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NUTRITIONAL INTERVENTIONS AND SUPPLEMENTATION AS SUPPORTIVE THERAPY FOR ENDOMETRIOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Endometriosis is a chronic disease characterised by the presence of endometrial tissue outside the uterine cavity. It is associated with pain, menstrual disorders, and infertility. Despite advances in research, its aetiology remains incompletely understood; however, genetic, hormonal and immunological factors and microbiome disorders are believed to contribute to its development. Diagnosis of the disease is frequently delayed, and laparoscopy remains the gold standard for confirmation. Current treatment options include hormonal pharmacotherapy, most commonly oral contraceptives and progestogens such as dienogest, and surgical intervention, which is associated with a risk of recurrence and postoperative complications. An increasing body of evidence highlights the role of nutritional interventions and supplementation in modulating inflammatory processes, oxidative stress, angiogenesis and estrogen metabolism. Nutrients and bioactive compounds such as omega - 3 fatty acids, vitamins D, C and E, phytoestrogens, resveratrol, curcumin and melatonin may reduce the severity of symptoms and the size of ectopic endometrial lesions. The microbiome also plays an important role - probiotics, short-chain fatty acids and faecal microbiota transplantation demonstrate therapeutic potential through modulation of the immune response and estrogen metabolism. A multidirectional approach integrating pharmacotherapy, surgical treatment, and lifestyle modification may improve patients' quality of life; however, further research is required to evaluate the efficacy and safety of adjuvant therapies.

KEYWORDS

Endometriosis, Nutrition, Nutrients, Microbiome, SCFA, Phytoestrogens, Flavonoids, Resveratrol, Curcumin, Melatonin

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Introduction

Endometriosis is a disease characterised by the presence of endometrial tissue outside the uterine cavity. [2, 3] It may occur within the pelvic cavity, ovaries (where it forms ovarian endometriomas, commonly referred to as chocolate cysts), fallopian tubes, sigmoid colon, lymph nodes as well as in distant organs. [1, 2] The condition affects more than 10% of women of reproductive age and is associated with symptoms such as dysmenorrhea, dyspareunia, dyschezia, dysuria, chronic pelvic pain, abdominal discomfort, and symptoms consistent with irritable bowel syndrome. [6] Moreover, endometriosis is recognised as one of the leading causes of female infertility. [1, 2, 3]

The aetiology of endometriosis remains incompletely understood. However, it is suggested that genetic, hormonal and immunological factors contribute to chronic inflammation. [3] The highest risk of endometriosis development occurs shortly after puberty, whereas the incidence declines significantly after the age of 30. This is due to an increase in estrogen levels in the body and the onset of menstruation, as well as changes in the peritoneal microbiome after the onset of sexual activity. [1]

The most accurate diagnostic method for endometriosis is laparoscopy with excision of suspicious lesions followed by histopathological examination. However, this procedure is invasive and carries a risk of complications, including infection and bleeding. Non-invasive imaging techniques, such as transvaginal ultrasonography and magnetic resonance imaging, may also be used. These modalities allow for accurate visualisation of ovarian endometriomas but have limited sensitivity for detecting lesions located within the peritoneal cavity. [1, 2] On the other hand, the blood biomarker CA-125, which may be elevated in patients with endometriosis, demonstrates low specificity, as increased levels can also be observed in numerous other conditions. For this reason, it should not be used as a single test. [2] Overall, the diagnostic process for endometriosis remains challenging, often resulting in a substantial delay in diagnosis that may extend up to 12 years. This significantly reduces the quality of life of patients and has a considerable negative impact on their mental health. [3]

Currently available treatment options for endometriosis remain limited. These include non-steroidal anti-inflammatory drugs, hormonal therapy, and surgical intervention. [5] Hormonal drugs mainly include oral contraceptives and progestogen monotherapy, which are safe for most patients and cause remission of the disease. However, after discontinuation, symptoms often recur. [4] Surgical management mainly involves laparoscopic excision of endometriotic lesions and, in selected cases, more radical procedures such as oophorectomy or hysterectomy. Due to the recurrent nature of the disease, repeated surgical interventions are often required, resulting in increased healthcare costs and additional psychological burden for patients [5].

In recent years, an increasing number of studies have reported beneficial effects of dietary interventions, nutritional supplementation, and physiotherapy in alleviating pain and gastrointestinal symptoms associated with endometriosis. These approaches may reduce the intensity of inflammatory processes and estrogen activity and have a positive effect on the microbiome of both the gastrointestinal and reproductive tracts. Consequently, effective management of endometriosis requires not only hormonal and surgical treatment but also patient-directed lifestyle modifications. This review summarises the most commonly applied treatment strategies for endometriosis, with particular emphasis on the role of dietary and nutritional interventions in the prevention and management of the disease, while underscoring the need for further research in this area. [5, 6]

Materials and methods

An extensive literature review was conducted using the PubMed database, encompassing publications from 2020 to 2025. We analysed the main factors associated with the pathogenesis of endometriosis, including inflammation, the microbiome and hormonal disorders, and discussed how diet and nutrition can influence these processes. We searched for current studies on dietary interventions and suggested directions for future research. The following keywords were used in the search: " endometriosis", "endometriosis treatment", "pathophysiology of endometriosis", "dienogest", "levonorgestrel", "endometriosis and nutrition", "phytoestrogens", "resveratrol", "curcumin", and "melatonin".

Most commonly used treatment methods

Hormonal therapy:

Oestrogens and their receptors play a crucial role in the pathogenesis of endometriosis. 17-**β**-estradiol (E2) is the primary hormone responsible for stimulating the growth of endometrial tissue by binding to estrogens receptors and including their activation. In addition, E2 contributes to increased pain perception and inflammatory responses associated with the disease. [6] Therefore, treatment focuses on inhibiting the endogenous production of these hormones and includes: combined oral contraceptives, progestogens such as levonorgestrel-releasing intrauterine systems and oral dienogest, gonadotropin-releasing hormone (GnRH), agonists and antagonists, aromatase inhibitors, and androgen analogues. [5, 6]

Combined oral contraceptives

According to international clinical guidelines, combined oral contraceptives or progestogens used as monotherapy should be offered as first- line treatment to patients with endometriosis. This is a suppressive treatment aimed at slowing the progression of the disease and reducing the severity of symptoms. However, its use is limited to patients who are not planning pregnancy in the near future, due to its inhibitory effects on ovarian function. Among combined hormonal regimens, preparations containing dienogest and ethinylestradiol are most commonly prescribed. This treatment improves dysmenorrhoea, non-menstrual pelvic pain, dyspareunia, dyschezia, and quality of life. [7]

Dienogest

The most commonly used progestogen for monotherapy in endometriosis is dienogest, a derivative of 19- nortestosterone. [7, 8] Dienogest binds to progesterone receptors, suppresses FSH and LH secretion, inhibits ovulation, promotes apoptosis of endometrial cells, suppresses angiogenesis, and reduces oxidative stress. It has demonstrated beneficial effects across all endometriosis phenotypes, particularly in cases of deep infiltrating endometriosis. It reduces the size of endometrial lesions, reduces the number of recurrences after surgery and alleviates menstrual pain, chronic pelvic pain, dyspareunia, dysuria and dyschezia. Dienogest is considered safe for long-term use; however, its adverse effects may include vaginal spotting, headaches, vaginal dryness, decreased libido, mood changes, weight gain, and fluid retention. These side effects are most commonly reported during the first year of therapy and can lead to treatment discontinuation [8].

Dydrogesterone

Dydrogesterone is an orally administered hormone with the ability to slow progesterone metabolism and to inhibit angiogenesis and proliferation of ectopic endometrial cells. These effects contribute to atrophy of endometriotic lesions and prevent the formation of new foci. An additional effect of dydrogesterone is the inhibition of the synthesis of pro-inflammatory cytokines, including: Il- 6, Il- 8, TNF- α, and COX- 2, thereby reducing inflammation, a key factor in the pathogenesis of endometriosis. The drug exhibits a favourable safety profile, and its lack of ovulation inhibition preserves fertility in women of reproductive age. These properties suggest that dydrogesterone may represent a promising therapeutic option for endometriosis. However, further studies are needed to determine the exact dosage and long-term side effects. [9]

Levonorgestrel Intrauterine Device

Levonorgestrel is a derivative of progesterone that, when administered via an intrauterine device, exerts a local effect on the endometrium while minimizing systemic side effects. This method of treatment is highly effective and convenient, as it eliminates the need for daily medication intake and reduces the risk of missed doses. Hormonal contraceptives belonging to the progestogen group are also recommended in cases where estrogen use is contraindicated, such as in patients with migraines with aura, or when adverse effects occur following estrogen administration. [7]

Surgical Treatment of Endometriosis

Surgical intervention is indicated when patients continue to experience significant symptoms, particularly pain, or when the side effects of hormonal therapy outweigh its benefits. [2] Laparoscopy is the most commonly employed surgical approach. The primary goal of the procedure is to restore the normal pelvic anatomy, which is often distorted in patients with endometriosis due to adhesions and scarring. Complete excision of all visible ectopic endometrial lesions is always the objective. [2, 3, 27] People with intestinal or urinary tract obstruction are also eligible for surgical treatment. Following the removal of ectopic endometrial lesions, improvements in both pain and fertility rates are typically observed. [2] However, symptom recurrence after surgery occurs in up to 40% of women, [3] and excision of ovarian endometrial cysts may reduce ovarian reserve and promote the formation of new adhesions. [27] Definitive surgery, including hysterectomy with or without oophorectomy, may be considered in women who have completed childbearing and in whom prior pharmacological or surgical interventions have not achieved the desired outcomes. [2, 3] The cure rate following hysterectomy with bilateral salpingo-oophorectomy and removal of all endometrial lesions reaches 90%. [2]

Nutritional Interventions

An increasing number of studies indicate that an appropriate diet and supplementation may positively influence the course of endometriosis. Supplementation with specific nutrients can modulate inflammation by reducing the production of pro-inflammatory cytokines, inhibiting angiogenesis and the proliferation of ectopic cells, and reducing estrogen synthesis and oxidative stress. These factors play a significant role in the pathogenesis of endometriosis, therefore, their modulation may help reduce disease severity and may even prevent its development in women at increased risk. [2, 5, 6, 10, 12-16, 19-23]

Certain nutritional components may also improve patients' quality of life by alleviating pain. Most of the supplements discussed in this paper occur naturally in foods and, because they do not adversely affect fertility in women of reproductive age, represent a promising alternative to hormonal and surgical treatments, which currently constitute the standard of care for endometriosis. Nevertheless, further research is necessary to elucidate their exact mechanism of action, determine optimal dosages, and identify potential side effects.

[5, 6, 10, 12-16, 18, 20]

Saturated Fats and Red Meat

One dietary factor that patients should consider is reducing their intake of saturated fatty acids. Evidence indicates that lower consumption of saturated fats decreases circulating estrogen levels, whereas high intake of trans fats - naturally present in meat and dairy products is associated with an increased risk of developing endometriosis. In addition, women who consume higher amounts of animal fats have an elevated risk of ovarian cancer, which is more common in individuals with endometriosis. [5] A prospective cohort study demonstrated that women consuming more than two servings of red meat per day had a 56% higher risk of developing endometriosis compared to those consuming no more than one serving per week. Red meat, including beef, may exert pro-inflammatory effects and elevated blood estrogen levels, which is associated with the pathogenesis and progression of the disease. [5, 6]

Omega-3 Fatty Acids

Polyunsaturated fatty acids (PUFAs), which are divided into omega-3 and omega-6 fatty acids, exert opposing effects. [5, 6, 10] Omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are essential components primarily found in fish oil. Alpha-linolenic acid (ALA), another omega-3 fatty acid, is of plant origin. [10] Studies indicate that women who consume higher amounts of omega-3 fatty acids are less likely to be diagnosed with endometriosis. [5, 10] In addition, the anti-inflammatory properties have a beneficial effect on the course of other diseases, such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, atherosclerosis, and asthma. [10]

Omega-3 PUFAs inhibit the conversion of arachidonic acid into leukotriene B4 and prostaglandin E2, which are classified as pro-inflammatory compounds. This mechanism contributes to a reduction in inflammation in the lower pelvis. [6, 10] In vitro studies have demonstrated that higher levels of eicosapentaenoic acid reduced the survival of endometrial cells. [6] Randomized clinical trials conducted in patients with endometriosis have examined the effects of omega-3 supplementation on inflammatory markers and disease - related symptoms. A significant reduction in the inflammatory response was observed, manifested by decreased levels of pro-inflammatory cytokines, including: IL-1, IL-6, and TNF-**α**. [23] However, these studies also indicated that omega-3 supplementation did not result in a clinically significant improvement in pain reduction when compared with the placebo group. [6, 23] In contrast, another study conducted among female students with primary dysmenorrhea demonstrated that a daily intake of 1000 mg of fish oil was more effective in pain reduction than the use of ibuprofen administered on an as-needed basis after the onset of pain. [6]

Alpha-linolenic acid (ALA) is a naturally occurring sulphur- containing substance. It is found mainly in mitochondria and is essential for many enzymatic processes. It has antioxidant properties. In an experimental rat model with endometrial implants, ALA was administered for 14 days to assess biochemical and histopathological parameters. It was shown that in the group receiving ALA, the levels of oxidative stress indicators were significantly lower, the volume of endometrial implants was smaller, and reduced concentrations of TNF-**α** were found in the peritoneal fluid and serum compared to the control group. A limitation of this study was the use of a rat model, which does not fully reflect the complexity of endometriosis in humans. In another study conducted on human epithelial and stromal endometriosis cells, ALA therapy reduced the adhesion and invasiveness of these cells. [6]

Vitamin D

In addition to its classic role in calcium and phosphate metabolism, vitamin D has important immunomodulatory, anti- inflammatory and anti- proliferative functions, which is why it has been intensively studied in the context of endometriosis pathogenesis for several years. [5, 6, 11] In vitro studies have shown that the active form of vitamin D inhibits the proliferation and invasiveness of endometrial cells by triggering apoptosis, affects cytokine production,

T lymphocyte function, and macrophage activation, migration and adhesion. [6, 11] Some observational studies report that women with endometriosis are more likely to have lower serum 25(OH)D concentrations than healthy women. [11]

Abbas et al. and Yildrim et al. showed in their studies on mouse models that endometriotic implants were reduced after intramuscular or intraperitoneal administration of vitamin D. It was also suggested that oral vitamin D supplementation may have the same effect. However, another study by Akyol et al. showed no improvement after a similar injection of vitamin D.

The results of clinical trials are therefore inconsistent, and the role of vitamin D in endometriosis is complex. Some randomised trials show an improvement in quality of life, a reduction in pelvic pain and a reduction in the progression of lesions after vitamin D supplementation. [5, 6, 11] Other analyses, however, do not confirm significant differences in the size of lesions or the frequency of disease recurrence. Further well- designed clinical trials are needed to clearly determine its therapeutic efficacy and optimal supplementation regimens in patients with endometriosis. [11]

Vitamins C and E

Oxidative stress, resulting from excessive production of reactive oxygen species (ROS) and antioxidant deficiency, leads to damage to cell membranes, proteins and DNA, exacerbating the inflammatory process and the development of endometrial changes. In the context of reducing oxidative stress, particular importance is attached to antioxidants such as vitamins C and E. [5, 12]

Ascorbic acid is a powerful, water- soluble antioxidant that protects cells from oxidative damage, strengthens immunity and regenerates other antioxidants. Tocopherol, on the other hand, is the main fat-soluble antioxidant that protects cell membranes and lipids from peroxidation. Their simultaneous use may have a synergistic effect - vitamin C regenerates the reduced form of vitamin E, prolonging its antioxidant activity. [12]

Clinical studies confirm that women with endometriosis consume lower amounts of vitamins C and E compared to the healthy population. Studies have shown that after three months of antioxidant supplementation, peripheral vitamin concentrations increased and clinical symptoms such as pelvic pain, painful menstruation and dyspareunia were significantly reduced. In a randomised clinical trial in which patients received vitamin C (1000 mg/day) and vitamin E (800 IU/day) for 8 weeks, a decrease in oxidative stress markers and ROS was observed, with a simultaneous improvement in clinical parameters compared to the placebo group. [5, 6, 12] In addition, an increase in **β**- endorphin levels was observed after vitamin E supplementation, which may further alleviate the pain associated with endometriosis. Due to the safety, availability and low cost of these vitamins, they may be a valuable component of supportive therapy. However, further clinical studies with longer follow-up periods are needed to conclusively confirm their efficacy and determine the optimal supplementation doses. [12]

Phytoestrogens

Phytoestrogens are plant-derived compounds abundant in foods such as vegetables (beans, sprouts, cabbage, spinach, soybeans), fruits and green tea. Due to their chemical structure and biological function, they resemble endogenous human estrogens. They exhibit weak estrogenic activity in conditions of low estrogen levels, which may contribute to the alleviation of menopausal symptoms. Conversely, in tissues characterized by high estrogen activity, such as those affected by endometrial cancer or endometriosis, they demonstrate antiestrogenic effects. Based on their chemical structure, phytoestrogens are classified into three main groups: stilbenes, which include resveratrol, flavonoids: quercetin, kaempferol, puerarin, genistein, naringenin, coumestrol, epicatechin, and lignans, i.e. enterolactone. Numerous studies have demonstrated that phytoestrogens possess anti-inflammatory, anti-proliferative, antioxidant, antiangiogenic and proapoptotic properties. In animal models, it has been proven that they lead to a reduction in the growth and development of endometrial lesions through their influence on hormonal pathways, regulation of oxidative stress and inhibition of inflammatory processes. However, the number of clinical studies conducted in women with endometriosis is very limited. [24]

Flavonoids

Studies conducted in murine models have demonstrated that the administration of kaempferol and quercetin inhibits the proliferation of endometrial cells. [25, 26] Both compounds act as antagonists of the NR4A1 nuclear receptor, thereby suppressing its transcriptional activity in epithelial and stromal cells, inhibiting the mTOR signalling pathway, and reducing fibrosis-related signalling. Treatment with these flavonoids inhibited the growth of endometriotic lesions in mice without inducing weight loss. In addition, kaempferol and quercetin have been widely studied in the context of cardiovascular diseases due to their antihypertensive and anti-inflammatory properties. [25] Furthermore, an in vitro study involving patients with adenomyosis who had previously undergone hysterectomy demonstrated that quercetin effectively inhibited the migration, proliferation, and invasion of endometrial cells. Quercetin has also been shown to suppress the activity of inflammatory mediators, including leukotrienes and prostaglandins. When combined with curcumin and N-acetylcysteine, quercetin exhibits a pronounced analgesic effect. [6]

Another flavonoid, puerarin, is a compound widely used in the treatment of cardiovascular and neurological disorders. Additionally, puerarin inhibits cytochrome P450 aromatase and cyclooxygenase-2 (COX-2) enzymes and increases the expression of 17**β**-hydroxysteroid dehydrogenase type 2 (17**β**-HSD2), leading to a reduction in systemic estradiol and PGE2 levels. A study conducted by Kim et al. showed that puerarin significantly reduced the adhesion and migration of endometrial cells and decreased the size of endometrial lesions in a murine model. [2]

Other flavonoids, including chrysin, daidzein, and nobiletin, modulate the activity of peroxisome proliferator-activated receptors PPAR**γ** and PPAR**α**, thereby promoting apoptosis, reducing inflammation, and improving lipid metabolism. The multidirectional interactions of flavonoids with pathophysiological processes and cellular receptors highlight their therapeutic potential and suggest that they may serve as a basis for the development of novel strategies for the treatment of endometriosis. [26]

Resveratrol

Resveratrol is a natural phenolic compound found primarily in grapes and red wine, as well as in tea, peanuts, beans, and microorganisms such as *Penicillium, Cephalosporium* and *Botulinum.* [13] This compound exhibits a wide range of biological activities, including anti-inflammatory, antiproliferative, antiangiogenic, proapoptotic, antioxidant, and anti-adhesive effects. [10, 13]

Angiogenesis plays a crucial role in the development and progression of endometriosis, and resveratrol has been shown to modulate the expression of genes involved in this process. It leads to a decrease in the expression of MMP-2 and MMP-9 and an increase in TIMP1 and MMP-2 inhibitor. Furthermore, resveratrol decreases the levels of TGF-**β**, Ang-1 and VEGF. The anti-inflammatory effects of resveratrol are mediated through the downregulation of pro-inflammatory factors such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), COX-2 and sirtuin-1 (SIRT-1). Resveratrol also inhibits the expression of survivin, an antiapoptotic protein implicated in endometriosis, thereby limiting the growth of endometrial tissue. In addition, cell proliferation is suppressed through modulation of molecules, including metastasis-associated protein 1 (MTA1), insulin-like growth factor (IGF-1), hepatocyte growth factor (HGF), and zinc finger E-box-binding homeobox 2 (ZEB2). [10] Moreover, resveratrol influences the activity of PPAR-**γ** and PPAR-**α** receptors, contributing to the regulation of lipid metabolism and attenuation of inflammatory processes. It also modulates the aryl hydrocarbon receptor (AhR), which plays a key role in immune regulation and detoxification. Through the modulation of AhR-dependent signalling pathways, resveratrol inhibits cell proliferation and cholesterol synthesis, ultimately leading to a reduction in the growth of endometrial lesions. [26]

Resveratrol has been demonstrated to be a well-tolerated and safe compound that alleviates pain in women [10] and decreases the size of endometrial lesions. Its multifaceted effects on the pathogenesis of endometriosis suggest that resveratrol may represent a promising adjunctive therapeutic option. [13]

Curcumin

Curcumin is a natural polyphenolic compound derived from the rhizomes of *Curcuma longa*, a member of the ginger family. It exhibits potent anti-inflammatory, antiangiogenic, and antioxidant properties [6, 14]. Numerous studies have indicated that the anti-inflammatory activity of curcumin may contribute to both the prevention and treatment of malignancies affecting the respiratory, digestive, reproductive, lymphatic and integumentary systems.

The anti-inflammatory effects of curcumin are mediated through the downregulation of several pro-inflammatory factors, including: IL-1, IL-6, IL-8, TNF-**α**, NF-**κβ**, and TGF-**β**. Similar to resveratrol, curcumin inhibits the expression of COX-2, resulting in reduced cell proliferation and the induction of apoptosis. [14] Endometrial cell proliferation is further suppressed through a decrease in estradiol levels. [6] Moreover, curcumin attenuates oxidative stress by scavenging free radicals, including nitrogen dioxide radicals and reactive oxygen species (ROS), while simultaneously increasing intracellular levels of glutathione and superoxide dismutase. The antioxidant capacity of curcumin has been suggested to be comparable to that of vitamins C and E. The formation of ectopic endometrial lesions is facilitated by adhesion processes regulated by molecules such as matrix metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-9, MMP-11), ICAM-1, VCAM-1 and TIMP-1. Elevated levels of these molecules are commonly observed in the peritoneal fluid of women with endometriosis. Studies in mice have demonstrated that curcumin administration significantly reduces the expression of these proteins in endometrial implants. In addition, curcumin decreases the production of the antiapoptotic protein B-cell lymphoma (Bcl-2) while inducing caspase-9 activation, cytochrome c release, and the expression of the tumour suppressor protein p53. Curcumin has also been shown to inhibit the expression of MMPs, ICAM-1, and VCAM-1 in cancer cells. Overall, studies indicate that curcumin suppresses the growth and number of endometrial cells in a dose-dependent manner.

Curcumin therefore represents a promising agent for both nutritional prevention and adjunctive support in the management of endometriosis. Nevertheless, the limited number of studies analysing the diverse mechanisms of action of curcumin in women with endometriosis currently hampers its definitive and widespread incorporation into clinical practice. [14]

Melatonin

Melatonin is a neurohormone primarily synthesized and secreted by the pineal gland in mammals, where it plays a central role in the regulation of circadian rhythm. [15, 16] Recent studies have demonstrated that melatonin is also produced in various peripheral tissues, where it exerts pleiotropic local effects, including the modulation of immune responses, cell proliferation, angiogenesis, and inflammatory processes. [15]

Emerging evidence indicates that melatonin inhibits the growth of ectopic endometrial lesions by directly binding to the EGFR receptor and suppressing its phosphorylation. Furthermore, melatonin blocks the PI3K/Akt signalling pathway and induces cell cycle arrest through the inhibition of cyclin D1 expression. [16] Similar to the bioactive compounds discussed previously, melatonin limits the adhesion and invasion of endometrial cells by regulating the expression of MMP and TIMP genes. It also reduces angiogenesis by downregulating the expression of VEGF and VEGFR. Another important effect of melatonin is the suppression of 17-**β**-estradiol production. Experimental studies in rat models have demonstrated a significant reduction in plasma E2 concentrations, as well as decreased expression of estrogen receptors in ovarian and uterine tissues following long-term melatonin administration. Notably, a four-month supplementation regimen of melatonin at a dose of 300 mg per day was reported to confirm these effects. [15]

Melatonin has been shown to improve sleep quality and alleviate pain in women with endometriosis. [17] Sleep disturbances and chronic pain are mutually reinforcing: disrupted sleep increases pain sensitivity, while persistent pain negatively affects both the duration and quality of sleep. These factors often contribute to more frequent use of hypnotic medications. Impaired sleep quality is also associated with mood disorders, including depression and anxiety, thereby significantly affecting the overall quality of life in patients with endometriosis. [18] Although melatonin is primarily employed as a sleep-promoting agent, it also exhibits additional analgesic properties. Specifically, it reduces levels of BDNF (brain-derived neurotrophic factor), which is associated with the alleviation of various types of pain, including daily pain, dyspareunia, dysuria, dysmenorrhea, and dyschezia. [15, 18].

The results of clinical studies evaluating the effects of melatonin on pain relief in patients with endometriosis remain inconclusive. [17, 18] In a randomized study published in 2025, 80 infertile women with endometriosis and concomitant sleep disturbances received melatonin supplementation at a dose of 5 mg per day for two months. The study demonstrated that melatonin significantly improved sleep quality, reduced the use of hypnotic medications, and alleviated chronic pelvic pain. [18] In contrast, another clinical trial administering 20 mg/day of melatonin reported by Söderman et al. found no significant difference in pain intensity between in patients receiving melatonin and those receiving a placebo. [17]

Although melatonin is not currently recommended as a first-line therapy for endometriosis, its molecular mechanisms and potential analgesic effects suggest that it may serve as a valuable adjunctive treatment. [18]

Microbiome

The human microbiome participates in numerous physiological processes, including protection against pathogens, development of the immune system, vitamin synthesis, energy metabolism, and the production of short-chain fatty acids (SCFAs). Its composition is strongly influenced by diet. Disruption of the microbiome, or dysbiosis, has been associated with a variety of health disorders. [6, 22] Emerging evidence suggests that alterations in the human microbiome may contribute to the development of endometriosis. Patients with the disease exhibit higher levels of pathogenic bacteria in the oral cavity, vagina, cervix, and faeces. Particular attention has been directed toward opportunistic pathogens of the genus *Fusobacterium,* detected both in the oral cavity and endometrial tissues of affected individuals, indicating a potential role in disease pathogenesis. However, it is unlikely that any single microbial species is solely responsible; rather, the complex interactions between microorganisms and the host are critical. [6] Genomic analyses of gut microbiota have revealed that bacteria such as *Bacteroides, Bifidobacterium* and *Escherichia coli* possess the ability to produce **β**-glucuronidase. [20] This enzyme causes the deconjugation of estrogens and increases the reabsorption of free estrogen, raising its level in the blood. [6, 20] Women with endometriosis often exhibit a higher abundance of **β**-glucuronidase-producing bacteria, which may contribute to increased estrogen levels and enhanced proliferation of endometrial cells. [6]

Restoration of a healthy gut microbiota can be achieved through dietary modifications, faecal microbiota transplantation, antibiotic therapy and the administration of probiotics. Among these strategies, probiotics - live microorganisms administered in appropriate amounts and formulations, play a particularly important role in supporting intestinal homeostasis. Both animal model studies and clinical trials in women have demonstrated that *Lactobacillus* species reduce the production of pro-inflammatory cytokines, including IL-1,

IL-6 and IL-12. Additionally, by enhancing the activity of NK cells, they contribute to a reduction in the size of endometriotic lesions. In a clinical study involving women with advanced endometriosis, eight weeks of oral *Lactobacillus* supplementation resulted in a decrease in pain intensity, particularly menstrual and lower pelvic pain, with the most pronounced improvements observed after two months of treatment. The results of the study indicate that probiotics containing *Lactobacillus* strains are a promising and non-invasive adjunctive approach to support the treatment of endometriosis. [20]

Fecal Microbiota Transplantation (FMT)

In a study conducted on animal models, faecal microbiota transplantation (FMT) was performed. This method involves the transfers of intestinal microbiota from donors into the gastrointestinal tract of recipients with the aim of restoring the balance between microorganisms, modulating the immune system and regulating metabolism. In the study under discussion, gut microbiota from women with endometriosis and from healthy controls was introduced into the digestive tract of mice. FMT from healthy donors was shown to alter the composition of the gut microbiota, increasing the abundance of *Lactobacillus* species while reducing *Bacteroides* populations. It also elevated acetate levels in both endometriosis lesions and faeces, enhanced intestinal barrier integrity, and promoted macrophage polarization toward the M1 phenotype via activation of the JAK1/STAT3 signalling pathway, as indicated by increased expression of proteins such as occludin, ZO-1 and claudin. [21] M1-polarized macrophages are characterized by high production of pro-inflammatory cytokines and enhanced phagocytic activity, leading to an intensified immune response against ectopic endometrial lesions. [2, 21] Acetate, a microbiota - derived metabolite, similarly activates the JAK1/STAT3 pathway and supports M1 macrophage polarization. [21] In contrast, M2-polarized macrophages promote the development of ectopic lesions. [2, 21] In mice receiving microbiota from healthy women, these combined effects contributed to a reduction in the mass and volume of ectopic endometrial lesions and mitigated disease progression.

In contrast, mice receiving microbiota derived from patients with endometriosis exhibited decreased acetate levels, impaired intestinal barrier function, macrophage polarization toward the M2 phenotype, and inhibition of the JAK1/STAT3 signalling pathway.

Faecal microbiota transplantation may represent a potential alternative to conventional hormonal therapies, offering multidirectional benefits, including modulation of gut microbiota composition and increased acetate levels in both faeces and ectopic endometrial lesions. [21]

Short-Chain Fatty Acids (SCFAs)

The human gut microbiota is capable of producing short-chain fatty acids (SCFAs), including acetate, propionate and butyrate. These metabolites exhibit anti-inflammatory and antiproliferative properties. Numerous studies have reported that patients with endometriosis possess lower abundances of SCFA-producing bacteria. [19]

To date, research has largely focused on the role of butyrate in the pathogenesis and potential treatment of gynecological diseases, including endometriosis, PCOS and cancers such as colon, cervical, and ovarian cancer. Butyrate is produced through the fermentation of dietary fiber in the large intestine, primarily by bacteria of the *Firmicutes* phylum. It serves as an energy source for colon epithelial cells and enhances barrier integrity. Additionally, butyrate exhibits anti-inflammatory and anticancer properties and exerts epigenetic effects by inhibiting histone deacetylases (HDACs), thereby regulating the expression of genes involved in cell proliferation, differentiation, and apoptosis. In mouse models, butyrate has been shown to reduce the size and proliferation of endometriotic lesions. However, its therapeutic application is limited by its short half-life, prompting the search for butyrate analogues or probiotics capable of stabilizing its levels. [22] Researchers emphasize the importance of dietary strategies, including high-fiber diets and the Mediterranean diet, which promote butyrate production by the gut microbiota and may enhance therapeutic outcomes. [19, 22]

Recent evidence suggests that modulation of the gut microbiota and supplementation with short-chain fatty acids represent promising therapeutic strategies for the management of endometriosis. However, further well-designed studies are required to comprehensively assess their safety, efficacy and optimal treatment regimens in human populations.

Conclusions

Endometriosis is a complex disease with an incompletely understood etiology, and its diagnosis and management continue to pose significant clinical challenges. The diagnosis is often delayed for many years. Endometriosis profoundly affects multiple aspects of women's lives, including physical, psychological, sexual, and social well-being.

Despite the availability of hormonal and surgical treatment options, a considerable proportion of patients experience disease recurrence and persistent chronic pain, leading to a marked reduction in quality of life. Most hormonal therapies exert their effects through suppression of ovarian function, which limits their applicability in women of reproductive age who wish to preserve fertility. Consequently, there is a critical need to develop novel therapeutic strategies that are effective yet do not interfere with the reproductive plans of young women.

A growing body of evidence suggests that nutritional interventions, target supplementation, and microbiome modulation may serve as valuable adjuncts to standard endometriosis treatment. Nutrients and bioactive compounds such as omega-3 fatty acids, vitamins D, C and E, phytoestrogens, resveratrol, curcumin, melatonin and probiotics exhibit anti-inflammatory, antiproliferative, and antioxidant properties, enabling them to influence key pathways involved in the pathogenesis of endometriosis. Consequently, these interventions may contribute to a reduction in the size of ectopic endometrial lesions and alleviation of pain symptoms. The role of the gut microbiota and its metabolites, particularly short-chain fatty acids, has emerged as one of the most promising areas for future research. Despite encouraging results, further well-designed clinical trials are required to confirm the efficacy and safety of these approaches. In the future, a holistic strategy integrating pharmacotherapy, surgical intervention, and lifestyle modification may form the basis of more effective and patient-centered endometriosis management.

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