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MATERNAL AND CHILDHOOD NUTRITION (AC WOOD, SECTION EDITOR)

Effect of Antioxidant Supplementation on Endometriosis-Related Pain: A Systematic Review

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Abstract

Purpose of Review This study was conducted to determine the effects of antioxidant supplementation on endometriosis-related chronic pelvic pain, dysmenorrhea, and dyspareunia.

Methods PubMed/MEDLINE, Scopus, and Cochrane Library databases and the Google Scholar search engine were searched from early 2012 to 2022 using appropriate keywords for clinical trials receiving antioxidant supplements and reporting endometriosis-related pelvic pain (PROSPERO registration number CRD42022318924). The qualities of the included studies were evaluated using the Joanna Briggs Institute (JBI) Checklists Critical Appraisal Tools and the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group. This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.

Results In this systematic review, 8 studies (5 RCTs and 3 non-comparative trials) published in 2012–2022 were included.

Conclusions The studies we included showed promising results in the use of antioxidants in endometriosis-related pain. However, many scientific studies are needed for clear statements.

Keywords Endometriosis · Antioxidant supplementation · Chronic pelvic pain · Dysmenorrhea · Dyspareunia

Introduction

Endometriosis, a frequently idiopathic condition, is a gynecological disease characterized by ectopic growth of endometrial tissue outside the uterine cavity and affects approximately 190 million (~%10) of reproductive-age women and girls, globally. This condition may occur with chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, and menstruation change, or it may be asymptomatic. Diagnosis is by histological identification of ectopic parts and by laparoscopy [1, 2]. There is currently no known cure for endometriosis, and treatment is usually directed at controlling symptoms, and diagnosis of the disease is usually delayed by an average of 4 to 11 years from the onset of symptoms, including in developed countries [3, 4]. Endometriosis is a disease with a high burden and has been shown that the average annual cost for each patient in Europe is approximately € 10,000, while in the USA, the cost of health care is 63% higher than costs averaged across all other nations [5].

Chronic pelvic pain is firmly associated with endometriosis because it has been the cause in 71 to 87% of women suffering from chronic pelvic pain [6]. Complications also cover a wide spectrum such as infertility, dysmenorrhea, dyspareunia, and dysgeusia [7]. Treatment of endometriosis symptoms usually begins with the least invasive methods and progresses toward more invasive interventions [8]. The main goal of medical treatment is to prevent recurrence and reduce symptoms, thus eliminating the need for repeat surgery or prolonging the time between surgeries [9].

Modulation of hormonal signaling through gonadotropin-releasing hormone (GnRH) agonists, oral contraceptive pills, and aromatase inhibitors are known to suppress pain symptoms through estrogen inhibition and prevention of menstruation. However, when the treatment ends, the

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symptoms return with menstruation. Non-hormonal pain-reducing agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and potent analgesics (opioids), decrease inflammation and mask pain. Nevertheless, while these drugs represent a relatively non-invasive treatment plan, they either lack efficacy or cause tolerance and dependence [10, 11•, 12]. In surgical treatment, which is an invasive option, it has been reported that endometriosis recurs at rates as high as 40–50% within 5 years after surgery [13].

Given the limitations of currently available treatments, new therapeutic options for endometriosis have emerged. It is known that oxidative stress, defined as an imbalance between antioxidants and reactive oxygen species (ROS), may play a role in the pathophysiology of endometriosis, which causes a general inflammatory response in the peritoneal cavity [14, 15]. For this reason, the effectiveness of antioxidant therapy in the treatment of endometriosis has started to attract attention in recent years [16–20]. In the current systematic review, we aimed to review the effects of natural antioxidant supplements on endometriosis-related chronic pelvic pain, dysmenorrhea, and dyspareunia in endometriosis patients and to discuss the deficiencies in the current literature.

Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guideline 2020 [21] with the following research question: Does antioxidant supplementation reduce pain associated with chronic pelvic pain, dysmenorrhea, and dyspareunia in endometriosis patients? The study protocol has been registered in PROSPERO [Registration number CRD42022318924) [22].

Search Strategy

Two researchers (BS and VS) independently performed a systematic search of the literature across the PubMed/MEDLINE, Scopus, Cochrane Library databases, and Google Scholar search engine using the keywords "antioxidant" OR "Vitamin C" OR "Vitamin E" OR "Vitamin E" AND "endometriosis" OR "endometrioma." To keep the articles included in the review up-to-date, articles published in the last 10 years were preferred. For this reason, articles published since 2012 are included. The language was restricted to English only.

Inclusion and Exclusion Criteria

Using the PICO (Population/patients, Intervention/exposure, Control/comparison, and Outcome) strategy, the studies that meet the following criteria were included in the study. The PICO strategy is presented in Table 1.

The exclusion criteria adopted in the present study are as follows:

- Drug or hormone interventions with antioxidant properties
- Individuals under the age of 15 or over the age of 45
- Studies with no accessible full-text
- Studies written in languages except for English
- Reviews, comments, editorials, letters to the editor, animal studies, and in vitro studies

Study Selection and Data Extraction

Two researchers (BS and VS) independently screened the results by titles and abstracts to exclude duplicate studies and to evaluate according to the inclusion/exclusion criteria. Database and search engine search results were combined, and duplicate studies were removed both manually and by using Mendeley Reference Manager.

Two independent researchers (BS and VS) extracted the following data from the included studies for further assessment:

1. Research characteristics, research type, study period, date of publication, and the number of endometriosis patients
2. Patient characteristics, including age, gender, nationality, and the number of subjects receiving antioxidant supplementation
3. Dose and duration of antioxidant supplementation, formulation, and clinical outcomes

Table 1 Formulated question of the study based on PICO(S)

Components of PICO(S)	Defined as
Population/patients	Endometriosis patient (15–45 years)
Intervention/exposure	Antioxidant supplementation
Control/comparison	No supplementation or placebo
Outcome	Chronic pelvic pain, dysmenorrhea, dyspareunia
Study design	Randomized controlled trials and observational studies

Quality Assessment

The methodological quality of the studies included in the current analysis was assessed by the two researchers (BS and VS) using the Joanna Briggs Institute (JBI) Checklists Critical Appraisal Tool for Randomized Controlled Trials (RCTs), and non-comparative studies were assessed for quality using the National Institutes of Health (NIH) Quality Assessment Tool for before-after (Pre-Post) study with no control group [23, 24].

The risk of bias in the studies was classified into 3 types such as low risk, uncertain risk, and high risk according to the assessment results. No significant inconsistency was found in data extraction. Based on the number of "yes" responses, < 40% was considered "high risk," 40–80% "moderate risk," and > 80% "low risk."

Results

Study Selection and Characteristics

As shown in the PRISMA flow diagram (Fig. 1) [25], 375 studies were searched from all databases and search engines. Of these studies, 49 were excluded as duplicates both manually and by Mendeley Reference Manager software. The remaining 221 studies were filtered according to the titles and abstracts; 177 studies were excluded due to unrelated topics. A full-text review was done for the remaining 44 studies, and 8 studies that met the inclusion criteria for this review were identified. Of these studies, 5 were RCTs [26–29], and 3 were non-comparative studies [30, 31]. The antioxidant intervention used in 5 studies consisted of drugs or hormones. The full text of 2 studies was not published in English. Therefore, it was not included in the study. The databases in which the protocols were recorded were also searched. Three studies for which study results have not yet been announced were not included. Outcomes or patient profiles of 6 studies were not suitable for PICOS. The full text of a study in the gray literature could not be reached.

Quality Evaluation

Four of the studies were appraised by the JBI Critical Appraisal Tools for Randomized Controlled Trials (RCTs) and two of them by the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group [23, 24]. Quality assessment results are presented in Tables 2 and 3.

The results of the quality assessment of the articles carried out with the JBI Checklists Critical Appraisal Tool for randomized controlled trials indicated that four of the thirteen

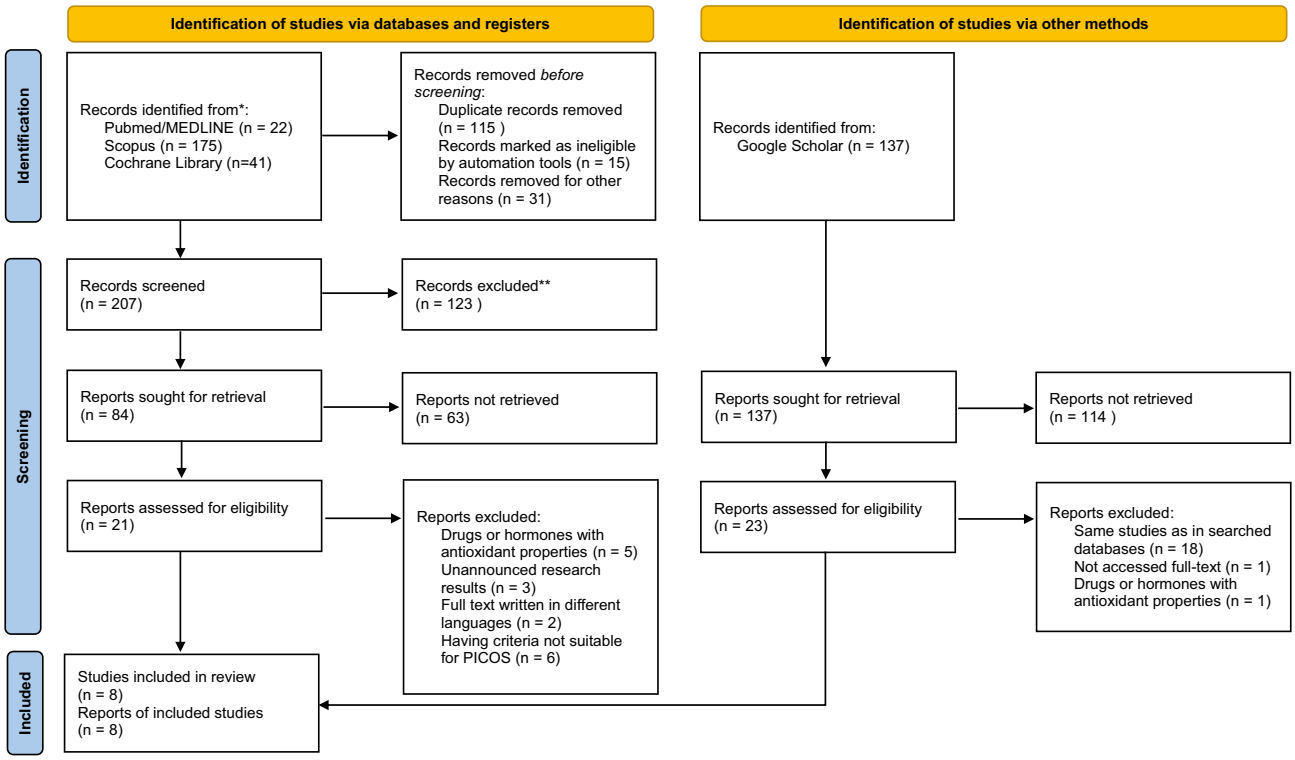


Fig. 1 PRISMA flow diagram

Table 2 Quality assessment of the included randomized controlled trials

	Santanam et al. [26]	Amini et al. [27]	Ibrahim Abd El-Fadil Sehsah et al. [28]	Amirsalari et al. [29]	da Silva et al. [30]
1-Was true randomization used for the assignment of participants to treatment groups?	U	Y	U	U	Y
2-Was allocation to treatment groups concealed?	U	Y	U	Y	Y
3-Were treatment groups similar at the baseline?	U	Y	Y	Y	Y
4- Were participants blind to treatment assignment?	U	Y	U	Y	Y
5- Were those delivering treatment blind to treatment assignment?	N	Y	U	Y	Y
6- Were outcomes assessors blind to treatment assignment?	N	Y	U	Y	N
7- Were treatment groups treated identically other than the intervention of interest?	U	Y	U	Y	Y
8- Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Y	U	Y	N	Y
9- Were participants analyzed in the groups to which they were randomized?	NA	NA	NA	NA	NA
10- Were outcomes measured in the same way for treatment groups?	Y	Y	Y	Y	Y
11- Were outcomes measured in a reliable way?	Y	Y	Y	Y	Y
12- Was appropriate statistical analysis used?	Y	Y	Y	Y	Y
13- Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	U	Y	U	Y	Y

Y yes, *N* no, *U* unclear, *NA* not applicable

Table 3 The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group

	Lete et al. [31]	Caruso et al. [32]	Maia et al. [33]
1. Was the study question or objective clearly stated?	Y	Y	Y
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Y	Y	Y
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Y	Y	Y
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Y	Y	Y
5. Was the sample size sufficiently large to provide confidence in the findings?	Y	N	N
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Y	Y	Y
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Y	Y	Y
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	N	N	N
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Y	N	Y
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *p* values for the pre-to-post changes?	Y	N	Y
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Y	Y	Y
12. If the intervention was conducted at a group level (e.g., a whole hospital and a community), did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA

Y yes, *N* no, *NA* not applicable

(4/13) criteria were met in the study by Santanam et al., eleven of the thirteen (11/13) criteria by Amini et al., five of the thirteen (5/13) criteria by Ibrahim Abd El-Fadil Sehsah et al., ten of the thirteen (10/13) criteria by Amirsalari et al., and eleven of the thirteen (11/13) criteria by da Silva et al.

The results of the quality assessment of the articles carried out with the National Institutes of Health (NIH) Quality Assessment Tool for before-after (Pre-Post) study with no control group indicated that ten of the twelve (10/12) criteria were met in the study by Lete et al., seven of the twelve (7/12) criteria by Caruso et al., and nine of the twelve (9/12) criteria by Maia et al.

Relationship Between Antioxidant Supplementation and Endometriosis-Related Pain in Randomized Controlled Trials

Five studies [26–30] analyzed the relationship between antioxidant supplementation and endometriosis-related pain. Three studies used vitamins E and C as antioxidant supplements. The doses and durations of these studies were similar [26–28]. One study was included because it mentioned garlic tablets as an antioxidant supplement [29]. Four of the RCTs investigated the relevance of antioxidants to chronic pelvic pain, dysmenorrhea, and dyspareunia. There was an RCT examining the effect of the combined use of resveratrol and an oral contraceptive on pelvic pain. In addition, all of them evaluated their pain scores using the Visual Analogue Scale (VAS) [26–34]. Two RCTs [26, 28] reported numbers of patients with decreased pain scores in both groups, while three RCTs reported pain scores before and after treatment in both groups. While the use of supplements was found to be significantly effective ($P < 0.001$) in 2 RCTs whose pain scores were reported, the results of the other study were not statistically significant ($P = 7$) [27, 29, 30] (Table 4).

Relationship Between Antioxidant Supplementation and Endometriosis-Related Pain in Non-comparative Studies

Three non-comparative studies [31–33] have examined the effect of antioxidant supplementation on endometriosis-related pain. While Lete et al. used an antioxidant-effective combination of N-acetyl cysteine, alpha-lipoic acid, and bromelain [31], Caruso et al. used palmitoylethanolamide and alpha-lipoic acid [32]. Also, Maia et al. used a combination of resveratrol and oral contraceptive [33]. Two studies [31, 32] showed that antioxidant supplementation was effective in chronic pelvic pain ($P < 0.001$), and two studies [32, 33] showed that supplementation was effective in dysmenorrhea-related pain ($P < 0.001$). Two studies used the VAS to evaluate the pain score [34]. The cutoff point for assessment was accepted as VAS > 4 by Lete et al. and VAS > 5 by Caruso et al. [31, 32]. Maia et al. used a questionnaire designed to investigate the presence and severity of dysmenorrhea, graded according to a 0–3 point multidimensional categorical rating scale developed by Biberoğlu and Behrman [33, 35] (Table 4).

Discussion

Among the reviews in the literature, there are studies dealing with the relationship between oxidative stress biomarkers and endometriosis [14, 36]. To the best of our knowledge, this is the first systematic review that considers the findings and critically appraises the quality of the studies addressing the relationship between antioxidant supplementation and endometriosis-related pain.

Quality Assessment of the Studies

Correct randomization and blinding were not performed in three of the randomized controlled trials [26, 28, 30]. Therefore, there was a higher risk of bias compared to the other two studies [27, 29]. Only one study did a further analysis that evaluated confounding factors [30]. No analysis of confounding factors was performed in all of the remaining four studies. [26–29]. However, two studies did rule out some confounding possibilities, such as endocrine and pelvic inflammatory diseases. [27, 29]. Not all studies precluded the use of NSAIDs for ethical reasons. The pain scores of the participants who used NSAIDs during the study may have been affected by the dose and frequency of the drug. Only one study analyzed analgesic users in a separate group [30]. No studies have shown conflicting data on the association between antioxidant supplementation and endometriosis-related pain, adding further confidence to the findings on this association.

Impact of Antioxidant Supplementation on Endometriosis-Related Pain

CPP, defined as cyclical or non-cyclical and lasting at least 6 months, affects 24% of women worldwide [37] and accounts for 20% of gynecological clinical referrals [38]. Recently, 10 research priorities for endometriosis have been identified in the UK and Ireland through the James Lind Alliance Research Priority Setting Initiative for Endometriosis. These include "What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?" that contains a research question [39•]. Recently, evidence for non-surgical approaches has begun to increase. The focus is on the effectiveness of approaches such as exercise [40], acupuncture [41, 42], and psychological interventions [43, 44]. In addition, nutritional

Table 4 Characteristics of the studies included in the meta-analysis

References	Country	Study type	Sample size (intervention/control)	Age (Mean ± SD)	Type and duration of supplementation		Clinical outcomes			Risk of bias
					Intervention group	Placebo group	Chronic pelvic pain	Dysmenorrhea	Dyspareunia	
1- Santanam et al. [26]	Atlanta	RCT	(46:13)	19–41 years	1200 IU vitamin E and 1000 mg vitamin C combination daily for 8 weeks	Placebo pills daily for 8 weeks	Intervention group patient with decreased pain (43%) Control group patient with decreased pain (0%)	Intervention group patient with decreased pain (37%) Control group patient with decreased pain (36%)	Intervention group patient with decreased pain (24%) Control group patient with decreased pain (0%)	High
2- Amini et al.[27]	Iran	RCT	(30:30)	Intervention: 35.7 ± 5.71 Control: 38.03 ± 6.47	800 IU vitamin E and 1000 mg vitamin C combination daily for 8 weeks	Placebo pills daily for 8 weeks	Intervention VAS score pre-post: (26.66 ± 27.84–12.43 ± 13.28) Control group VAS score pre-post: (16.96 ± 16.28–18.63 ± 18.35) $P < 0.001$	Intervention VAS score pre-post: (50.53 ± 32.12–17.56 ± 16.65) Control group VAS score pre-post: (51.00 ± 34.21–31.56 ± 26.39) $P < 0.001$	Intervention VAS score pre-post: (26.66 ± 28.27–15.43 ± 18.47) Control group VAS score pre-post: (20.73 ± 21.77–18.10 ± 19.93) $P < 0.001$	Low
3- Ibrahim Abd El-Fadil Sehsah et al. [28]	Egypt	RCT	(50:50)	Intervention: 25.36 ± 3.75 Control: 26.18 ± 4.24	1200 IU vitamin E and 1000 mg vitamin C combination daily for 6–8 weeks	Placebo pills for 6–8 weeks	Intervention group patient with decreased pain (48%) Control group patient with decreased pain (10%)	Intervention group patient with decreased pain (40%) Control group patient with decreased pain (18%)	Intervention group patient with decreased pain (32%) Control group patient with decreased pain (8%)	Moderate
4- Amirsalari et al. [29]	Iran	RCT	(60:60)	Intervention: 29.41 ± 8.54 Control group 29.71 ± 5.67	400 mg garlic tablets for 4,8, and 12 weeks	Placebo pills for 4,8, and 12 weeks	Intervention group VAS score pre-post (8 weeks): (7.15 ± 1.58– 3.93 ± 1.63) Control group VAS score (8 weeks) pre-post: (7.03 ± 1.59– 7.21 ± 1.65) $P < 0.001$	Intervention VAS score pre-post (8 weeks): (6.71 ± 1.55—3.38 ± 1.69) Control group VAS score pre-post: (6.35 ± 1.65–6.51 ± 1.68) $P < 0.001$	Intervention VAS score pre-post (8 weeks): (6.13 ± 1.41–2.91 ± 1.21) Control group VAS score pre-post: (6.43 ± 1.89–6.63 ± 1.98) $P < 0.001$	Low
5- da Silva et al. [30]	Brazil	RCT	(22:22)	Intervention: 35.4 ± 7.1 Control Group: 32.4 ± 7	0.15 mg levonorgestrel /0.03 mg EE and 40 mg resveratrol daily for 42 days	0.15 mg levonorgestrel/EE 0.03 mg and placebo daily for 42 days	Intervention group VAS score pre-post (median): 5.7 (4.8 to 6.6)- 3.2 (2.1 to 4.3) Control group VAS score pre-post (median): 5.4 (4.2 to 6.6)- 3.9 (2.2 to 5) $P = 0.7$	NR	NR	Low
6- Lete et al. [31]	Spain	Non-comparative study	398	Total: 34.6 ± 7.2	N-acetyl cysteine 600 mg, alpha-lipoic acid 200 mg, bromelain 25 mg, and zinc 10 mg (1 administration 2 times a day) for 6 months	None	Baseline VAS score 398 patients: 6.68 ± 1.97 Visit 1 (3 months) VAS score 373 patients: 4.55 ± 1.97 Visit 2 (6 months) VAS score 346 patients: 3.52 ± 1.91 $P < 0.0001$	NR	NR	Low

Table 4 (continued)

References	Country	Study type	Sample size (intervention/control)	Age (Mean ± SD)	Type and duration of supplementation		Clinical outcomes			Risk of bias
					Intervention group	Placebo group	Chronic pelvic pain	Dysmenorrhea	Dyspareunia	
7-Caruso et al. [32]	Italy	Non-comparative study	56	Total 26 ± 6	300 mg palmitoylethanolamide and 300 mg alpha-lipoic acid (1 administration 2 times a day) for 9 months	None	Baseline VAS score > 5 (56 patients): (100%) Visit 1 (3 months) VAS score > 5 (51 patients): (54.9%) Visit 2 (6 months)VAS score > 5 (46 patients): (28.3%) $P < 0.001$	Baseline VAS score > 5 (56 patients): (91.1%) Visit 1 (3 months) VAS score > 5 (51 patients): (35.3%) Visit 2 (6 months) VAS score > 5 (46 patients): (19.6%) $P < 0.001$	Baseline VAS score > 5 (56 patients): (57.1%) Visit 1 (3 months) VAS score > 5 (51 patients): (41.2%) Visit 2 (6 months) VAS score > 5 (46 patients): (19.6%) $P < 0.001$	Moderate
8- Maia et al. [33]	Brazil	Non-comparative study	12	Total 30 ± 5	3 mg DRSP, 30 µg EE, and 30 mg resveratrol daily for 6 months	None	NR	Baseline pain score: 3 DRSP/EE pain score (3 months): 2.1 ± 0.5 $P < 0.001$ DRSP/EE + resveratrol pain score (6 months): 0.2 ± 0.4 $P < 0.0001$	NR	Low

RCT randomized controlled trial, *NR* not reported, *DRSP* drospirenone, *EE* ethinylestradiol, *IU* international unit, *VAS* visual analogue scale

interventions such as diet [16] or micronutrients are also being explored (19,45,46].

Pain in endometriosis can be nociceptive (including inflammatory), neuropathic, or a combination of these [5]. The experience of pain includes several different mechanisms and interactions between the peripheral and central nervous system (CNS), regardless of the underlying disease [47]. Peripheral mechanisms in endometriosis-associated pain are numerous. Changes in the peritoneal fluid (PF) in women with endometriosis can activate or sensitize peripheral nociceptors. In PF of endometriosis patients, various cytokines, chemokines (such as IL-1, IL-6, TNF-α, and monocyte chemoattractant protein (MCP)-1) [47–50], and growth factors (such as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF)) [51, 52] are secreted by non-neuronal cells at high levels and play an active role in pain in the endometrium [53].

It is now widely accepted that oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and antioxidants, may play a role in the pathophysiology of endometriosis, which causes a general inflammatory response in the peritoneal cavity [14, 53, 54]. Chronic pelvic pain (CPP) is also associated with cell dysfunction, which promotes chronic inflammation and oxidative stress, including macrophages and mast cell activation [55]. Peritoneal macrophage concentration appears to be higher in women with endometriosis and can release cytokines, prostaglandins, and growth factors. Macrophages may play an important role in the initiation, maintenance, and progression of endometriotic disease [36]. In the presence of pelvic endometriosis, macrophage activation in the peritoneal cavity can promote oxidative stress and produce a variety of proteins, including lipids and low-density lipoprotein peroxidation [53]. Mast cells and macrophages play an active role in pain in the ectopic endometrium through the release of proinflammatory cytokines [56, 57].

Three of the studies included in the review applied vitamins E and C as antioxidant supplements [26–28]. In studies investigating the relationship between antioxidant vitamins and endometriosis, it was determined that endometriosis patients had lower serum levels of vitamins A, C, and E compared to the control groups. It is thought that this situation arises from the use of antioxidants during oxidation reactions [58–60]. The direct effect of vitamin E and C supplements on antioxidant markers in women with endometriosis has still not been demonstrated [19, 61]. Although the results of these three studies we included looked promising (Table 4), only one measured markers of oxidative stress along with pain. In the findings of Amini et al. [27], who also included oxidative stress markers in their study, the administration of vitamin C and E combination significantly decreased MDA ($P = 0.002$) and ROS ($P < 0.001$) levels but did not change TAC levels compared to the placebo group.

After hemolysis and bleeding in endometriosis, prooxidant hemoglobin transfers iron and heme derivatives to endometriotic lesions. Iron plays an important role in the stable and reversible binding of oxygen to hemoglobin. However, once released from hemoglobin, free heme and iron are generally considered toxic compounds and oxidize most biomolecules via autooxidation and Fenton reaction. This situation contributes to the formation of ROS in the endometriotic cyst [62]. Animal studies have shown that ovarian endometriosis causes iron-catalyzed oxidative stress in follicles [63•], and garlic treatment can prevent iron-induced oxidative stress and increase TAC levels [64, 65]. Clinical studies on the use of garlic in the treatment of endometriosis are limited. Garlic may also be effective in the pain associated with endometriosis through decreased prostaglandin production and estrogen elimination [66, 67]. The study of Amirsalari et al. [29] showed that garlic tablets are effective in reducing the pain symptoms associated with endometriosis. However, further studies are needed to show through which mechanisms this effect occurs. In addition, studies that include different doses and durations of use of garlic tablets or examining the effectiveness of consumption as food can be carried out.

The two studies we included in the review involved the administration of resveratrol in patients with endometriosis [30, 33]. The reason we included resveratrol application was due to the presence of an antioxidant effect [68–70]. However, the studies we included focused on inhibiting aromatase activity and antiproliferative effects rather than antioxidant properties. Indeed, the mechanism of action of resveratrol in the treatment of endometriosis is not clear. The study of de Silva et al. [30] showed a decrease in the pain scores of the resveratrol group at the end of the 7-day period but did not show a significant difference at the end of the 42-day period. Maia et al. [33] showed that resveratrol treatment is effective. More studies are needed to show the effect and mechanisms of action of resveratrol used in endometriosis-related pain.

Administration of alpha-lipoic acid (ALA) was common in both studies we included [31, 32]. Both oxidized and reduced forms of lipoic acid show antioxidant properties [71]. A recent in vitro study showed that ALA inhibits cytoplasmic pattern-recognition receptor-3 (NALP-3)-induced cytokine production by inhibiting ER-B expression in endometriotic cell lines [72]. In an animal study, 15 days of oral ALA treatment in rats with forming experimental endometriosis showed positive effects on the severity of the disease by reducing oxidative stress [73]. More studies are needed to show by which mechanisms the beneficial effects of ALA on endometriosis occur. The non-comparative studies we included showed beneficial effects in humans but had several limitations.

When we searched the databases of systematic reviews, we did not find any records similar to our current systematic review in the International Prospective Register of Systematic Reviews (PROSPERO). In the Cochrane Database of Systematic Reviews (CDSR), we encountered two somewhat similar meta-analyses. Pattanittum et al. [74] conducted a study addressing the relationship between dietary supplements and dysmenorrhea, but the study focused on primary dysmenorrhea, not due to pathology. They included only one study [20] addressing secondary dysmenorrhea due to endometriosis in the review. Showell et al. [75] examined the effect of antioxidant supplementation on subfertility in females in their study. According to the subgroup analysis results, there was no clear evidence of the effect of antioxidant supplementation on clinical pregnancy rates in women with endometriosis. A systematic review [36] that was not registered in these databases and did not follow a specific protocol, however, addressed the relationship between oxidative stress markers and endometriosis. We hope that the current systematic review will make an important contribution to the literature as it is the first systematic review to address the relationship between endometriosis-related pain and antioxidant supplementation.

Conclusion

Reducing symptoms in the treatment of endometriosis is important for the well-being of the patient. The process of reducing pain, which is perhaps the most important symptom, ranges from drug therapy to surgery. However, the existence of reasons such as drug addiction or recurrence after surgery pushes scientists to search for new ones. Therefore, in recent years, new methods used in the treatment of pain in endometriosis and generally non-invasive have come to the fore.

So, could antioxidants be a new way to reduce the pain associated with endometriosis? This systematic review was made in order to obtain a general conclusion based on the results of studies seeking answers to this question. According to the results of the study, the studies we included in the review show that the use of antioxidant supplements in patients with endometriosis is generally effective in reducing endometriosis-related pain. With the exception of just one study, the results of other studies look impressive. The results give hope that antioxidants can be an alternative treatment method used alone or in combination with other methods in the management of pain in endometriosis. However, given the limitations and quality of the studies we included, more scientific studies are needed to make clear statements. We also propose a future meta-analysis when new and similar studies are added to the literature.

Limitations

We hoped to be able to conduct a meta-analysis when planning the study, but the heterogeneity of the data made this impossible. We tried to include as many antioxidant supplements as possible in the study. However, we should state that there may be studies examining the relationship of other natural antioxidants, which are outside our search terms and do not include these terms in the articles, with endometriosis-related pain. This may be due to the fact that supplements focus on different functions apart from their antioxidant properties.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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