Providing Antioxidants to Reduce Symptoms of Endometriosis Related Pain: Systematic Review

Raissa Nurwany,¹ Muhammad Farhan Alfaroib, Syifa Alkaf ³
¹Department of Obstetrics and Gynecology, Faculty of Medicine, Sriwijaya University, Palembang, South Sumatra
²Medical Professional Study Program, Faculty of Medicine, Sriwijaya University, Palembang, South Sumatra
³Department of Obstetrics and Gynecology, Faculty of Medicine, Sriwijaya University, Palembang, South Sumatra

Korespondensi: Raissa Nurwany; Raissa.nurwany@fk.unsri.ac.id

Abstract
Introduction: Approximately 10 - 15% of women in their reproductive age experience endometriosis. Endometriosis is defined by chronic discomfort and pain, specifically dysmenorrhea, dyspareunia, and dyschezia. A recent study has provided insight into the involvement of oxidative stress in the progression of endometriosis. Oxidative stress refers to an imbalance between reactive oxygen species (ROS) and antioxidants, resulting in inflammation within the peritoneal cavity. This comprehensive analysis examined the efficacy of antioxidant administration and its impact on pain symptoms associated with endometriosis.

Method: This study reviewed literature by searching the PubMed, ScienceDirect, and Cochran Library databases. The search query included “endometriosis” and “antioxidant.” The study was reviewed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The scope of analysis was restricted to clinical trials conducted exclusively from 2012 to 2023.

Result: A total of 10 studies were incorporated, encompassing the utilisation of vitamin C and vitamin E, N-acetylcysteine, alpha-lipoic acid, bromelain, zinc, melatonin, and combination oral contraception. After administering antioxidants, the analysis of different groups consistently revealed a greater degree of improvement in dysmenorrhea, dyspareunia, and chronic pelvic pain. Vitamin C, vitamin E, and N-acetylcysteine act as antioxidants and effectively decrease oxidative stress and the development of endometriosis discomfort.

Conclusion: using antioxidants, including vitamin C and vitamin E, or N-acetylcysteine, has a beneficial effect in decreasing pain sensations associated with endometriosis.

Key words: Endometriosis; antioxidant; dysmenorrhea; dyspareunia; chronic pelvic pain

Pemberian Antioksidan untuk Mengurangi Gejala Nyeri Endometriosis: Sistematik Review

Abstrak


Hasil: Terdapat 10 penelitian yang disertakan, meliputi penelitian menggunakan vitamin C dan vitamin E, N-asitsisistin, asam alfa lipoat, bromelain, zinc, melatonin dan kontraspei oral kombinasi. Perbandingan antar kelompok secara umum menunjukkan perbaikan nyeri dismenore, dispareunia, dan nyeri panggul kronis yang lebih baik setelah suplementasi antioksidan. Hal ini berkaitan dengan peran vitamin C, vitamin E, N-asitsisistin sebagai antioksidan yang dapat mengurangi stress oksidatif sebagai pathogenesis terjadinya nyeri endometriosis.

Kesimpulan: Pemberian antioksidan secara umum terutama vitamin C, vitamin E, dan N-asitsisistin berkaitan dengan berkurangnya gejala nyeri pada endometriosis.

Kata kunci: Endometriosis; antioksidan; dismenore; dispareunia; nyeri pelvik kronis
Introduction

Endometriosis is a pelvic inflammatory disease that is associated with oestrogen. It is characterised by the proliferation of endometrial tissue (glands and stroma) outside the uterus. It frequently impacts women who are in the age range where they are capable of reproduction. Approximately 10-15% of women in their reproductive years suffer from endometriosis, a condition characterised by ongoing pelvic discomfort and is known to contribute to infertility. Common symptoms of endometriosis include painful menstrual cramps (dysmenorrhea), pain during sexual intercourse (dyspareunia), and pain during bowel movements (dyschezia). The cause of endometriosis is intricate and revolves around three primary theories: retrograde menstruation, coelomic epithelial metaplasia, and induction theory. Recent studies have provided insight into the involvement of oxidative stress in developing endometriosis and its ability to trigger an inflammatory reaction in the peritoneal cavity. Oxidative stress is an imbalance between reactive oxygen species (ROS) and antioxidants. Reactive oxygen species (ROS) are byproducts generated during oxygen metabolism. They act as inflammatory mediators, influencing cell proliferation and causing harmful effects. 1,2

In order to reduce the creation of reactive oxygen species (ROS) and restore damaged cells, cells employ many antioxidant mechanisms, such as superoxide dismutase, catalase, glutathione peroxidase, and vitamins E and C. Nevertheless, oxidative stress can arise when there is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant system. 2,3 An elevation in oxidative stress indicators, including Cu, ceruloplasmin, 8-hydroxyl-2-deoxyguanosine, and total oxidant status characterises this. Furthermore, those with endometriosis exhibited a significant decrease in serum total antioxidant status and thiol levels, with statistical significance (p < 0.001). 2 Low levels of antioxidants are associated with the underlying cause of endometriosis, as indicated by this data. According to the literature, administering antioxidant treatment has effectively alleviated symptoms associated with endometriosis. 2 Endometriosis treatment may involve long-term therapeutic options, such as implementing a diet abundant in antioxidants or administering cost-effective antioxidant supplements with low adverse effects, alongside medication or surgical interventions. 1,3 This systematic review examines existing evidence on the function of antioxidants in the manifestation of pain symptoms in endometriosis.

Method

This systematic review satisfied the Professional Reporting for Systematic Review and Meta-analysis (PRISMA) criteria. The literature was acquired through electronic database searches, significantly Pubmed and Science Direct, for works published between 2012 and 2023. This study utilised a literature search using keywords and Boolean operators (AND, OR, NOT, AND NOT) to obtain precise results. The criteria for inclusion are as follows: 1) the journal must be in English, 2) the material must be complete and easily available, and 3) the participants must be women diagnosed with post-operative endometriosis. 4) Utilise antioxidants as a therapy for endometriosis; 5) Assess their efficacy and correlation with pain symptoms. 7) Recent clinical research published from 2012 to 2023; 6) Clinical trials conducted as studies. Furthermore, the exclusion criteria encompass animal research and material that is both inaccessible and incomplete.

Subsequently, this study analysed and displayed the literature based on the attributes
of the studies, the attributes of the participants, and the research outcomes on the efficacy of vitamin delivery and its correlation with symptoms of endometriosis pain.

**Participants**  Women with confirmed post-operative endometriosis  
**Intervention**  Use antioxidants as endometriosis therapy  
**Control**  Placebo or without intervention  
**Outcome**  Endometriosis related-pain symptoms  
**Study**  RCT and Non comparative study

### Results

Figure 1 illustrates the process of choosing and identifying the pertinent literature. The initial search using the previous keywords resulted in 1695 pieces of literature. Subsequently, the selection procedure made necessary modifications by considering the article title, abstract, and keywords. This led to the retrieval and analysis of 93 pieces of literature. In addition, this study thoroughly reviewed the complete body of literature and identified just ten sources that satisfied the pre-established criteria for inclusion.
Table 1 displays the attributes of each study. The literature encompassed single-site studies conducted in the United States, Iran, Egypt, Italy, Spain, and Brazil, published from 2012 to 2023. Table 1 displays the attributes of research studies investigating the impact of antioxidants on alleviating endometriosis pain.

Amini et al. conducted a study to examine the effectiveness of delivering vitamins C and E to 60 women between the ages of 15 and 45 who had pelvic pain and stage 1-3 endometriosis. The vitamins were given through laparotomy. This analysis revealed that group A, which received the intervention, had average VAS scores of 50.53 ± 32.12 for dysmenorrhea, 26.66 ± 28.27 for dyspareunia, and 12.43 ± 13.28 for chronic pelvic pain. The scores exhibited statistical significance at a level of p < 0.001. In the control group (group B), the average VAS score was 51.00 ± 34.21–31.56 ± 26.39, with a p-value of less than 0.001. The average score for dyspareunia was 20.73 ± 21.77–18.10 ± 19.93, with a p-value of less than 0.001. However, in chronic pelvic pain, the average score climbed to 16.96 ± 16.28–18.63 ± 18.35, with a p-value of less than 0.571. The intervention group had a significantly more significant enhancement in pain and VAS scores for dysmenorrhea, dyspareunia, and chronic pelvic pain in comparison to the control group.

The efficacy of vitamins C and E on women with endometriosis was investigated in studies conducted by Santanam et al., Ibrahim Abd El-Fadil Sehsah et al., and Mahmoud A. Al-Naggar et al. Vitamin E, a lipid-soluble antioxidant, hinders the formation of vitamin E radicals, while vitamin C enhances this process by turning these radicals back into vitamin E. Although a VAS scale was not used to measure pain levels before, during, and after vitamin administration, this study categorised patients into four groups based on the severity of their discomfort: no pain, mild, moderate, and severe. The findings of these three trials consistently indicate that administering vitamins C and E significantly enhances chronic pelvic pain.

A study conducted by Anastasi et al. discovered that the use of N-acetylcysteine three months after treatment considerably alleviated pain symptoms associated with endometriosis, including dysmenorrhea, dyspareunia, and chronic pelvic discomfort. Söderman et al. found that the administration of 20 mg of melatonin did not have a significant effect on reducing pelvic pain scores related to endometriosis. On the other hand, the study by Schwertener et al. compared the administration of 10 mg of melatonin per day with a placebo. There were significant results in administering melatonin to reduce associated pelvic pain scores, endometriosis, and as an analgesic.

The study conducted by Maia Jr. et al. discovered that the administration of resveratrol (30 mg/day) in combination with oral contraceptives (drospirenone and ethinylestradiol) significantly alleviated the unpleasant symptoms associated with endometriosis-related dysmenorrhea.
<table>
<thead>
<tr>
<th>Sites</th>
<th>Sample Size (intervention/ control)</th>
<th>Sample age (Mean±SD)</th>
<th>Intervention Types</th>
<th>Duration</th>
<th>Chronic Pelvic Pain</th>
<th>Results</th>
<th>Dysmenorrhea</th>
<th>Dyspareunia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalini Santanam et al. (2013)</td>
<td>USA (46/13)</td>
<td>19-41 years</td>
<td>Vit E 1200IU and Vit C 1000mg</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>Intervention group with a decrease in pain by (43%)</td>
<td>Control group with decreased pain (0%)</td>
<td>p=0.0055</td>
<td>Intervention group with reduced pain (37%)</td>
</tr>
<tr>
<td>Leila Amini et al. (2021)</td>
<td>Iran (30/30)</td>
<td>35.7 ± 5.71; Control: 38.03 ± 6.47</td>
<td>Vitamin E 1200mg/day and vitamin C 1000mg/day</td>
<td>Placebo</td>
<td>6–8 weeks</td>
<td>VAS score intervention group before study: (66.26 ±27.84), after intervention: (12.43 ±13.28)</td>
<td>VAS score control group before study: (16.96 ±16.28), after intervention: (18.63 ±18.35);</td>
<td>P &lt; 0.001</td>
<td>VAS score intervention group before study: (50.53 ±32.12), after intervention: (17.56 ±16.65)</td>
</tr>
<tr>
<td>Ibrahim Abd El-Fadil Sehsah et al.(2022)</td>
<td>Egypt (50/50)</td>
<td>Intervention: 25.36 ± 3.75; control: 26.18 ± 4.24</td>
<td>Vitamin E 800IU and vitamin C 1000mg</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>Intervention group with a decrease in pain by (48%)</td>
<td>Control group with decreased pain (10%)</td>
<td>P =0.855</td>
<td>Intervention group with a decrease in pain by (40%)</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of Studies Providing Antioxidant Supplementation for Endometriosis Symptoms
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Country</th>
<th>Participants</th>
<th>Age</th>
<th>Intervention Details</th>
<th>Control Details</th>
<th>Duration</th>
<th>Primary Outcome Measures</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahmoud A. Al-Naggar et al (2022)</td>
<td>Egypt</td>
<td>(30/30)</td>
<td></td>
<td>Intervention: 32.5 ± 4.5 Vitamin E1200IU/day and Vitamin C 1000mg/day</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>Intervention group with a decrease in pain (30%) and Control group with decreased pain (0%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Anastasi et al (2023)</td>
<td>Italy</td>
<td>120</td>
<td></td>
<td>N-acetylcysteine 600mg</td>
<td>No intervention</td>
<td>12 weeks</td>
<td>VAS score intervention group before study: (7.2 ± 1.8), after intervention: (5.7 ± 2.0)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Leite et al (2018)</td>
<td>Spain</td>
<td>398</td>
<td></td>
<td>N-acetylcysteine 600mg, alfa lipoic acid 200mg, bromelain 25mg, and zinc 10mg 2x/day</td>
<td>No intervention</td>
<td>24 weeks</td>
<td>Baseline VAS score: (6.68 ± 1.97) VAS Score after 1 month: 4.55 ± 1.97 Visit VAS Score after 3 month: 3.52 ± 1.91</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Söderman et al (2023)</td>
<td>Egypt</td>
<td>(20/20)</td>
<td></td>
<td>Intervention: 35.90 ± 6.61 Melatonin 20mg</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>VAS score intervention group before study: (2.87 ± 1.86) after intervention: (2.9 ± 1.9)</td>
<td>P = 0.446</td>
</tr>
</tbody>
</table>

Note: VAS = Visual Analog Scale
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Intervention Group Before Study</th>
<th>Control Group Before Study</th>
<th>VAS Score Intervention Group After Study</th>
<th>Control Group After Study</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwertner et al (2013)</td>
<td>Brazil</td>
<td>20/20</td>
<td>Melatonin 10mg</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>(6.46 ± 2.6)</td>
<td>(6.08 ± 1.86)</td>
<td>(2.78 ± 1.35)</td>
<td>(4.68 ± 1.51)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mendes da Silva et al (2017)</td>
<td>Brazil</td>
<td>22/22</td>
<td>Oral Contraception (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) + Resveratrol 40 mg</td>
<td>Placebo</td>
<td>6 weeks</td>
<td>-</td>
<td>-</td>
<td>VAS score: (5.4 ± 1.2)</td>
<td>-</td>
<td>0.7</td>
</tr>
<tr>
<td>Maia Jr et al (2012)</td>
<td>Brazil</td>
<td>12</td>
<td>Oral Contraception (drospirenone + ethinylestradiol) + resveratrol 30 mg</td>
<td>-</td>
<td>24 weeks</td>
<td>-</td>
<td>-</td>
<td>VAS score: (3)</td>
<td>-</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Discussion

The pain experienced in endometriosis can be categorised as nociceptive, which includes both inflammatory and neuropathic components. ROS (reactive oxygen species) are byproducts of normal oxygen metabolism, serving as inflammatory regulators and influencing cell growth. ROS can interact with other molecules, leading to the inhibition of biological components and functions. Persistent overproduction of reactive oxygen species (ROS) can negatively affect several cellular signalling pathways. Additionally, interleukin (IL)-1 beta and tumour necrosis factor (TNF)-alpha can regulate the release of pro-inflammatory cytokines, leading to harm. This activation initiates the apoptotic cascade, resulting in cellular demise. The detrimental consequences of an excessive amount of reactive oxygen species (ROS) include the activation of ion channels, the oxidation of lipids, the alteration of proteins, and the oxidation of DNA.

Researchers have identified macrophages, lipid peroxides, and prostaglandins as the primary factors responsible for the pathophysiology of endometriosis pain. The presence of macrophages, eosinophils, and neutrophils in endometrial lesions leads to the generation of free oxygen radicals, which trigger oxidative stress in endometriosis. In endometriosis, the peritoneal cavity experiences an elevated number of macrophages, which is a result of retrograde menstruation or the presence of endometrial cells undergoing apoptosis. Regulated and activated macrophages create inflammatory cytokines and prostaglandins that stimulate neurons, increasing transient receptor potential (TRP) levels. The term “TRP” stands for “Television Rating Point.”

Inflammation increases lipid peroxide levels, which in turn enhances the activity of the chemotactic factor monocyte chemotactic protein-1 (MCP-1). Macrophages, leukocytes, and endometriotic tissue release MCP-1, a chemotactic agent that attracts mononuclear phagocytes by binding to the chemokine receptors CCR-2 and CCR-4. The effect of vitamin C and vitamin E on endometriosis pain symptoms

Ascorbic acid, also known as vitamin C, is a vital vitamin that aids cellular immunity and diminishes oxidative stress. Research has demonstrated that vitamin C decreases NF-activation and the synthesis of the inflammatory cytokines TNF-alpha and IL-6. Researchers have hypothesised that vitamin E can impede lipid peroxidation, inflammation, and platelet aggregation. Vitamin E insufficiency is linked to a higher likelihood of developing endometriosis in sub-Saharan populations. Vitamins E and C, acting as antioxidants, can potentially diminish the presence of free radicals and ROS, which have a role in the proliferation and attachment of endometrial cells in women with endometriosis. The study conducted by Santanam et al. demonstrated a noteworthy decrease in inflammatory markers, including IL-6 and MCP-1. Microglia are immune cells that aid in combating infections. Reducing MCP-1 levels can inhibit the release of pain-inducing cytokines and prostaglandins by macrophages.

In addition, the research by Amini et al. two reports the presence of markers indicating oxidative stress in patients with endometriosis. These markers include elevated lipid peroxidation levels caused by free radicals, which break down into malondialdehyde (MDA) in the bloodstream. MDA serves as an indicator of cellular harm resulting from the actions of free radicals. The addition of antioxidant vitamins to one’s diet is linked to a decrease in the levels of MDA in the blood plasma of women with endometriosis. Mier-Cabrera et al. conducted a comparable
study, demonstrating that supplementation of vitamins C and E reduced oxidative stress indicators (MDA and lipid hydroperoxides) levels in women diagnosed with endometriosis. The study conducted by Amini et al. discovered a noteworthy decrease in MDA (malondialdehyde) and ROS (reactive oxygen species) when vitamins C and E were administered together. However, there was no significant alteration in total antioxidant capacity (TAC) compared to the placebo group.

**Effect of N-acetylcysteine on endometriosis pain symptoms**

N-acetylcysteine is a precursor to glutathione, a key intracellular antioxidant in the body. N-acetylcysteine mitigates oxidative stress by augmenting intracellular levels of free glutathione through its interaction with glutamic acid and glycine. Additionally, 20-N-acetylcysteine has demonstrated the ability to suppress the function of IL-6, IL-8, and TNF-alpha.

Administering N-acetylcysteine for three months had a significant impact in alleviating pain symptoms associated with endometriosis, including dysmenorrhoea, dyspareunia, and chronic pelvic discomfort. This pertains to the function of N-acetylcysteine as an antioxidant in diminishing oxidative stress and inflammatory reactions, which contribute to pain symptoms associated with endometriosis. Lete et al.’s research likewise yielded comparable findings, indicating that the administration of a combination of n-acetylcysteine and alphalipoic acid resulted in improved pelvic pain among those with endometriosis. In Mohiuddin et al.’s study, similar findings demonstrated that n-acetylcysteine had an analgesic impact on chronic pain. Anastasi et al. seven discovered a significant decrease in Ca125 levels, which indicates several inflammatory diseases in the periosteum. Ca125 is commonly linked to ovarian cancer; however, it can be raised in cases of endometriosis. This rise may be attributed to the rapid multiplication of endometrial cells.

**Effect of melatonin on endometriosis pain symptoms**

The pineal gland produces and combines melatonin, a neurohormone derived from the breakdown of tryptophan. Melatonin functions as an antioxidant by serving as a scavenger of free radicals. Elevated levels of melatonin as an antioxidant are linked to decreased oxidative stress. In an in vivo study, it was discovered that melatonin effectively reduced the levels of oxidative stress markers, including cyclooxygenase 2 (COX-2) and MDA. Additionally, melatonin increases the levels of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase enzymes. Melatonin exerts an anti-inflammatory impact on peripheral tissue by suppressing the secretion of pro-inflammatory cytokines. Melatonin suppresses the growth of endometrial cells, which suggests a potential connection to the development of endometriosis. In vivo experiments also produced comparable findings, indicating that melatonin administration effectively decreased the extent of endometrial implantation in mice.

The study by Schwertener et al. also established melatonin’s function as a pain reliever in endometriosis. The administration of a daily dose of 10 mg of melatonin resulted in a significant reduction in pelvic pain scores and the usage of pain-relieving medication in individuals with endometriosis. The study conducted by Stefani et al. likewise yielded comparable findings, indicating that administering high amounts of melatonin can elevate the pain threshold. However, the study conducted by Söderman et al. produced contrasting findings, indicating that the application of a 20 mg dosage of melatonin did not have a significant impact on reducing pelvic pain scores associated
with endometriosis. The study population’s low baseline scores may account for this phenomenon, as pain relief in those with higher NRS ratings may be more noticeable than those with lower NRS ratings. 9

**Effect of resveratrol on endometriosis pain symptoms**

Plants such as grapes, blueberries, and almonds produce resveratrol, a molecule that acts as a phytoalexin and phytoestrogen, in response to UV radiation and fungal diseases. Researchers have demonstrated that resveratrol functions as an antioxidant by decreasing the levels of cytokines such as IL-6, IL-8, and TNF-alpha. 22 These cytokines are linked to inflammatory reactions and immunopathological damage. Resveratrol enhances the expression of sirtuin 1 (SIRT1), which is linked to inflammatory responses in case of insufficiency. Elevated SIRT1 activity and excessive expression can also impede the generation of pro-inflammatory cytokines. 23

Co-administration of resveratrol at a dosage of 30 mg per day with oral contraceptives, including drospirenone and ethinylestradiol, leads to a reduction in the expression of COX-2 and aromatase in the endometrium. This reduction is linked to the advancement and deterioration of symptoms associated with endometriosis. Higher levels of COX-2 are additionally related to cell growth, the formation of new blood vessels, pain due to endometriosis, and the inability to conceive. 12 The level of COX-2 expression in patients with ectopic and eutopic endometrium was elevated compared to healthy individuals. 24 Nevertheless, alternative findings were derived from additional research. 25 According to Silva et al., the combination of oral contraceptives (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) and resveratrol 40 mg did not show a significant reduction in the pain scale for endometriosis compared to using oral contraceptives alone and a placebo. 11 This discrepancy may be attributed to differences in the trial length and the pain measurement tool used. 11,12

**Conclusion**

A comprehensive analysis revealed that administering antioxidants, including vitamins C, E, and N-acetylcysteine, reduced pain symptoms in individuals with endometriosis. Vitamin C, E, and N-acetylcysteine act as antioxidants and are essential in mitigating oxidative stress, contributing to endometriosis pain development. Additional studies and larger sample sizes are required to provide conclusive evidence supporting the potential effects of antioxidant supplements in endometriosis therapy.

The author expresses gratitude to everyone who has contributed to the composition of this scholarly manuscript. No conflict of interest.

**Daftar Pustaka**


6. Alnaggar M, abdelfattah ahmed, Saeed I. Role of Antioxidants (Vitamin E and Vitamin C) Supplementation for Management of Chronic Pelvic Pain Related to Endometriosis. Zagazig Univ Med J. 2020;0(0):0–0.


19. Raghu G, Berk M, Campochiaro PA,