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## Nutritional interventions in the management of endometriosis – review of the literature

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## **Abstract**

**Introduction:** Endometriosis, a chronic inflammatory condition, affects approximately 10% of women in their reproductive years, impacting around 176 million individuals globally. Characterized by endometrium-like tissue outside the uterine cavity, it leads to symptoms like chronic pelvic pain, dysmenorrhea, and infertility, severely impairing quality of life. This study aims to investigate the role of nutritional interventions in managing endometriosis, highlighting their potential impact and clinical implications.

**Keywords:** endometriosis, diet, supplementation, nutrition

## **Introduction**

Endometriosis is a chronic inflammatory condition, characterized by the presence of endometrium-like tissue outside the uterine cavity.(1) It affects about 10% of women of reproductive age, which accounts for about 176 million women worldwide.(2) This condition manifests through a spectrum of symptoms, including chronic pelvic pain, dysmenorrhea, gastrointestinal disturbances, pain during intercourse, and infertility, significantly impairing the quality of life.(3) The pathophysiology of endometriosis is complex and multifactorial, and may involve several mechanisms, such as retrograde menstruation, metaplastic transformation of peritoneal cells, and a combination of genetic and immunological factors.(3)Endometriosis often faces delays in diagnosis, leading to prolonged suffering and management challenges.(4) The intricate interplay between diet, lifestyle, and the symptomatic burden of endometriosis has garnered increasing attention, suggesting a potential path for therapeutic intervention.

Current treatment methods for endometriosis primarily focus on symptom relief and pain management, utilizing pharmacological and surgical options.(5) Pharmacological treatment often includes pain relievers and hormonal therapies such as oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists, and other hormonal cycle-regulating medications aimed at reducing endometrial activity.(6) In more severe cases, surgical options like laparoscopy may be employed to remove endometrial implants and adhesions, and in extreme cases, hysterectomy may be considered.(7)However, these methods often do not guarantee a permanent cure and may require further interventions. Additionally, there is an ongoing search for alternative and complementary methods for symptom reduction in endometriosis, such as various types of physical activity, physiotherapeutic interventions, and the use of dietary supplements.(8)

The aim of this review is to evaluate the existing literature on nutritional interventions in the management of endometriosis, offering insights into their efficacy and implications for clinical practice.

## **Vitamin D**

Vitamin D, a fat-soluble vitamin, is crucial for the regulation of calcium levels, essential for optimal bone and dental health, and contributes to the proper functioning of the immune system.(9) It is synthesized in the skin through exposure to sunlight, particularly UVB rays, and can also be obtained from dietary sources. It is found in the highest concentrations in foods such as fatty fish (e.g. salmon, sardines), cod liver oil, egg yolks, dark chocolate, fortified foods, and certain mushrooms.(10) A study on animal models showed that the administration of vitamin D at a dose of 24 IU for 3 weeks was found to modulate the expression of IL-17 in endometriotic lesions, leading to a notable inhibition in their development.(11)

Research shows that patients with severe endometriosis had statistically significantly lower serum vitamin D values compared to healthy subjects or those with mild endometriosis.(12)

A randomized double-blind placebo-controlled trial evaluating the effect of 12-week vitamin D supplementation among 60 patients showed significant improvements, including a decrease in pelvic pain ( $p=0.03$ ), in the total-/HDL-cholesterol ratio ( $p=0.04$ ), and a reduction in high-sensitivity C-reactive protein ( $p<0.001$ ) compared to placebo.(13) However, another clinical trial among 39 patients over the same duration found no significant differences between the vitamin D and placebo groups in terms of the severity of pelvic pain and dysmenorrhea.(14) Metanalysis including three clinical trials and a total of 130 patients, showed no beneficial effects of vitamin D supplementation in patients with endometriosis on dysmenorrhea or non-cyclic pelvic pain.(15)

## **Resveratrol**

Resveratrol is a natural polyphenolic compound found in certain plants, especially in the skins of red grapes, berries, and nuts.(16) Its presence in the diet can have a range of health benefits, primarily due to its antioxidant, and anti-inflammatory properties.(17, 18) Animal studies have shown that resveratrol lowers the levels of pro-inflammatory cytokines, including IL-6, IL-8, TNF- $\alpha$  and INF- $\gamma$ , and notably reduces the expression of insulin-like growth factor-1 (IGF-1) and hepatocyte growth factor (HGF) responsible for the proliferation,

invasion, and angiogenesis of endometriotic implants.(19, 20) A clinical trial on 34 patients with endometriosis receiving resveratrol (400 mg) or placebo for 12-14 weeks showed a decrease in the expression of MMP-2 and MMP-9 in the serum and endometrial fluid. (21)

### **Curcumin**

Curcumin is the primary bioactive substance found in turmeric, a spice derived from the *Curcuma longa* plant, renowned for its vibrant yellow color.(22) This compound is known for its potent anti-inflammatory and antioxidant properties, which may provide a multitude of health benefits.(23) Studies conducted in vitro and on mouse models have shown that curcumin can inhibit proinflammatory pathways through the reduction of IL-6, IL-8, MPC-1, NF-kB, and G-CSF, inhibit angiogenesis processes, through decreased expression of VEGF and induce a reduction in the size of ectopic endometrial implants in experimental animal models. (20, 24, 25)

### **Omega-3**

Omega-3 fatty acids are essential fats that the body cannot produce on its own, thus they must be obtained through diet. They are primarily found in fish, such as salmon, mackerel, and sardines, as well as in flaxseeds, chia seeds, and walnuts.(26) Omega-3 fatty acids are known for their significant health benefits, including reducing inflammation, lowering the risk of heart disease, and supporting brain health. Their regular consumption is often associated with improved cardiovascular health and cognitive function.(27) Research on mouse models has demonstrated a reduction in the size of lesions associated with endometriosis after fish-oil supplementation.(28) In a double-blind placebo-controlled trial the study, with 69 young women with endometriosis, participants received either 2000 IU of vitamin D3, omega-3 fatty acid or a placebo daily for 6 months. The results showed a reduction of pelvic pain measured by the visual analog scale (VAS), however not statistically significant. (29)

## **Vitamin C and E**

Vitamin C, also known as ascorbic acid, is a vital nutrient famous for its antioxidant properties. It plays a crucial role in various bodily functions, including the formation of collagen, absorption of iron, and maintenance of bones, cartilage, and teeth.(30) Rich sources of vitamin C include citrus fruits like oranges and lemons, strawberries, bell peppers, broccoli, and kale. Vitamin E is a group of fat-soluble compounds with distinct antioxidant properties, playing a vital role in protecting cells from oxidative stress. It is commonly found in a variety of foods such as vegetable oils, nuts, seeds, green leafy vegetables, and fortified cereals. A study on mice demonstrated that vitamin C therapy significantly reduces the growth and adhesion of endometrial implants in ovarian endometriosis, while also showing potential in improving ovarian fertility and preventing endometriosis-related cancers.(31) In a clinical trial involving 60 women aged 15-45 with laparoscopic-proven endometriosis, the effects of vitamin C and vitamin E IU supplementation were evaluated. The participants were divided into two groups, with one receiving a combination of vitamin C (1000 mg/day) and vitamin E (800 /day), and the other receiving placebo pills for 8 weeks. Results indicated a significant reduction in the severity of pelvic pain, dysmenorrhea, and dyspareunia in the treatment group, supporting the potential role of these antioxidants in managing endometriosis.(32)

## **Quercetin**

Quercetin, a major dietary flavonol, is found in various fruits and vegetables such as onions, cauliflower, apple skin, lettuce, and chili peppers.(33) Known for its broad range of biological effects including antioxidant, anti-inflammatory, and antiangiogenic properties, quercetin has been studied in the context of diseases like obesity, diabetes, and various cancers.(34, 35) A study on a mouse model demonstrated that quercetin inhibited cell proliferation, induced cell cycle arrest, and promoted apoptosis in endometriosis cell lines.(36)

## **Zinc**

Zinc is an essential mineral that plays a crucial role in numerous metabolic processes, immune system function, and wound healing.(37, 38) It naturally occurs in various foods, including meat, fish, nuts, seeds, and whole grains.

A study involving 86 women, including 42 with pelvic endometriosis and 44 healthy controls, revealed that zinc levels in women with endometriosis are significantly lower compared to the control group.(39) In vitro studies showed that Zinc induced apoptosis in melanoma cells through increase in reactive oxygen species (ROS), p53 and FAS ligand proteins. (40) To our knowledge, no studies evaluating zinc supplementation in endometriosis patients have been conducted so far.

## **Conclusions**

This review highlights the potential role of various nutritional interventions in the management of endometriosis. The findings suggest that while some supplements, like vitamins D, C, and E, omega-3 fatty acids as well as resveratrol, show promise in alleviating symptoms and reducing inflammatory markers, the results are not uniformly conclusive across all studies. Curcumin and zinc showed beneficial effects in laboratory settings.

Future research should focus on larger, well-designed clinical trials to better understand the role of these nutrients in endometriosis and to integrate them effectively into patient care strategies.

## **Conflict of Interest Statement**

The authors declare no conflict of interest.

## Disclosure

Conceptualization MK and GRS; methodology MK, GRS, PSR; check, WZ, AZYG and KZ; formal analysis, MK and KK; resources, KK; data curation, MK and KK; writing - rough preparation, MK, GRS, PSR; writing - review and editing, WZ, AZYG, KZ, KK, AZIE; supervision, AZIE; project administration, MK;

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