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Anti-inflammatory effects of selected dietary components on endometriosis- review

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ABSTRACT:

Background: Endometriosis is a chronic inflammatory disorder that is among the most common gynaecological problems in women of reproductive age. The disease involves the presence of endometrial tissue outside the uterus, which manifests as pelvic pain and infertility. The main theory for its development suggests that endometrial cells move into the abdominal cavity during menstruation and implant there. This process leads to an increase in inflammatory cells and increased concentrations of cytokines, chemokines and prostaglandins, resulting in chronic inflammation.

Objective: The aim of this work is to analyse in detail the available studies on the anti-inflammatory effects of selected dietary components such as polyphenols, vitamin D and omega-3 fatty acids. The work aims to evaluate their potential as future therapeutic options for the treatment of endometriosis, with a critical approach to their efficacy and possible application in the treatment of this disease.

Materials and methods: A review of the literature available in the PubMed database was conducted using the following phrases in English: endometriosis, pain, diet, polyphenols, resveratrol, curcumin, vitamin D₃, OMEGA-3 acids, polyunsaturated acids

State of knowledge: Changing dietary patterns in patients with endometriosis may result in a reduction in levels of inflammatory markers, which are typically elevated in this disease. Polyphenols, such as resveratrol and curcumin, show anti-inflammatory effects and inhibit endometrial cell proliferation. Vitamin D3 shows anti-inflammatory effects and influences angiogenesis. Omega-3 fatty acids may reduce inflammation and endometrial proliferation.

Conclusions: The literature review indicates that polyphenols, vitamin D3 and omega-3 fatty acids offer promising therapeutic properties for the treatment of endometriosis, with anti-inflammatory, anti-proliferative and pain-relieving effects. Despite these promising results, further clinical trials are needed to fully evaluate their efficacy and application in practice.

Keywords: endometriosis, pain, diet, polyphenols, resveratrol, curcumin, vitamin D3, OMEGA-3 acids, polyunsaturated acids

INTRODUCTION AND AIM OF THE STUDY

Endometriosis is a chronic inflammatory disease and one of the most common gynaecological disorders in women of reproductive age. It is characterised by oestrogen dependence and the presence of endometrial tissue outside the uterus. Symptoms of endometriosis mainly include pelvic pain, including dysmenorrhoea, dyspareunia, dysuria and dyschezia, and infertility. More than 60% of patients report chronic pelvic pain, which is not necessarily correlated with the severity of the disease. [1,4]

One of the most plausible theories of the pathogenesis of endometriosis is the retrograde menstruation theory, according to which endometrial cells migrate into the uterine cavity during menstruation and implant there. During menstruation, which is an inflammatory process, there is an increase in the number of inflammatory cells in the endometrium. Therefore, both in the endometrial lesions and in the peritoneal fluid of patients with endometriosis, an increased presence of inflammatory cells can be found, as well as elevated concentrations of cytokines,

chemokines and prostaglandins. In addition, cytokines, chemokines and inflammatory mediators can increase the recruitment of inflammatory cells, leading to chronic inflammation in a 'vicious circle' mechanism. The implantation of endometrial cells in the peritoneum is made possible, among other things, by the action of matrix metalloproteinases (MMPs) enzymes, which degrade and remodel the extracellular matrix of the peritoneal mesothelium around endometrial fragments. Matrix metalloproteinases are mainly regulated by progesterone, interleukin-1 (IL-1), interleukin-6 (IL-6) and growth factors. [2]

Elevated levels of inflammatory mediators such as IL-1, IL-6, IL-8, IL-17, TGF- β , TNF- α , VEGF, cyclooxygenase-2 (COX-2) and monocyte chemoattractant protein 1 (MCP-1) are observed in the serum and peritoneal fluid of patients with endometriosis. Abnormal levels of these inflammatory mediators are associated with dysfunction of inflammatory cells, including macrophages, mast cells and neutrophils. [2,3]

Macrophages, which are inflammatory cells recruited to endometrial lesions, exhibit proangiogenic effects and promote the growth of the ectopic endometrium. They activate the pro-inflammatory nuclear transcription factor kappa B (NF- κ B), which has an anti-apoptotic effect and induces endometrial cell proliferation, which promotes the development of endometriosis [2,4]. In the context of the NF- κ B pathway, increased expression of insulin-like growth factor 1 (IGF-1) and hepatocyte growth factor (HGF) has also been observed in the ectopic lesions and peritoneal fluid of patients with endometriosis, compared to women without endometriosis. These factors play a key role in the processes of invasion, proliferation and angiogenesis of endometrial lesions, contributing to the development and progression of endometriosis [5].

The interleukin IL-1 β can exacerbate pain, inflammation and endometrial cell proliferation. IL-1 β activates interleukin IL-6 and IL-8, which in turn stimulate inflammatory cells and promote angiogenesis in endometrial lesions. Furthermore, increased cyclooxygenase-2 (COX-2) expression in endometriosis is associated with an increase in prostaglandins, which play a key role in the occurrence of pain in this condition [2,6]. The aim of this study is to analyse the research on the anti-inflammatory effects of polyphenols, vitamin D and omega-3 fatty acids, and to evaluate their potential as future therapies for the treatment of endometriosis, considering their efficacy and possible clinical application.

CURRENT STATE OF KNOWLEDGE

1. Therapeutic potential of polyphenols in endometriosis

Polyphenols are a diverse group of chemical compounds synthesised by plants that are widely recognised for their antioxidant and anti-inflammatory properties. In the context of food, polyphenols are classified into six main groups: flavonoids, lignans, non-phenolic metabolites, phenolic acids, stilbenes and other polyphenols.

The health-promoting effects of polyphenols suggest their potential beneficial effects in the context of endometriosis. Preclinical and clinical studies have analysed the mechanisms of action of resveratrol and curcumin, among others. [7,8]

Resveratrol

Resveratrol is a natural phytoalexin polyphenol produced by plants. It occurs naturally in grapes, berries, legumes and grasses, among others.

In a study by Bruner-Tran et al. it was shown that resveratrol, depending on its concentration, can act as an agonist or antagonist of oestrogen receptors. At high concentrations, resveratrol shows an antagonistic effect on oestrogen receptors, resulting in reduced proliferation of human endometrial xenografts in a mouse model and reduced angiogenesis in endometrial lesions. [7-9,11]

An in vitro study by Kolahdouz-Mohammad et al. documented that resveratrol, at concentrations of 25, 50 and 100 $\mu\text{mol/L}$, exhibits an inhibitory effect on the expression of chemokine MCP-1, interleukin-6 (IL-6), interleukin-8 (IL-8) in ectopic endometrial stromal cells from women with endometriosis, which supports the anti-inflammatory effect of this polyphenol. [12]

Recent studies have shown that resveratrol has an inhibitory effect on the expression of IGF-1 and HGF. Both growth factors promote the growth of endometrial lesions and angiogenesis in these lesions. The effects were found in both ectopic and eutopic endometrial stromal cells from patients with endometriosis. [8,13]
The research team of Maia and colleagues conducted an evaluation of the potential beneficial

effect of combining resveratrol with oral contraceptives in the context of endometriosis-related pain. The study involved 12 patients who did not experience pain relief after treatment with an oral contraceptive containing drospirenone and ethinylestradiol. They were given an additional 30 mg of resveratrol for two months. The results showed that 82% of the patients reported complete resolution of dysmenorrhea and a significant reduction in pain intensity. In another study, after 42 days of administration of 40 mg/day of resveratrol in combination therapy with a monophasic oral contraceptive, no difference in pain was observed in female patients compared to the placebo group. [8,14,15]

Curcumin

Curcumin is a naturally occurring polyphenol present in turmeric (*Curcuma longa* L.). In a study by Vallée and Lecarpentier, curcumin was shown to exhibit anti-inflammatory effects by reducing the expression of inflammatory factors such as COX-2, TNF α and interleukin IL-1, IL-6 and IL-8 through inhibition of the NF- κ B pathway. In addition, curcumin exhibits antioxidant activity through inhibition of MAPK/ERK pathway signalling. [10,16]

The anti-inflammatory effects of curcumin have also been confirmed by inhibiting the expression of pro-inflammatory and pro-angiogenic chemokines and cytokines in eutopic endometrial cells in patients with endometriosis. [17] The study authors, however, emphasise the need for further clinical trials to confirm the therapeutic effect of resveratrol in the context of endometriosis. [7,8,10]

2. Therapeutic potential of vitamin D₃ in endometriosis

Studies in vitro and in animal models have shown that vitamin D₃ exerts anti-inflammatory effects by reducing pro-inflammatory cytokines, (such as interleukin-6 (IL-6), interleukin-17 (IL-17), interleukin-8 (IL-8)), COX-2 cyclooxygenase mRNA and reducing prostaglandin E2 (PGE2) activity. Vitamin D₃ and its metabolites reduce angiogenesis in endometrial lesions by reducing vascular endothelial growth factor-A (VEGF-A) and inhibiting the NF- κ B pathway. Furthermore, vitamin D₃ has been shown to inhibit the activity of matrix metalloproteinases (MMP-2 and MMP-9) and affect the Wnt/ β -catenin pathway, which may lead to inhibition of endometrial lesion invasion and proliferation [18,19].

Studies on the apoptotic effects of vitamin D₃ on endometrial cells are conflicting. A study by Miyashita et al. showed a pro-apoptotic effect of vitamin D₃ on endometrial cells, while a study by Rashidi et al., 2023, indicated inhibition of apoptosis in endometriosis [13,20]. Contradictory results were also obtained in clinical studies evaluating the effect of vitamin D₃ on endometriosis-related pain. In a study in which patients were given 50,000 IU of vitamin D₃ every 2 weeks for 12 weeks, a significant reduction in pain sensation was noted compared to the placebo group [21]. In contrast, a 6-month study in which patients were given 2,000 IU of vitamin D₃ daily showed no difference in pelvic pain sensation compared to the placebo group [22].

3. Therapeutic potential of omega-3 fatty acids in endometriosis

Omega-3 polyunsaturated acids (omega-3-PUFAs) are characterised by the presence of at least two double bonds. In the diet, they are mainly provided through oily fish, seed and vegetable oils. The main examples of omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). [22] Analyses of research findings suggest that a diet enriched in omega-3 fatty acids may be beneficial in reducing inflammation in patients with endometriosis. Studies in animal models have shown that omega-3 fatty acids can reduce levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor α (TNF- α) and reduce VEGF levels in the peritoneal fluid [19].

In in vivo studies, eicosapentaenoic acid (EPA) has been found to inhibit the conversion of arachidonic acid (AA) to pro-inflammatory prostaglandins E₂ (PGE₂) and leukotrienes B₄ (LTB₄), which may contribute to the relief of pelvic pain in patients with endometriosis. Furthermore, patients with higher levels of circulating EPA in serum are less likely to have endometriosis [22,23].

Studies by Tomio et al. and Attaman et al. indicate that supplementation with omega-3-PUFAs may lead to inhibition of endometrial cell proliferation and reduction of endometrial implants. This effect may be the result of a reduction in interleukin IL-6, cyclooxygenase COX-2 and the mitotic marker Ph-3 [19,16,24]. The authors emphasise the need for further clinical studies to evaluate the effect of omega-3 fatty acid supplementation on pain perception in patients [23,25].

SUMMARY

A review of the available literature has shown that polyphenols, vitamin D3 and omega-3 fatty acids show promising therapeutic properties in the treatment of endometriosis. Polyphenols, such as resveratrol and curcumin, have anti-inflammatory and antiproliferative effects, which may limit the growth and development of endometrial lesions. Vitamin D3 influences reducing inflammation and angiogenesis, although results on its effect on pain are mixed. Omega-3 fatty acids, especially EPA, reduce levels of pro-inflammatory cytokines and may alleviate pain and reduce endometrial cell proliferation. However, further clinical trials are needed to fully assess the efficacy of these therapies in clinical practice.

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Conceptualization, P.J. and P.Z.; **Methodology**, P.J. and M.R.; **Software** A.P.; **Check** A.S., P.J. and P.Z.; **Formal analysis** P.J. and A.P.; **Investigation** P.J.; **Resources** A.S. and D.O.; **Data storage**, D.O.; **Writing - rough preparation** P.J., P.Z. and M.R.; **Writing - review and editing**, A.S., D.O., D.O. and A.P.; **Visualization**, P.J.; **Supervision**, P.Z.; **Project administration**, M.R. and P.J.; **Receiving funding**, self-financed

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