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REVIEW

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Efficacy of antioxidant supplementation in alleviating endometriosis-related pain: insights from a systematic review and meta-analysis of RCTs

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Abstract

Background Endometriosis, a chronic inflammatory disorder, is a leading cause of pelvic pain and reduced quality of life in women, with oxidative stress implicated in its pathogenesis. While antioxidant supplementation has been proposed as a potential therapeutic strategy, its clinical efficacy remains controversial. This systematic review and meta-analysis evaluate the impact of antioxidants on endometriosis-related pain outcomes.

Methods We conducted a systematic review and meta-analysis. A comprehensive search of PubMed, Scopus, Cochrane, Web of Science, and clinical trial registries (2000–January 2025) was conducted for randomized controlled trials (RCTs) investigating the effect of any oral antioxidant supplement, without dose or duration restrictions, in endometriosis patients and reporting quantitative data on at least one of the primary pain outcomes (dysmenorrhea, dyspareunia, or chronic pelvic pain). Primary outcomes included dysmenorrhea, dyspareunia, and chronic pelvic pain. Study risk of bias was assessed using the Cochrane RoB 2 tool, and evidence certainty was graded via the GRADE framework. Random-effects meta-analyses were performed to estimate pooled effects.

Results Meta-analysis of available RCTs suggested a potential reduction in pain scores for dysmenorrhea (SMD = − 1.26, 95% CI: −2.19 to − 0.32) and chronic pelvic pain (SMD = − 1.07, 95% CI: −1.71 to − 0.42); however, extreme heterogeneity ($I^2 > 90\%$) in these analyses indicates that these average effects are highly uncertain and should not be generalized specific clinical contexts. No significant effect was observed for dyspareunia. Subgroup analyses indicated that melatonin may be associated with the most consistent potential pain reduction.

Conclusion Current low- to very low-certainty evidence suggests that antioxidant supplementation, particularly melatonin, may be associated with improvements in dysmenorrhea and chronic pelvic pain in endometriosis. However, due to considerable inconsistency and methodological limitations across studies, these findings must be interpreted with caution. The results underscore the urgent need for high-quality, large-scale RCTs to confirm any potential benefits and define the clinical role of antioxidants in endometriosis management.

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Keywords Endometriosis, Oxidative stress, Antioxidants, Pelvic pain, Melatonin, Meta-analysis

Introduction

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, commonly affecting women of reproductive age. One of the hallmark symptoms of endometriosis is chronic pelvic pain, which significantly impairs the quality of life for affected individuals [1].

Despite advancements in medical interventions, managing chronic pelvic pain associated with endometriosis remains a clinical challenge [2]. Oxidative stress has emerged as a potential contributor to the pathophysiology of endometriosis, with growing interest in the therapeutic potential of antioxidant interventions. Antioxidants play a crucial role in mitigating the deleterious effects of oxidative stress, which is implicated in inflammation, tissue damage, and pain perception While a myriad of antioxidant supplements is available, their efficacy in alleviating chronic pelvic pain associated with endometriosis has not been comprehensively evaluated [3].

Understanding the impact of antioxidant supplementation on endometriosis holds clinical significance, as it may offer novel insights into the development of targeted therapeutic strategies. Furthermore, a comprehensive analysis of existing studies will contribute to the existing body of knowledge and guide future research endeavors in this field. Research on the effectiveness of antioxidants like melatonin [4, 5], vitamin D [6, 7], vitamin C [8], and vitamin E [9] in reducing endometriosis-related pain and oxidative stress is inconclusive. For instance, while Soderman et al. [4] reported no significant pain relief with 20 mg melatonin compared to placebo, a Brazilian trial found that 5 mg melatonin daily significantly reduced pain scores [5]. This variability in melatonin's effects mirrors similar inconsistencies observed with other antioxidants investigated for endometriosis-related pain. Such disparities highlight the need for a rigorous, systematic evaluation of the broader antioxidant landscape in endometriosis management.

To the best of our knowledge, several systematic reviews and meta-analyses have been published on this topic in recent years, each with specific limitations. These include a 2022 systematic review without meta-analysis [10]. A 2023 meta-analysis focused solely on vitamin antioxidants [11]. In 2024, one review analyzed 10 studies up to April 2022 [12], However, this review has been subject to methodological concerns as highlighted in a subsequent letter to the editor [13], while another 2024 meta-analysis searched limited databases without assessing study quality, risk of bias, or reporting the search timeframe [14]. Most recently, Salmeri et al. (2025) published a meta-analysis on dietary supplements for endometriosis pain; however, their review had a broad scope beyond antioxidants, a literature search ending in November 2024, and included only 9 RCTs [15].

The aim of the present systematic review and meta-analysis is to examine the role of antioxidant supplementation in alleviating endometriosis-related pain. To this end, we seek to expand the temporal scope of the search and broaden the range of antioxidants considered by incorporating a wider array of keywords. We believe that this expanded scope will provide a more robust and informative assessment of the potential benefits of diverse antioxidant interventions for patients with endometriosis.

Method

To assess the effects of antioxidant supplementation on endometriosis-related pain, we completed a systematic review and meta-analysis. The study protocol was approved by Institutional Review Board at Babol University of Medical Sciences (No. IR.MUBABOL.REC.1401.009) and was registered in PROSPERO international prospective register of systematic reviews (Registration number CRD42022368226). We report our review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.

Data sources and search strategies

Two members of the research team (PM and AS) conducted a comprehensive electronic search across PubMed, Scopus, Cochrane databases, Web of Science (WoS/ISI), Google Scholar, WHO clinical trials registry systems, and ClinicalTrials.gov from 2000 to January 2025, using customized search strategies specific to each database. Additionally, manual searches were performed on the reference lists of included studies, as well as in key journals, conference proceedings, and theses to capture a broad range of gray literature and further enhance the comprehensiveness of the search. No restrictions were placed on the language of publications. The search strategy was developed using a combination of MESH indexing terms, Emtree database, and free-text methods. The search keywords used included "endometriosis" OR "endometrioma" OR "endometrium" OR "endometrioses" AND "pain" AND "antioxidant" OR "garlic" OR "Ascorbic Acid" OR "Melatonin" OR "Quercetin" OR "Selenium" OR "Silymarin" OR "Vitamin E" OR "Vitamin D" OR "curcumin" OR "Canthaxanthin" OR "Tocopherol" OR "Grape Seed Extract" OR "Allium sativum" OR "Vitamin C" OR "Vitamin A" OR "25 AND OHD" OR "25-hydroxyvitamin D" OR "N Acetylcysteine" OR

"Resveratrol" OR "Glutathione" OR "Allium sativum" OR "Turmeric Yellow" OR "N-acetylcysteine".

Inclusion and exclusion criteria

1-Randomized controlled trials (RCTs) with either parallel or cross-over design 2-Participants with endometriosis of any stage, aged 18 to 49 years 3-Diagnosis of endometriosis confirmed by laparoscopy, laparotomy, or histopathological report 4-Intervention group administered at least one antioxidant supplement matching the keywords of the study 5-Antioxidant supplements administered orally without dose or duration restrictions.

Exclusion criteria

Non-randomized controlled trials, including review studies, animal studies, cross-sectional studies, case-control studies, case reports and prospective cohort studies.

Data extraction

Two independent reviewers (PM and AS) screened titles and abstracts to identify potentially eligible studies. Full-text articles were obtained for all potentially relevant studies and were independently assessed by the two reviewers for inclusion based on the established inclusion and exclusion criteria. Duplicate studies were excluded. Following the screening process, the relevant data were extracted from each eligible study and compiled into a standardized Microsoft Excel (version 2016; Microsoft Corporation, Redmond, WA, USA) spreadsheet. The extracted data included:

First author name, year of publication, study location, study design, number of participants in the study overall and by intervention and comparison groups, mean and standard deviation of participant age, mean and standard deviation of participant BMI, type, dose, and duration of antioxidant administration, intervention type in the comparison group, follow-up during the intervention period, mean and standard deviation of chronic pelvic pain scores before and after intervention, mean and standard deviation of dysmenorrhea scores before and after intervention, mean and standard deviation of dyspareunia scores before and after intervention in the groups. Any disagreements between the investigators at any stage of the data extraction process were resolved by consulting with a third reviewer (SHA).

Risk of bias assessment

Risk of bias in the included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as low risk, some concerns, or high risk of bias based on responses to signaling questions. Two reviewers (PM, SHA) independently performed the assessments, and any disagreements were resolved through discussion and consensus. The overall risk of bias for each study was determined according to domain-level judgments: studies were classified as low risk if all domains were rated low risk; some concerns if at least one domain raised some concerns but none were high risk; and high risk if one or more domains were rated high risk or if multiple domains raised some concerns.

Statistical analysis

Data analysis was conducted using a random effects model. Study weighting was performed using the restricted maximum likelihood (REML) method. This model assumes that the differences between studies are not only due to sampling error, but also that the estimated parameters of the studies are not identical and differ from each other. The findings of each study were extracted and reported as standardized mean differences, which were then aggregated. Heterogeneity between studies was assessed using the Chi^2 test for heterogeneity, with heterogeneity reported using both the p-value and the Higgins I^2 index. The I^2 statistic was employed to assess statistical heterogeneity across the included studies, where an I^2 value of 50% or greater was considered indicative of substantial heterogeneity. To investigate the effect of study characteristics on heterogeneity and the aggregated effect size, subgroup analyses were performed based on the type of antioxidant, duration of intervention, and risk of bias assessment. This approach allowed exploration of whether observed variability could be explained by differences in the specific antioxidant, length of supplementation, or methodological quality of the included studies. Data analysis was performed using Stata software version 17.

Publication bias

To evaluate potential publication bias in the systematic review and meta-analysis, both visual and statistical methods were employed. A visual inspection of funnel plots was conducted to check for asymmetry, which can indicate missing studies, particularly smaller studies with negative outcomes. Egger's regression test was performed to quantitatively assess publication bias. A p-value of less than 0.05 was considered significant, suggesting the presence of bias if the intercept was significant. Upon confirming publication bias, the Duval and Tweedie "trim-and-fill" method was applied. This non-parametric approach adjusts for biases by estimating and imputing missing studies, thereby enhancing the robustness of the findings.

Sensitivity analysis

To assess the robustness of the pooled estimates, several sensitivity analyses were conducted. The Knapp–Hartung small-sample correction was applied to adjust for possible bias in studies with smaller sample sizes. Leave-one-out meta-analyses were performed to evaluate the influence of each individual study on the overall effect estimates. Furthermore, the impact of methodological quality was evaluated by sequentially excluding studies based on their risk of bias assessment, which included evaluations of the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

To specifically evaluate the influence of ethical and methodological trustworthiness on the results, additional sensitivity analyses were performed. These analyses restricted the evidence base by: (i) excluding studies with a declared conflict of interest with the supplement manufacturer or those authored by researchers with retracted publications on related topics, as identified through a search of the Retraction Watch Database; and (ii) including only those randomized controlled trials that fulfilled the 'Absolute' trustworthiness criteria as defined by the Obstetrics and Gynecology Editors' Integrity Group (OGEIG) [16].

Certainty of evidence

The certainty of evidence for primary outcomes (dysmenorrhea, dyspareunia, and chronic pelvic pain) was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), assessing five key domains: risk of bias (RoB 2. tool), inconsistency (I^2 statistic), indirectness, imprecision, and publication bias (Egger's test). Evidence was systematically downgraded for identified limitations in these domains and subsequently categorized into four certainty levels: high, moderate, low, or very low. Two independent reviewers conducted all assessments, with any discrepancies resolved through consensus or third-reviewer consultation when required.

Results

Protocol amendment

Two amendments were made to the original PROSPERO-registered protocol. First, the literature search was extended to include studies published up to 30 January 2025 to capture the most recent evidence. Second, although the initial protocol specified the use of the Delphi list for risk of bias assessment, we instead applied the revised Cochrane Risk of Bias tool for randomized trials (RoB 2), which is the current recommended standard for assessing risk of bias in Cochrane systematic reviews. This change was made to align with best practices and provide a more comprehensive evaluation of study quality.

A comprehensive literature search across PubMed (207), Scopus (669), Cochrane [12], Google Scholar [17], Web of Science (107), and clinical trial registries [5] yielded 1,025 records. After removing 329 duplicates, 696 unique articles remained for screening. Of these, 669 were excluded based on title and abstract review according to the eligibility criteria. The full texts of 27 articles were assessed for eligibility, resulting in 17 studies meeting the criteria and being included in the systematic review. The study selection process is detailed in the PRISMA flowchart (Fig. 1).

Two of these studies [9, 18] were excluded from the meta-analysis due to their presentation of pain reduction as percentages rather than the exact mean and standard deviation of pain scores pre- and post-intervention. Following two rounds of communication with the corresponding authors of these three studies at 10-day intervals, 15 studies were ultimately included in the quantitative analysis. Among the 15 trials included in this review, a total of 996 participants were analyzed. The intervention groups comprised 498 participants, with average ages ranging from 20 to 45 years. Participants in the intervention groups received antioxidant supplements, which were administered in various oral forms, including capsules and tablets. The control groups included 498 participants who received either a placebo, standard treatment for Endometriosis, or no intervention at all. The duration of the interventions varied across studies, spanning from eight to 24 weeks.

All included RCTs were parallel-arm studies published between 2013 and 2025. Among these, nine studies were conducted in Iran, two in Egypt, two in Brazil, one in China, two in the United States, and one in Sweden (Table 1).

The characteristics of the included studies are summarized in Table 1. The clinical outcomes measured by each study are detailed in Table 2. All studies were conducted between 2013 and 2025, and they possessed the necessary variables to investigate the impact of antioxidants on endometriosis-related pelvic pain.

Risk of bias assessment

Based on the assessment of 17 studies, seven exhibited a low risk of bias across all evaluated domains, indicating robust methodological quality (Fig. 2). Conversely, five studies were characterized by a high risk of bias, primarily due to issues in the randomization process, with one study also showing high risk related to missing outcome data. An additional five studies presented some concerns in one or more domains but did not reach an overall high-risk rating. Overall, approximately half of the included studies demonstrated a low risk of bias, while the remaining studies exhibited either some concerns or a high risk, predominantly due to weaknesses in randomization and

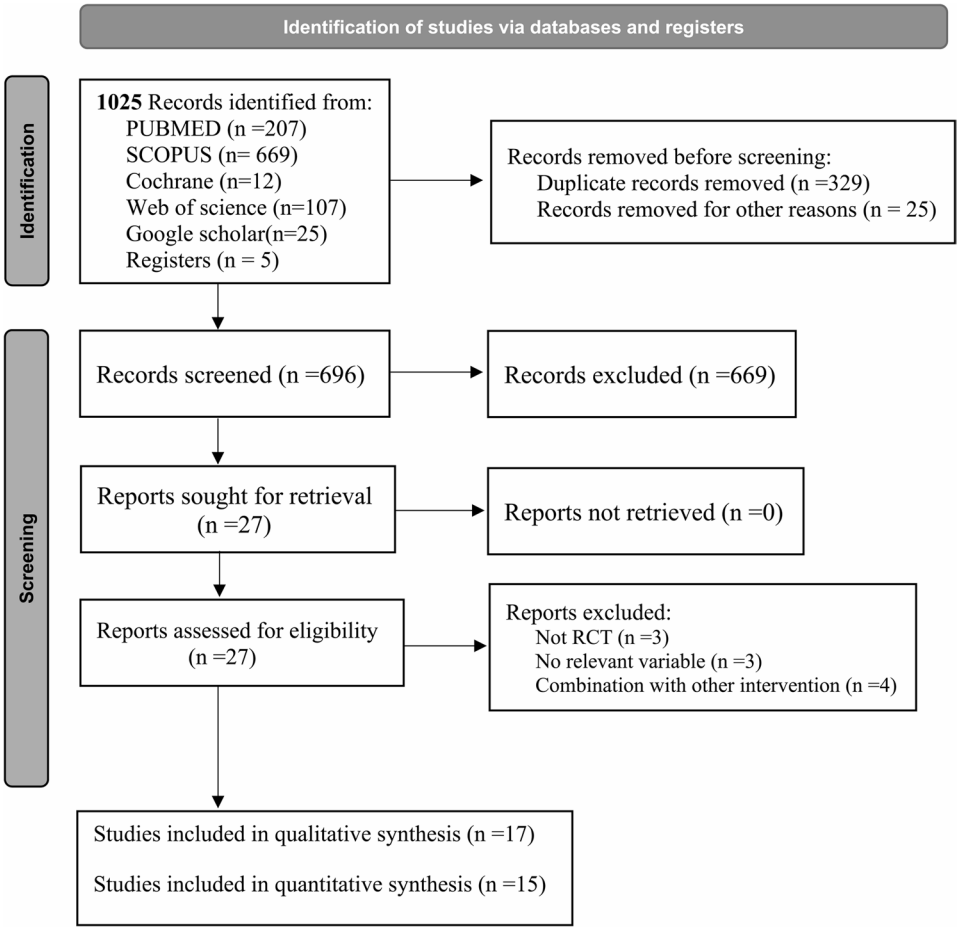

Fig. 1 PRISMA flowchart for item selection

outcome data handling. Notably, methodological quality appears to have improved over time, with four of the nine studies published between 2021 and 2025 (44%) achieving a low risk of bias across all domains.

Quantitative data synthesis

Effect of antioxidant on dysmenorrhea

A random-effects meta-analysis of twelve RCTs ($n = 706$ participants) suggested a potentially large reduction in dysmenorrhea severity y (SMD = −1.26, 95% CI: −2.19 to −0.32; $p < 0.001$). However, the extreme heterogeneity (I^2 = 90.1%) indicates that this pooled effect is highly uncertain and should be interpreted with caution. To contextualize this effect size, an SMD of −1.26 corresponds to an approximate mean reduction of 3.0 points on a 0–10-point pain scale, which is generally considered a clinically important difference. However, the evidence was rated as low certainty per GRADE criteria due to substantial heterogeneity (I^2 = 90.1%, $p < 0.001$) (Fig. 3) and serious risk of bias concerns (Supplementary Table 1). The wide confidence interval (95% CI: −2.19 to −0.32) indicates the true effect could range from a large, clinically crucial reduction to a small, potentially negligible one.

Publication bias was assessed using funnel plot inspection (Supplementary Fig. 5), Egger's test, and trim-and-fill analysis. While funnel plot asymmetry suggested possible small-study effects, Egger's test found no significant bias ($\beta = 2.69$, $p = 0.108$), and trim-and-fill estimated zero missing studies. The stable pooled effect (SMD=−1.90, 95% CI: −2.17 to −1.62) and Galbraith plot results collectively suggest robustness against publication bias, though heterogeneity may contribute to observed asymmetry.

Subgroup analysis by antioxidant type revealed significant variation in the effects on dysmenorrhea, with a significant difference between groups. This indicates that the substantial heterogeneity observed in the overall analysis is largely attributable to differences in the specific antioxidant interventions used. Among antioxidants, melatonin showed a significant reduction in pain severity with a moderate and consistent effect size (SMD = −1.89; 95% CI: −2.48 to −1.31) and moderate heterogeneity (I^2 = 34.72%). In contrast, Vitamin D, Vitamin C + Vitamin E, Omega-3 fatty acids, Resveratrol, and Curcumin subgroups did not show statistically significant improvements and exhibited low heterogeneity within groups (Table 2). This suggests variability in effect sizes across

Table 1 Participant and study characteristics

Ref. No.	Geographical location (First author, year)	Study design	Type of Antioxidant	Dosage	Inter-vention duration	Mean age, in Intervention/ Control years	Sample size intervention/ control	Outcomes
[5]	Brazil Schwertnerr,2013	Double-blind, RCT	Melatonin	10 mg/day	8 weeks	Intervention 36.7 ± 6.4 Control: 37.6 ± 5.5	Intervention:20 Control: 20	®Dysmenorrhea ®Dyspareunia
[19]	Iran Hosseinalizadeh, 2018	Triple-blind, RCT	Melatonin	5 mg/day	8 weeks	18–45 years	Intervention: 20 Control: 20	®Dysmenorrhea ®Pelvic pain
[20]	Brazil Mendes da Silva2017	Double-blind, RCT	Resveratrol	40 mg/day	6 weeks	Intervention:35.4 ± 7.1, Control: 32.4 ± 7	Intervention:22 Control:22	↔Dysmenorrhea
[6]	Iran Almassinoki-ani 2016	Double-blind, RCT	Vitamin D	50,000 IU/week	12 weeks	Intervention: 30.8 ± 5.7, control: 28.9 ± 4.7	Intervention: 19 Control: 19	↔Dysmenorrhea ↔Pelvic pain
[21]	USA Nodler, 2020	Double-blind, RCT	Omega-3+ Vitamin D	1000 mg omega 3+ 2000 IU/day vitamin D3	24 weeks	Intervention: 20.01 ± 2.7, control: 20.1 ± 3.5	Intervention:27 Control:22	↔Dysmenorrhea
[7]	Iran Mehdizadeh-kashi, 2021	Double-blind, RCT	Vitamin D	50,000 IU/2weeks	12 weeks	interventions: 34.8 ± 7.1, Control: 35.6 ± 7	Intervention: 30 Control: 30	®Dysmenorrhea ↔Dyspareunia
[8]	Iran Amini, 2012	Triple-blind, RCT	Vitamin C + Vitamin E	1000 mg/day Vitamin C 800 IU/day Vitamin E	8 weeks	Intervention: 35.7 ± 5.7, Control: 38.03 ± 6.4	Intervention: 30 Control: 30	®Dysmenorrhea ®Pelvic pain ®Dyspareunia
[22]	Egypt Abd El-Fadil Sehsah, 2022	RCT	Vitamin C + Vitamin E	1200 IU Vitamin E 1000 mg vitamin C daily	6–8 weeks	Intervention: 25.3 ± 3.7, Control: 26.1 ± 4.2	Intervention: 50 Control: 50	®Dysmenorrhea ®Pelvic pain ®Dyspareunia
[23]	Iran (Amirsalari, 2021)	Triple-blind, RCT	Dried garlic powder	400 mg/daily	12 weeks	Intervention: 29.4 ± 8.5, Control: 29.7 ± 5.6	Intervention: 60 Control: 60	®Dysmenorrhea ®Pelvic pain ®Dyspareunia
[24]	Iran (Mirzaei,2022)	Double-blind, RCT	Silymarin	140 mg silymarin twice per day	12 weeks	Intervention: 36.4 ± 8.1, Control: 33.9 ± 7	Intervention: 35 Control: 35	®Pelvic pain
[4]	Sweden (Soderman 2023)	Double-blind, RCT	Melatonin	20 mg/day	8 weeks	Intervention: 35.9 ± 6.61, Control: 34.2 ± 7.6	Intervention: 20 Control: 20	↔Pelvic pain ↔Dyspareunia
[18]	Florida (Santa-nam, 2014)	RCT	Vitamin C + Vitamin E	1200 IU vitamin E and 1000 mg vitamin C	8 weeks	19–41 years	Intervention: 46 Control: 13	↔Dysmenorrhea ®Pelvic pain ↔Dyspareunia
[25]	Egypt (Al-Naggar, 2022)	Double-blind RCT	Vitamin C + Vitamin E	1200 IU vitamin E and 1000 mg vitamin C	8 weeks	Intervention: 32.5 ± 4.5, Control: 31.4 ± 5.2	Intervention: 30 Control: 30	®Dysmenorrhea ®Pelvic pain ®Dyspareunia
[26]	Iran (Esmaeilza-deh, 2023)	Triple-blind, RCT	Melatonin	10 mg/day	8 weeks	Intervention32.6 ± 5.2, Control: 31.3 ± 4.9	Intervention:49 Control: 49	®Dysmenorrhea ®Pelvic pain
[9]	China (HuiMing Wang 2017)	RCT	Vitamin E 100 mg/d	100 mg/d	12 weeks	Intervention 37.9 ± 3.5, Control: 35 ± 3.03	Intervention: 32 Control: 32	®Pelvic pain
[27]	Iran Esmaeilzadeh 2025	Triple-blind, RCT	Melatonin	5 mg/day	2 months	Intervention 32.6 ± 5.7, Control: 31.8 ± 4.7	Intervention: 40 Control: 40	®Pelvic pain
[28]	Iran Gudarzi, 2024	Triple-blind, RCT	Curcumin	500 mg/twice per day	8 weeks	Intervention 33.5 ± 5.7, Control: 32.1 ± 4.8	Intervention: 34 Control: 34	↔Endometriosis pain

Symbols: ® indicates a significant decrease in the intervention group; ↔ indicates no significant difference between intervention and control groups

antioxidant types is a key driver of between-study heterogeneity. Thus, the type of antioxidant appears to be a significant contributor to the observed heterogeneity.

Subgroup analysis based on risk of bias indicated that these considerable reductions in dysmenorrhea persisted only in studies with some concerns (SMD (95% CI) = −2.17 (−4.27, −0.06) albeit still with high heterogeneity (Fig. 4).

Subgroup analysis by intervention duration revealed that 8-week antioxidant supplementation significantly reduced dysmenorrhea severity (SMD = −1.21; 95% CI: −1.98 to −0.43) with moderate-to-high heterogeneity

Table 2 Subgroup analyses of antioxidant effects on Endometriosis-Related pain outcomes

Subgroup	Category	No. Studies	Effect Size (95% CI)	Heterogeneity (I^2, *p*-value)	*p* for Subgroup Differences
Dysmenorrhea	**Overall effect**	**12 (706)**	**SMD – 1.26 (–2.19, –0.32)**	**I^2=90.1%, p < 0.001**	-
By antioxidant type					< 0.001
	Melatonin	4	–1.89 (–2.48, –1.31)	34.7%, $p = 0.27$	
	Vitamin D	3	–0.52 (–1.48, 0.43)	21.88%, $p = 0.30$	
	Vitamin C + E	2	–0.75 (–1.60, 0.09)	0%, $p = 0.58$	
	Omega-3	1	–0.90 (–0.99, 2.79)		
	Resveratrol	1	–1.00 (–2.66, 0.66)		
	Curcumin	1	–0.10 (–0.62, 0.82)		
By duration					0.05
	8 weeks	6	–1.21 (–1.98, –0.43)	77.9%, $p < 0.001$	
	12 weeks	4	–2.04 (–4.31, 0.22)	92.1%, $p < 0.001$	
	24 weeks	2	0.43 (–0.78, 1.65)	0%, $p = 0.98$	
By risk of bias					0.39
	Low risk	6	–0.64 (–1.49, 0.21)	69.4%, $p < 0.001$	
	Some concerns	4	–2.17 (–4.27, –0.06)	93.6%, $p < 0.001$	
	High risk	2	–1.29 (–3.50, –0.91)	84.6%, $p = 0.01$	
Dyspareunia	**Overall effect**	**5 (370)**	**SMD – 1.01 (–2.27, 0.24)**	**I^2=96.4%, *p < 0.001***	**-**
By duration					0.59
	8 weeks	1	–0.65 (–1.05, –0.25)		
	12 weeks	4	–1.11 (–2.72, 0.51)	96.8%, $p < 0.001$	
Chronic Pelvic Pain	**Overall effect**	**9 (313)**	**SMD – 1.07 (–1.71, –0.42)**	**I^2=92.1%, *p < 0.001***	**-**
By risk of bias					0.01
	Some concerns	3	–1.84 (–2.84, –0.85)	90.6%, $p < 0.001$	
	Low risk	3	–0.51 (–1.23, 0.21)	79.5%, $p = 0.01$	
	High risk	3	–0.85 (–2.13, 0.42)	93.4%, $p < 0.001$	

SMD Standardized Mean Difference

(I^2 = 77.9%, $p < 0.001$). Twelve-week interventions showed a smaller, non-significant effect (SMD = –2.04; 95% CI: –4.31 to 0.22) and higher heterogeneity (I^2 = 92.1%, $p < 0.001$), while 24-week interventions had no significant effect and low heterogeneity (SMD = 0.43; 95% CI: –0.78 to 1.65; I^2 = 0%) (Fig. 5). The borderline significant test for subgroup differences suggests intervention duration may partly explain variability in antioxidant efficacy for dysmenorrhea (Table 2).

To assess the robustness of these findings, a sensitivity analysis applying the Knapp-Hartung correction for small sample sizes was performed. This analysis maintained the significance of the results (SMD (95% CI) = –1.26 (–2.27, –0.24)) and suggests antioxidant supplementation may be effective in improving dysmenorrhea, but the high heterogeneity indicates variability in the evidence. To further assess robustness, a nonparametric trim-and-fill analysis was conducted. The analysis estimated zero imputed studies, indicating no missing studies due to potential bias. The pooled effect size remained unchanged (SMD = –1.896; 95% CI: –2.171 to –1.621), confirming the robustness of the meta-analytic estimate.

Sensitivity analyses evaluating ethical and methodological trustworthiness were performed to complement the statistical assessments. Leave-one-out analysis confirmed that no single study disproportionately influenced the overall pooled effect size for dysmenorrhea (Supplementary Fig. 1). When the analysis was restricted to studies without conflicts of interest or links to retracted publications, the significant reduction in dysmenorrhea persisted (Supplementary Fig. 2, i). Similarly, analysis including only studies that met predefined trustworthiness criteria also continued to show a significant beneficial effect (Supplementary Fig. 2, ii). The results of these analyses affirm that the primary finding for dysmenorrhea is robust across different assessments of study trustworthiness.

Effect of antioxidant on dyspareunia

Five RCTs comprising 370 participants examined the effect of antioxidant supplementation on dyspareunia. The overall meta-analysis showed no statistically significant difference between the antioxidant and control groups (SMD = –1.01, 95% CI: –2.27 to 0.24; $P = 0.11$), with considerable heterogeneity across studies (I^2 = 96.5%, $p < 0.001$) (Fig. 3, B). The certainty of evidence was graded as very low due to this heterogeneity, inconsistency in results, imprecision (CI crossing null), and potential methodological limitations within the included studies (Supplementary Table 1).

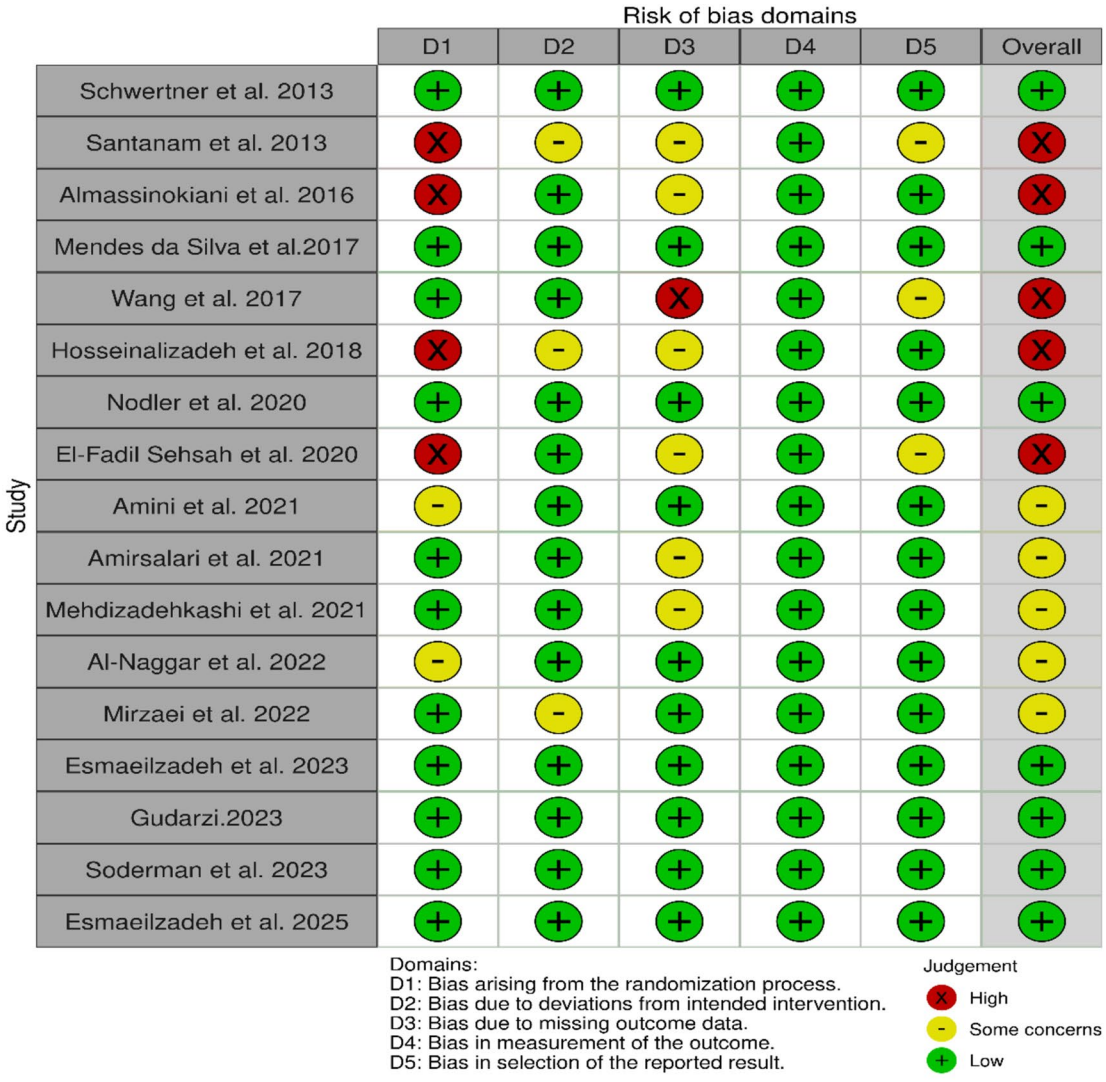

Fig. 2 Risk of Bias Assessment of Included RCTs Using Cochrane RoB 2 Tool

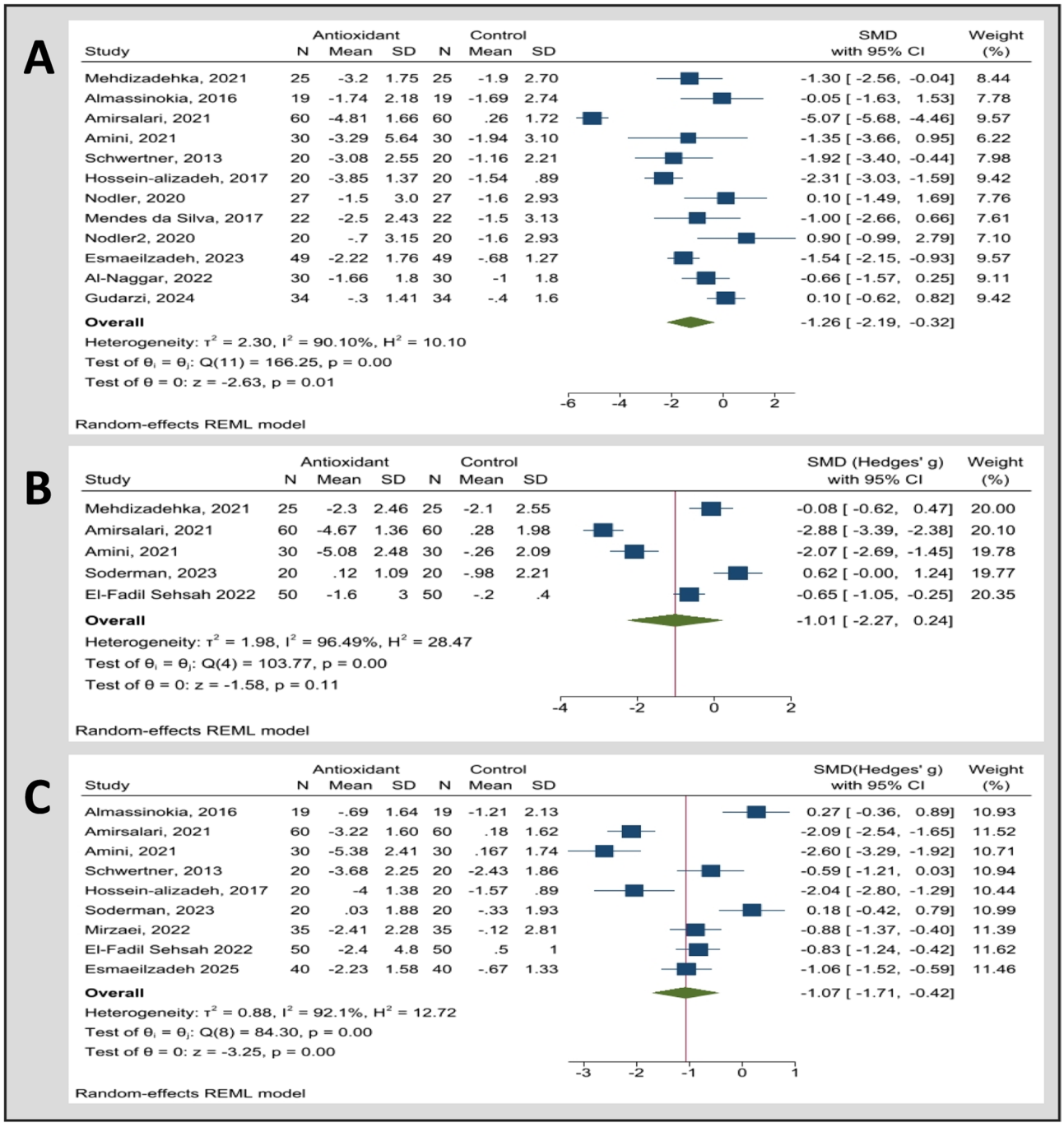

Fig. 3 Forest plot depicting SMD and the 95% CI for the impact of antioxidant on endometriosis-related pain outcomes: dysmenorrhea (**A**) dyspareunia (**B**) pelvic pain (**C**). Each panel displays standardized mean differences (SMD, squares) and 95% confidence intervals (CIs, horizontal lines) for individual studies, with the pooled effect estimate weighted by a random-effects model

In the subgroup analysis, a single 8-week intervention study showed a significant reduction in dyspareunia with antioxidants (SMD (95% CI) = −0.65 (−1.05, −0.25)). In contrast, the combined analysis of four 12-week studies revealed a larger but non-significant effect (SMD = −1.11, 95% CI: −2.72 to 0.51) (Table 2). The overall lack of statistical significance, despite the positive finding in the 8-week subgroup, suggests the impact of antioxidants on endometriosis-related dyspareunia remains unclear. The high heterogeneity (I^2 = 96.88; P = < 0.001) further highlights the variability in results across studies (Table 2).

To investigate potential sources of heterogeneity, a subgroup analysis was performed based on study risk of bias. Among the four low-risk-of-bias studies, antioxidant

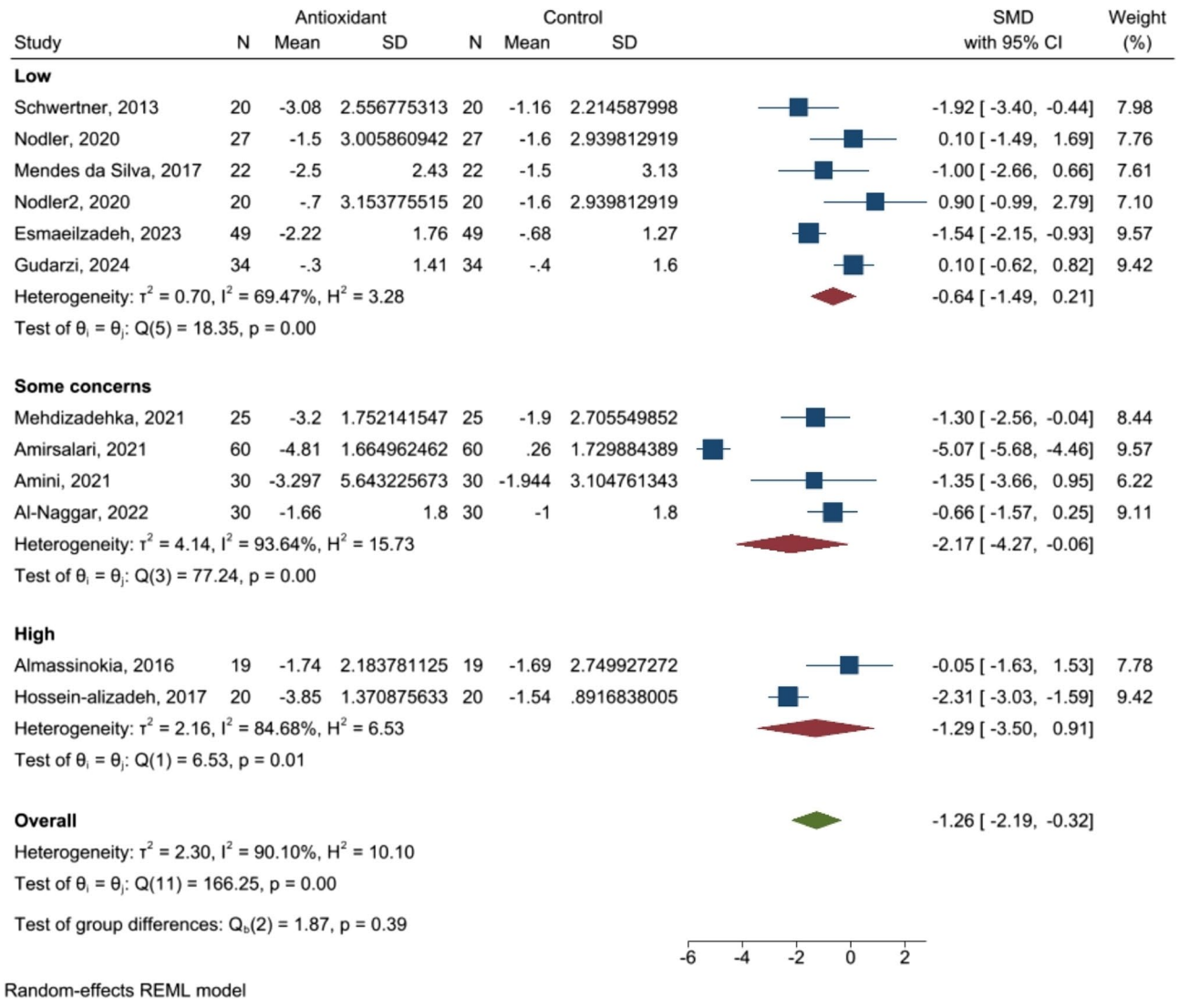

Fig. 4 Subgroup analysis of antioxidant effects on dysmenorrhea severity by Risk of Bias. Forest plot comparing SMDs in dysmenorrhea pain scores between antioxidant and control groups, stratified by study quality (low risk, some concerns, or high risk of bias per Cochrane RoB 2 tool). Pooled estimates (95% CIs) and heterogeneity (I^2) are shown for each subgroup

supplementation was associated with a non-significant reduction in dyspareunia (SMD = −1.11, 95% CI: −2.72 to 0.51; I^2 = 96.8%), indicating substantial variability. Conversely, the single high-risk-of-bias study demonstrated a statistically significant reduction in dyspareunia (SMD = −0.65, 95% CI: −1.05 to −0.25) (Table 2). The lack of significant findings in the low-risk subgroup suggests that antioxidant supplementation does not consistently alleviate dyspareunia associated with endometriosis.

Sensitivity analyses based on ethical and methodological trustworthiness supported these findings. Analyses restricted to studies without conflicts of interest or links to retracted publications, and to those meeting predefined trustworthiness criteria, continued to demonstrate a non-significant effect (Supplementary Fig. 3, i and ii). When applying the Knapp–Hartung correction for small sample sizes, the non-significant result persisted (SMD = −1.01, 95% CI: −2.80 to 0.77; $P = 0.19$; I^2=96.4). This indicates that even after accounting for potential biases associated with small sample sizes and study trustworthiness, antioxidants did not demonstrate a consistent, considerable effect on dyspareunia.

Effect of antioxidant on chronic pelvic pain

Nine RCTs with a total of 313 participants assessed the effects of antioxidant on chronic pelvic pain. Meta-analysis suggested a potential reduction in pelvic pain among antioxidant groups compared with control groups (SMD = −1.07, 95% CI: −1.71 to −0.42); however, extreme heterogeneity (I^2 = 92.1%, $p < 0.001$) indicates that this average effect is highly unreliable and should not be generalized to specific clinical contexts (Fig. 3, C).

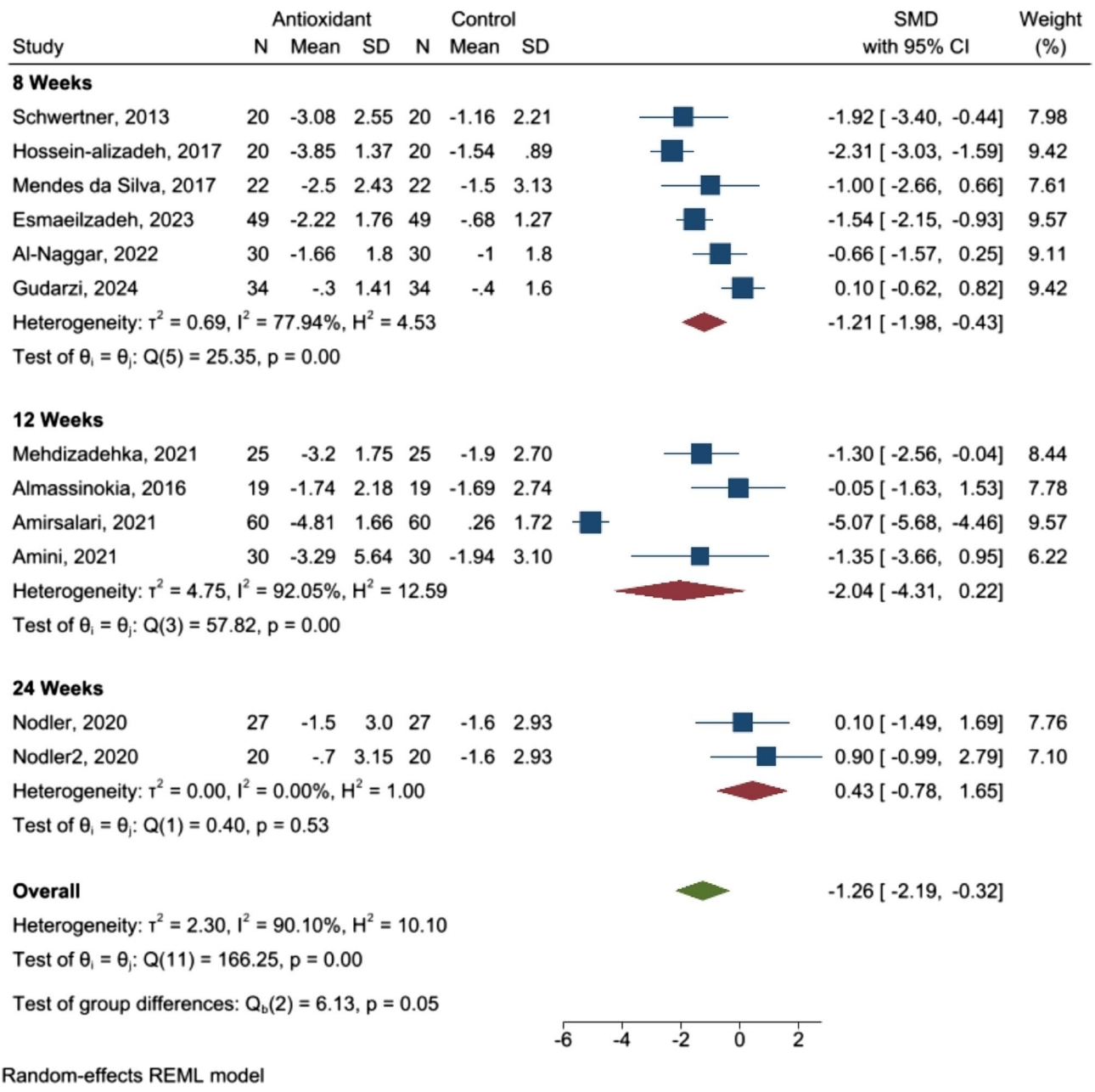

Fig. 5 Subgroup analysis of antioxidant effects on dysmenorrhea severity by treatment duration. Forest plot comparing SMDs in dysmenorrhea pain reduction between antioxidant and control groups, Stratified by intervention duration (8 weeks, 12 weeks, and 24 weeks). Pooled estimates (95% CIs) and heterogeneity (I^2) are presented for each subgroup

According to GRADE criteria, the evidence was rated as very low certainty due to serious risk of bias and inconsistency (Supplementary Table 1). No publication bias was detected.

Subgroup analysis based on the type of antioxidant, which included melatonin, vitamin D, allicin, vitamin C combined with vitamin E, and silymarin, did not indicate any specific antioxidant as a significant contributor to the high overall heterogeneity. The melatonin subgroup did not show a considerable reduction in pelvic pain versus control (SMD = −0.86, 95% CI: −1.75 to 0.02; I^2=88.5%). Similarly, the vitamin D subgroup did not demonstrate a significant effect (SMD = −0.27, 95% CI: −0.36 to 0.89). Despite these subgroup findings, the overall heterogeneity remained high, suggesting other factors may be driving the variability in results across studies (Table 2).

Subgroup analysis based on risk of bias revealed that potential reductions in pelvic pain were observed only when combining results from trials identified as having some concerns regarding risk of bias (SMD = −3.75,

95% CI: −5.58 to −1.93; I^2 = 91.34%; P for heterogeneity = 0.00). In contrast, trials at low risk of bias did not demonstrate a significant reduction in pelvic pain compared to controls (SMD = −0.88, 95% CI: −2.04 to 0.29; I^2 = 74.31%; P for heterogeneity = 0.02). Similarly, studies at high risk of bias also failed to show a significant effect (SMD [95% CI]: −1.61 [−3.68, 0.45]; I^2 = 90.88%; P for heterogeneity = 0.00). These findings suggest that the apparent effect is inconsistent and heavily influenced by heterogeneity, particularly in studies with methodological concerns (Table 2).

Sensitivity analyses based on ethical and methodological trustworthiness revealed important nuances. When the analysis was restricted to studies without conflicts of interest or links to retracted publications, the significant effect on pelvic pain was lost (Supplementary Fig. 4, i). Conversely, the analysis including only studies that met predefined trustworthiness criteria continued to show a significant reduction in pain (Supplementary Fig. 4, ii), though heterogeneity remained substantial.

To address the potential impact of small sample sizes, a sensitivity analysis using the Knapp-Hartung correction was performed. This analysis confirmed the statistical significance of the findings, with an SMD of −1.07 (95% CI: −1.83 to −0.30) and similarly high heterogeneity (I^2 = 92.1). These results suggest that antioxidants may reduce chronic pelvic pain, but the high heterogeneity and very low certainty of evidence warrant cautious interpretation.

Egger's regression test did not detect significant small-study effects (β = −1.99, SE = 6.06, t = −0.33, p = 0.75). Trim-and-fill analysis identified no missing studies, and the pooled effect size remained stable (SMD = −1.07; 95% CI: −1.24 to −0.89), indicating low risk of publication bias.

The overall finding of pain reduction is highly sensitive to the analytical approach. The loss of significance when excluding studies with conflicts of interest, coupled with the very low certainty of evidence, indicates that the apparent beneficial effect for chronic pelvic pain is not robust and should be interpreted with extreme caution.

Discussion

This systematic review and meta-analysis provide compelling evidence that antioxidant supplementation significantly reduces dysmenorrhea pain, with substantial heterogeneity observed across studies. The variability in results appears primarily driven by differences in the specific antioxidant compounds used, duration of treatment, and methodological approaches across trials. Our findings contribute to the growing understanding of oxidative stress mechanisms in endometriosis pathogenesis and their potential modulation through antioxidant interventions.

The findings of our study align with previous systematic reviews by Sukan et al. [10], Zheng et al. [11], and Atrick Bayu et al. [29], which reported efficacy of antioxidant vitamin supplementation in reducing endometriosis-associated pain. However, these earlier reviews focused narrowly on antioxidant vitamins (e.g., vitamins C, E, and D), whereas our analysis expands the scope to include non-vitamin antioxidants (e.g., melatonin, curcumin, resveratrol) and elucidates differential efficacy across compounds. Notably, our results corroborate their observations regarding the role of oxidative stress modulation in pain relief but further identify melatonin as the most clinically impactful intervention, a finding not previously emphasized due to limited data in earlier meta-analyses.

Melatonin emerged as the most effective and consistent antioxidant, demonstrating clinically meaningful reductions in pain severity. Its superior performance likely stems from its unique ability to target multiple pathways involved in endometriosis-related pain simultaneously. Melatonin functions as a potent free radical scavenger while also inhibiting the NF-κB pathway, thereby reducing inflammatory mediators. It additionally modulates prostaglandin synthesis and influences nociceptive signaling through HSP27-dependent microglial inhibition [30, 31]. Emerging evidence suggests melatonin may enhance pain relief by normalizing μ-opioid receptor expression and counteracting morphine-induced hypersensitivity, potentially explaining its robust clinical effects [32, 33]. The clinical relevance of these mechanisms is underscored by our meta-analysis results, where melatonin's effect size approached the MCID for pain scales. However, several knowledge gaps remain regarding optimal dosing regimens and the precise molecular interactions between melatonin and endogenous pain modulation systems.

In contrast, other antioxidants showed limited clinical efficacy despite promising theoretical mechanisms. Vitamin D possesses immunomodulatory properties that could potentially address several pathological processes in endometriosis, including angiogenesis, cellular adhesion, and inflammation [34]. However, clinical trials have failed to demonstrate consistent pain reduction, likely due to variations in baseline vitamin D status among participants, genetic differences in vitamin D receptor expression, and insufficient control of confounding factors across studies [35]. Similarly, curcumin exhibits strong anti-inflammatory and anti-angiogenic properties in experimental models [17, 36] but shows poor clinical translation, primarily because of its limited oral bioavailability and lack of standardized dosing regimens [28].

The duration of antioxidant supplementation also contributed significantly to the observed heterogeneity. Shorter intervention periods demonstrated stronger therapeutic effects compared to extended treatment

courses, a pattern consistent with findings in other chronic pain conditions. This duration-dependent response may reflect true pharmacological adaptations or methodological challenges in longer trials. Methodological differences between studies represented another important source of heterogeneity. Trials with less rigorous design features tended to report larger effect sizes but with greater inconsistency in results. This highlights the need for standardized protocols in future research, including consensus on outcome measures, systematic reporting of baseline characteristics, and careful control of concomitant treatments.

Among other antioxidants examined, vitamin E showed limited efficacy as monotherapy [9], though its combination with vitamin C [8, 18, 25] demonstrated marginal benefits that did not reach statistical significance in our analysis.

Although resveratrol demonstrates promising antioxidant and anti-inflammatory properties in preclinical studies, including Nrf2 pathway modulation and suppression of endometriotic lesion growth in animal models, clinical evidence remains remarkably scarce, yielded inconsistent clinical results potentially due to variability in dosing regimens and poor standardization of extracts [37, 38]. To date, only one RCT has evaluated resveratrol for endometriosis-related pain, finding no considerable effect compared to control [20]. This lack of clinical evidence coupled with resveratrol's well-documented pharmacokinetic challenges, including poor bioavailability and rapid metabolism substantially limits its current therapeutic potential for endometriosis management. Omega-3 fatty acids, while theoretically beneficial through their anti-inflammatory prostaglandin modulation, failed to show significant pain reduction, possibly because most trials used insufficient doses (< 2 g/day EPA/DHA) or did not control for concurrent dietary intake [21].

Our analysis also suggests antioxidant supplementation may reduce chronic pelvic pain in endometriosis, though significant variability and low certainty evidence warrant caution. The examined antioxidants including melatonin, vitamin D, allicin, vitamin C/E combinations, and silymarin showed inconsistent clinical effects despite promising preclinical data supporting their anti-inflammatory and antioxidative properties in endometriosis pathophysiology. While melatonin demonstrated efficacy for dysmenorrhea, its effects on chronic pelvic pain showed inconsistency. Schwartzer et al. reported pain improvement with 10 mg daily [5], Soderman et al. found no benefit with 20 mg nightly potentially reflecting differences in baseline pain severity or its complex dose-dependent analgesia involving both antioxidant effects and opioid-mediated CNS pathways [4], Similarly, vitamin D's lack of significant pain reduction contrasts with its established mechanisms, likely due to variations in study designs and unaccounted patient factors. The paradoxical finding that moderately biased trials showed more consistent pain reduction than higher-quality studies highlight key methodological challenges including small sample sizes and heterogeneous populations. These collective findings emphasize the need for optimized protocols addressing: [1] antioxidant-specific pharmacokinetics [2], rigorous phenotype stratification, and [3] standardized outcome assessments to clarify these compounds' therapeutic potential.

Our findings can be contextualized by a recent meta-analysis by Salmeri et al. (2025) [15], which concluded that dietary supplements lack efficacy for endometriosis-associated pain. This discrepancy arises from key methodological differences. Salmeri et al. employed a narrower search ending in November 2024 and stricter inclusion criteria, resulting in the analysis of 9 placebo-controlled RCTs. Our broader review, which included studies up to January 2025 and incorporated active-control trials, analyzed 15 RCTs. Crucially, our analysis included four studies on melatonin, which demonstrated a significant, consistent benefit for dysmenorrhea, whereas Salmeri et al. included only one null melatonin trial. Thus, while both reviews highlight the suboptimal quality of the existing evidence, our more comprehensive synthesis suggests a potential therapeutic signal for specific antioxidants, particularly melatonin, that merits rigorous investigation in future trials.

While antioxidants showed promise for dysmenorrhea and chronic pelvic pain, their effects on endometriosis-related dyspareunia appear limited. This discrepancy likely reflects fundamental differences in pain mechanisms, with dyspareunia's neuropathic components and association with deep lesions potentially making it less responsive to systemic antioxidant therapy. The mixed results across studies, where only shorter-duration interventions and lower-quality trials showed benefits, suggest methodological factors may influence outcomes. The consistent lack of effect in higher-quality studies [4, 7], coupled with extreme variability between trials, indicates current antioxidant approaches may not adequately target dyspareunia's complex pathophysiology.

Strengths and limitation

This systematic review and meta-analysis have several strengths. It is one of the most comprehensive reviews to date, including a wide range of antioxidant supplements both vitamin and non-vitamin types and covering studies published up to January 2025. The search strategy was extensive, with no language restrictions, and included gray literature, which helped reduce publication bias and ensured a more complete evidence base. The study followed PRISMA guidelines, was registered in PROSPERO,

and used rigorous tools such as the Cochrane RoB 2 and GRADE frameworks to assess methodological quality and certainty of evidence. Subgroup and sensitivity analyses further strengthened the findings by exploring sources of variability. However, some limitations must be considered when interpreting the results. The overall certainty of evidence was low to very low due to high heterogeneity among studies, small sample sizes, and potential biases in trial design. Many included studies varied widely in terms of antioxidant types, dosages, and treatment durations. While melatonin demonstrated consistent benefits, other antioxidants like vitamin D, resveratrol and curcumin showed variable effects, likely due to differences in study design and the limited number of RCTs available for these compounds. Furthermore, evidence on dyspareunia was particularly limited and inconsistent, making it difficult to draw reliable conclusions for this outcome. In some cases, studies with lower methodological quality showed larger effects, raising the possibility of overestimation. Lastly, most trials did not adequately control for confounding factors such as baseline vitamin levels, dietary habits, or concurrent treatments, which may have influenced the outcomes.

Conclusion

Antioxidant supplements may be associated with modest reductions in dysmenorrhea severity, with melatonin appearing to be the most promising agent. The effect on chronic pelvic pain was inconsistent, and no significant benefit was observed for dyspareunia. Due to the substantial heterogeneity, risk of bias, and imprecision of the effect estimates, these potential benefits remain uncertain. Future high-quality RCTs with standardized protocols are needed to establish whether any antioxidant regimens have a definitive clinical utility for specific endometriosis pain subtypes.

Clinical implications

Based on low-certainty evidence, melatonin may reduce endometriosis-related dysmenorrhea; however, this finding requires cautious interpretation and confirmation through high-quality trials. No significant benefit was found for dyspareunia, and evidence for chronic pelvic pain remains inconclusive. Therefore, current evidence does not support the routine use of antioxidants in endometriosis pain management. In specific contexts where first-line treatments are unavailable, unaffordable, or poorly tolerated, melatonin could be explored as a low-cost, accessible adjunctive therapy for refractory dysmenorrhea. A definitive recommendation awaits further evidence from rigorously designed studies that include formal cost-effectiveness analyses comparing antioxidants to established treatments.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' contributions

PM was responsible for defining the research question. PM and AS designed the strategy for the literature search. PM, AS, and SHA independently performed the primary search in the databases and participated in study selection. PM and SE performed the quality assessment of included studies. DM was methodologist, providing substantial contributions to the design and critical revision of the manuscript. Data extraction was carried out by PM and AS. Data analysis was performed by PM and MS. PM and AS were the major contributors in manuscript writing. All of the authors have read and confirmed the final manuscript. SE and AS are co first authors.

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Data availability

The datasets during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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