral contraceptive. Serum CA-125 concentrations decreased in both treatment groups, although the study did not demonstrate a clear additional effect attributable specifically to resveratrol. Prolactin concentrations did not differ according to treatment or duration of therapy [25]. Thus, the reduction in CA-125 cannot be interpreted as evidence of a specific anti-inflammatory effect of resveratrol.

3.1.5. Overall synthesis

Overall, randomized evidence suggests that selected antioxidant and antioxidant-related interventions may modulate inflammatory and inflammation-related biomarkers in women with endometriosis. The most consistent findings included reductions in hs-CRP following vitamin D supplementation [9], IL-1β, IL-6, and TNF-α following astaxanthin supplementation [11], RANTES and MCP-1 following vitamin C and vitamin E supplementation [14], and IL-8 and TNF-α following nanomicelle curcumin supplementation [16]. Resveratrol was additionally associated with reductions in MMP-2, MMP-9, TNF-α, and VEGF, suggesting potential effects on inflammatory signaling, extracellular matrix remodeling, and angiogenesis [23,32]. However, substantial heterogeneity in the biomarkers assessed, biological compartments, interventions, treatment duration, and study populations limits direct comparisons between studies and precludes conclusions regarding a uniform anti-inflammatory effect of antioxidant supplementation.

3.2. Quality of life and sleep

To comprehensively evaluate the health-related quality of life (HRQoL) in women diagnosed with endometriosis, studies frequently employ three primary standardized instruments: the Endometriosis Health Profile-30 (EHP-30), the World Health Organization Quality of Life-BREF (WHOQOL-BREF), and the Pittsburgh Sleep Quality Index (PSQI). Among these, the EHP-30 stands out as the most targeted and disease-specific tool, explicitly tailored to capture how endometriosis-related symptoms impair daily functioning across personal, occupational, and sexual domains [15, 17, 21, 29]. Despite its high sensitivity to disease-specific burdens, trials evaluating antioxidant supplementation failed to demonstrate statistically significant differences in EHP-30 domain scores when comparing intervention cohorts to placebo control groups [15, 17, 21, 29].

In contrast, broader dimensions of well-being are captured using the generic WHOQOL-BREF questionnaire, which measures health across four core domains: physical health, psychological well-being, social relationships, and environmental factors. Demonstrating the utility of generic tools in adjunct therapy trials, one study highlighted that combining dienogest with curcumin yielded a statistically significant improvement in overall quality of life compared to dienogest with placebo at the end of the follow-up period (adjusted mean difference [aMD]: −11.29, 95% CI: −16.05 to −6.53; $p<0.001$) [12, 28]. Additionally, sexual function—assessed via the Female Sexual Function Index (FSFI)—showed substantial gains in both arms, yet the improvement was markedly higher in the curcumin co-treatment group (rising from 21.10±4.79 to 30.08±5.13, representing a 42.55% increase) than in the control group (rising from 22.41±4.11 to 26.81±2.96, a 19.63% increase), establishing a robust between-group disparity (difference in change: 4.42, 95% CI: 2.46 to 6.37; $p<0.001$; aMD: 3.76, 95% CI: 2.08 to 5.45; $p<0.001$) [12].

Finally, given that chronic sleep disruption severely aggravates daily fatigue and pain perception in endometriosis, the PSQI provides crucial insights into subjective sleep parameters, fatigue, and insomnia patterns [13]. Investigating sleep-targeted therapies, melatonin administration led to a statistically significant reduction in global PSQI scores over time (9.05 to 6.90 in the intervention group versus 8.65 to 8.20 in the placebo group; between-group difference: −1.70, 95% CI: −2.63 to −0.77; $p<0.001$). However, because the pre-established Minimal Clinically Important Difference (MCID) threshold for the PSQI is set at 3 points, this improvement, while statistically significant, fell short of clinical meaningfulness. A sub-component analysis revealed that melatonin supplementation successfully yielded notable gains in sleep latency, sleep duration/disturbances, and reduced reliance on sleep medications, whereas metrics such as habitual sleep efficiency, daytime dysfunction, and overall subjective sleep quality remained largely unchanged.

3.3. Pain outcomes

The most frequently assessed pain symptoms included dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain, defined as pain lasting for at least 3 or 6 months. To assess pain intensity, sixteen studies utilized the Visual Analogue Scale (VAS), and three used the Numerical Rating Scale (NRS).

A significant number of RCTs demonstrated a reduction in pain severity following the administration of antioxidant compounds, including vitamins C and E [8, 14], nanocurcumin [12], selenium [19], and pentoxifylline [24]. In the case of vitamin D, therapy was effective only for pelvic pain (50,000 IU every 2 weeks for 12 weeks) [9] or exclusively for dysmenorrhea (50,000 IU weekly for 8 weeks) [18]. Notably, in the latter study, all participants presented with vitamin D deficiency. Conversely, supplementation failed to demonstrate comparable efficacy in another cohort of vitamin D-deficient patients evaluated by Shabani et al. [29].

Furthermore, a study by Nodler et al. [10] comparing the efficacy of vitamin D (2,000 IU/day), fish oil (488 mg EPA, 178 mg DHA), and placebo over a 6-month period in young women with surgically confirmed endometriosis found no significant difference in VAS score changes among the cohorts. Similar outcomes were also reported in trials evaluating curcumin [17], fish-derived lipids (FDL, including EPA, DHA, alkylglycerols, squalene, and vitamins A and D) [21], olive oil capsules [27], resveratrol [25], and N-acetylcysteine combined with oral contraceptives [20].

Findings regarding melatonin remain inconclusive. Söderman et al. found no superiority of adjuvant melatonin therapy (20 mg/day) over placebo during a 2-month follow-up [15], while in a similar RCT, therapy (5 mg/day) led to a statistically significant reduction in symptoms that nonetheless failed to reach the threshold for clinical significance [13]. In contrast, Schwertner et al. reported different findings following 8 weeks of melatonin treatment (10 mg/day) with an average reduction of nearly 40% in VAS scores for pelvic pain and dysmenorrhea compared to placebo [26]. Among patients with ovarian endometrioma, co-administration of melatonin and dienogest was associated with an improvement in dysmenorrhea, without significant changes in other pain domains [28].

3.4. Fertility

The impact of antioxidant supplementation on fertility treatment outcomes in women with endometriosis was directly evaluated in three randomized controlled trials (RCTs) [11, 16, 31]. Two of these studies assessed fertility using a multiparametric approach during assisted reproductive technology (ART) procedures (IVF/ICSI), analyzing the total number of retrieved oocytes, the number of mature oocytes, embryological parameters, as well as chemical and clinical pregnancy rates [11, 16]. In one trial, the cumulative pregnancy rate achieved during the intervention served as the sole measure of fertility [31].

Two RCTs demonstrated a significant improvement in fertility parameters and oocyte/embryo quality following the administration of antioxidants, specifically astaxanthin [11] and nanocurcumin [16]. A 12-week supplementation with astaxanthin (6 mg/day) and a 10-week administration of nanocurcumin (120 mg/day) in women with stage III/IV endometriosis undergoing IVF/ICSI yielded consistent, favorable clinical and biological effects. At the cellular level, both substances reduced oxidative stress (MDA) and inflammation (TNF-α, IL-1β, IL-8) within the follicular fluid. This translated into a significant increase in the total number of retrieved oocytes, a higher yield of mature metaphase II (MII) oocytes, and a greater number of high-quality embryos, thereby enhancing the success rates of ART procedures [16]. However, this improvement in early embryonic development parameters did not directly result in a statistically significant increase in the clinical pregnancy rate (44% vs. 40%; $p=0.241$ for astaxanthin) [11].

The study by Mier-Cabrera et al. [31] presented divergent results, showing no significant effect of the therapy on pregnancy rates. A six-month supplementation with vitamin C (343 mg/day) and vitamin E (84 mg/day) led to a significant reduction in oxidative stress markers in plasma and peritoneal fluid; however, the pregnancy rate in the intervention group did not differ significantly from that of the placebo group (19% vs. 12%; $p>0.05$).

4. Discussion

This systematic review indicates that selected antioxidant and antioxidant-related interventions may modify individual components of the oxidative and inflammatory pathways involved in endometriosis. Favorable effects were observed for some systemic and local biomarkers, as well as for selected measures of quality of life, sexual function, sleep, and reproductive laboratory outcomes. However, these benefits were not consistent across interventions or outcome domains and frequently concerned surrogate rather than patient-important endpoints. The considerable heterogeneity in antioxidant compounds, study populations, concomitant treatments, biological samples, and assessment methods precludes interpretation of antioxidants as a uniform therapeutic class.

Several interventions affected systemic inflammatory and redox biomarkers. Vitamin D supplementation reduced serum hs-CRP and increased total antioxidant capacity [9], whereas astaxanthin was associated with favorable changes in IL-1β, IL-6, TNF-α, MDA, SOD, and TAC [11]. These findings support a possible effect on systemic redox balance and inflammatory activity. Nevertheless, the number of studies evaluating each compound was limited, and the assessed biomarker panels differed substantially. Therefore, the available evidence does not demonstrate that antioxidant supplementation produces a consistent or generalized systemic anti-inflammatory response in women with endometriosis.

Changes were also observed in local reproductive compartments. Combined vitamin C and vitamin E supplementation reduced RANTES and MCP-1 concentrations in peritoneal fluid, while the reduction in IL-6 did not reach conventional statistical significance [14]. Astaxanthin and nanomicelle curcumin affected selected cytokines in follicular fluid [11,16]. These findings are biologically relevant because the peritoneal and follicular environments may contribute to inflammatory cell recruitment, oxidative injury, and impaired reproductive function. However, results obtained from peritoneal fluid, follicular fluid, endometrial fluid, serum, and tissue represent distinct biological compartments and should not be considered interchangeable. The observed changes may reflect local or systemic effects specific to a given intervention rather than a common antioxidant mechanism.

The findings for fish-derived lipid supplementation further illustrate the complexity of this response. Although no consistent reductions were observed in the evaluated proinflammatory cytokines, IL-10 increased significantly [21]. This pattern may indicate selective immunomodulation rather than broad suppression of inflammation. However, the large variability in IL-10 concentrations and the absence of a corresponding change in fecal calprotectin warrant caution. A statistically significant change in an isolated cytokine cannot, by itself, establish a clinically relevant anti-inflammatory effect.

The effects of resveratrol on MMP-2 and MMP-9 provide preliminary evidence of altered extracellular matrix remodeling [23]. Reductions in TNF-α and VEGF expression additionally suggest potential modulation of inflammatory and angiogenic signaling [27]. Importantly, these outcomes were evaluated in eutopic endometrial tissue located within the uterine cavity, as well as in endometrial fluid and serum, rather than directly in ectopic endometriotic lesions. The findings therefore indicate molecular changes within the eutopic endometrium but do not demonstrate reduced activity, invasion, growth, or regression of endometriotic lesions. Moreover, these studies were small and exploratory, and their molecular findings were not directly linked to improvements in pain, lesion recurrence, fertility, or quality of life.

The interpretation of the resveratrol findings is further complicated by changes observed in the comparator groups. Serum CA-125 decreased in both women receiving resveratrol combined with a monophasic oral contraceptive and those receiving the contraceptive alone, without a clear additional effect attributable to resveratrol [25]. Similarly, selected MMP concentrations decreased to a smaller extent in the control group in the exploratory MMP study [23]. These observations emphasize the importance of basing conclusions on between-group differences rather than within-group changes and of accounting for concomitant treatment and surgical removal of endometriotic lesions.

Potential effects on the follicular microenvironment were observed in studies involving women undergoing assisted reproductive treatment. Astaxanthin and nanomicelle curcumin improved selected oxidative and inflammatory parameters in follicular fluid and were accompanied by favorable changes in some embryological outcomes [11,16]. These results are biologically plausible because oxidative stress and inflammation may affect oocyte competence and embryo development. Nevertheless, changes in the numbers of mature oocytes or high-quality embryos should not be equated with improved fertility. The included studies were not adequately powered to establish effects on clinical pregnancy or live birth, and follow-up was

generally insufficient to assess later reproductive outcomes. Consequently, these findings should be considered hypothesis-generating.

Evidence regarding health-related quality of life was inconsistent. Studies using the disease-specific EHP-30 generally failed to demonstrate significant differences between antioxidant supplementation and placebo [15,17,21,29]. In contrast, nanomicelle curcumin administered alongside dienogest improved WHOQOL-BREF and FSFI outcomes compared with dienogest plus placebo [12,28]. Because both groups received dienogest, these findings support a potential incremental benefit of nanomicelle curcumin as an adjunct to hormonal therapy. They cannot, however, be extrapolated to curcumin monotherapy, other curcumin formulations, or other antioxidant compounds. Differences between the EHP-30, WHOQOL-BREF, and FSFI may also have contributed to the divergent findings, as these instruments measure different aspects of disease burden, general well-being, and sexual function.

Melatonin demonstrated statistically significant improvements in the global PSQI score and in selected sleep domains, including sleep latency, sleep duration, sleep disturbances, and the use of sleep medication [13]. However, the between-group difference in the global score did not reach the prespecified threshold for clinical importance. Thus, although the observed effect suggests biological and statistical activity, the average improvement may not have been sufficiently large to represent a clearly perceptible benefit for patients. This distinction between statistical significance and clinical relevance is particularly important in endometriosis, where treatment decisions should prioritize meaningful improvements in symptoms and daily functioning.

The variation in findings across interventions suggests that any therapeutic effects are likely to be compound-specific. Vitamin D, vitamins C and E, astaxanthin, melatonin, omega-3 fatty acids, curcumin, and resveratrol differ in their pharmacokinetic properties, bioavailability, molecular targets, and interactions with inflammatory and hormonal pathways. Grouping these agents under the broad category of antioxidants may therefore obscure clinically important differences. Evidence supporting a particular compound, dose, formulation, or treatment duration should not be generalized to antioxidant supplementation as a whole.

Differences between the study populations constitute another important source of heterogeneity. The included trials enrolled adolescents and young women, patients with pain, women with surgically confirmed disease, women with advanced endometriosis and infertility, and patients undergoing assisted reproductive treatment. Disease phenotype and stage, baseline symptom severity, fertility goals, nutritional status, and concomitant hormonal or surgical treatment may all modify the response to supplementation. As a result, findings from narrowly selected populations, particularly women undergoing assisted reproduction, may not be generalizable to the broader population of patients with endometriosis.

The clinical implications of the available evidence remain limited. Favorable changes in inflammatory or oxidative biomarkers provide mechanistic support for further investigation but are insufficient to establish therapeutic effectiveness. Likewise, statistically significant improvements in questionnaire scores or reproductive laboratory parameters should be interpreted in relation to predefined thresholds of clinical importance and definitive patient-important outcomes. The current findings do not establish antioxidant supplementation as an alternative to standard hormonal, analgesic, surgical, or fertility-directed management. At most, selected compounds may represent potential adjunctive interventions that require further compound-specific evaluation.

Safety reporting was limited and inconsistent across the included trials. The absence of reported serious adverse events in individual studies cannot be interpreted as definitive evidence of safety, particularly because many trials were small, of short duration, and not designed to detect uncommon or delayed adverse effects. In addition, adverse events, treatment discontinuation, adherence, and tolerability were not uniformly reported. Safety should therefore be evaluated separately for each compound, dose, and treatment duration, especially when supplementation is combined with hormonal therapy or assisted reproductive protocols.

This review has several strengths. By focusing on randomized controlled trials, it prioritized evidence from comparative intervention studies. The evaluation of systemic and local biomarkers alongside clinical, reproductive, quality-of-life, and sleep outcomes allowed the biological effects of supplementation to be considered in relation to their potential clinical relevance. Particular attention to between-group effects and thresholds of clinically meaningful improvement also reduced the risk of equating statistical significance with patient-important benefit.

Several limitations should nevertheless be acknowledged. Many trials included small samples and short follow-up periods, limiting statistical power and the ability to assess sustained efficacy or uncommon adverse events. The interventions differed substantially in compound, formulation, dose, treatment duration, and concomitant therapy. Clinical heterogeneity was also considerable with respect to age, disease stage, symptoms,

infertility, and assisted reproductive treatment. Different studies evaluated different biomarkers in different biological compartments, which limited direct comparisons. Furthermore, multiple trials focused predominantly on surrogate molecular or embryological outcomes, while clinically meaningful improvement, responder rates, live birth, recurrence, and long-term safety were insufficiently evaluated.

Future randomized trials should assess individual antioxidant interventions rather than treating antioxidants as a homogeneous therapeutic category. Adequately powered, multicenter studies should prespecify primary clinical outcomes and report between-group effect estimates with confidence intervals. Pain, health-related quality of life, sexual function, treatment discontinuation, and adverse events should be measured using standardized instruments and clinically meaningful response thresholds. Fertility-focused trials should prioritize clinical pregnancy, ongoing pregnancy, and live birth rather than relying primarily on oocyte or embryo parameters. Baseline nutritional status, disease phenotype and stage, concomitant treatment, and adherence should also be reported to identify patient subgroups in whom a specific intervention may be most effective.

In summary, selected antioxidant and antioxidant-related interventions may modulate systemic and local markers of oxidative stress and inflammation in women with endometriosis. Some compounds may also influence molecular pathways within the eutopic endometrium and improve selected dimensions of sleep, quality of life, sexual function, or reproductive laboratory outcomes. However, these findings are heterogeneous, frequently based on small trials, and not consistently supported by clinically meaningful benefits. Antioxidant supplementation should therefore be regarded as a promising but still investigational adjunctive strategy. Robust compound-specific trials with standardized clinical outcomes and systematic safety assessment are required before recommendations for routine use can be formulated.

5. Conclusions

The available randomized evidence indicates that selected antioxidant and antioxidant-related interventions may influence systemic inflammatory and oxidative stress markers in women with endometriosis. Vitamin D supplementation was associated with reduced hs-CRP and increased total antioxidant capacity, while astaxanthin produced favorable changes in selected cytokines and oxidative stress parameters. Nevertheless, these effects were not consistent across all evaluated interventions or biomarkers. The observed changes should therefore be interpreted as compound-specific biological signals rather than evidence of a uniform systemic anti-inflammatory effect of antioxidant supplementation.

Selected interventions also modified inflammatory mediators within local reproductive compartments. Combined vitamin C and vitamin E supplementation reduced RANTES and MCP-1 concentrations in peritoneal fluid, whereas astaxanthin and nanomicelle curcumin affected selected cytokines in follicular fluid. These findings suggest that some antioxidants may influence the local inflammatory microenvironment associated with endometriosis and infertility. However, the small number of studies and differences in biological samples, study populations, and measured biomarkers prevent firm conclusions regarding the reproducibility and clinical relevance of these effects.

Resveratrol was associated with reduced expression and concentrations of MMP-2 and MMP-9 and with lower expression of TNF-α and VEGF. These findings suggest possible effects on inflammation, extracellular matrix remodeling, and angiogenic signaling within the eutopic endometrium. Importantly, the evaluated samples were obtained from the endometrium located within the uterine cavity rather than directly from ectopic endometriotic lesions. It therefore remains unknown whether these molecular changes translate into reduced activity, growth, or progression of endometriotic lesions or into improved clinical outcomes.

Evidence concerning health-related quality of life was inconsistent. Most trials using the disease-specific EHP-30 instrument did not demonstrate a significant advantage of antioxidant supplementation over placebo. Improvements observed with nanomicelle curcumin in the WHOQOL-BREF and FSFI suggest a possible benefit for general quality of life and sexual function. Because curcumin was administered in addition to dienogest, these findings support a potential incremental effect of curcumin as an adjunct to hormonal therapy but cannot be extrapolated to curcumin monotherapy or to other antioxidant compounds.

Melatonin produced statistically significant improvements in the global PSQI score and in selected sleep domains, including sleep latency, sleep duration, sleep disturbances, and the use of sleep medication. However, the between-group difference in the global PSQI score did not reach the prespecified threshold for clinical importance. This finding highlights the need to distinguish statistical significance from an improvement that

is likely to be meaningful to patients. Further studies should determine whether longer treatment or carefully selected patient subgroups could achieve a clinically relevant and sustained improvement in sleep.

The safety of antioxidant supplementation remains insufficiently established. Adverse events, treatment discontinuation, and tolerability were not consistently or comprehensively reported across the included trials. Consequently, an absence of reported harms cannot be interpreted as evidence that these interventions are safe, particularly when used at high doses, for prolonged periods, or in combination with hormonal treatment or assisted reproductive protocols.

Overall, the findings provide biological evidence that selected antioxidants may modulate pathways involved in oxidative stress and inflammation in endometriosis. Nevertheless, favorable biomarker changes were not consistently accompanied by clinically meaningful improvements in symptoms, quality of life, sleep, or reproductive outcomes. The substantial heterogeneity among interventions and study populations also prevents the formulation of recommendations for antioxidants as a single therapeutic class. Antioxidant supplementation should therefore be considered an investigational adjunct rather than an established component of routine endometriosis treatment. Larger and adequately powered randomized trials should evaluate individual compounds using standardized, patient-important outcomes, clinically meaningful response thresholds, longer follow-up, and systematic safety reporting.

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Conceptualization, W.Ż, K.Ś.; methodology, K.Ś,, J.T, J.S, W.Ż and M.L; validation, K.Ś and W.Ż.; formal analysis, K.Ś, W.Ż; resources, K.Ś, J.T, J.S, W.Ż and M.L.; data curation,K.Ś, J.T, J.S, W.Ż, M.L; writing—original draft preparation, K.Ś, J.T, J.S, W.Ż. and M.L.; writing—review and editing, K.Ś; visualization, K.Ś, J.T, J.S, W.Ż and M.L.; supervision, K.Ś and W.Ż.; project administration, K.Ś and W.Ż .; funding acquisition, K.Ś, W.Ż. , J.T., J.S, M.L. All authors have read and agreed to the published version of the manuscript.

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