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The effect of two anti-inflammatory dietary components, omega-3 and resveratrol, on endometriosis

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ABSTRACT

Endometriosis is an inflammatory condition defined by the presence of endometrial glands and stroma outside the uterine cavity. Given the substantial body of evidence supporting the role of inflammation in the pathophysiology of various chronic illnesses, the concept of an anti-inflammatory diet has garnered significant attention in recent research. Some nutrients, such as omega-3 fatty acids and resveratrol (RES), have demonstrated distinct anti-inflammatory properties. Therefore, the objective of this systematic review was to search the Embase, Medline, and PubMed databases for literature from August 2008 to August 2023 regarding the effects of two anti-inflammatory dietary components, omega-3 and RES, on endometriosis. A total of 215 records were identified, out of which 58 were screened, 23 met the eligibility criteria, and 19 were included in this review.

The results of this systematic review indicate that EPA is suggested to have anti-inflammatory properties and may serve as a potential marker for illness severity. RES offers a range of advantages, including inflammation reduction, angiogenesis suppression, proliferation inhibition, and apoptosis induction. To validate these findings and assess their clinical relevance, future research and clinical trials are warranted.

Keywords: endometriosis; resveratrol; omega-3; anti-inflammatory diet; pathogenesis; diagnosis; treatment

INTRODUCTION

The dietary pattern is a widely recognized environmental factor influencing physical well-being. Adopting healthy eating habits not only helps maintain a normal body weight but also lowers the risk of various diseases that can significantly impact health-related quality of life (QoL) [1]. Providing nourishment to the expanding global population with high-quality food presents a significant challenge, contributing to a notable rise in malnutrition, obesity, and related health conditions. Conversely, scientific literature provides insights into the potential utilization of specific dietary compounds to mitigate the severity of particular chronic illnesses and modify their clinical course. This raises the question of whether enriching diets with these compounds could be considered a potential therapeutic approach for certain conditions.

Given the extensive array of evidence supporting the involvement of inflammation in the pathophysiology of diverse chronic illnesses, the concept of an anti-inflammatory diet has attracted significant attention in recent research. While there is no unambiguous definition of this dietary pattern, some nutrients, including omega-3 fatty acids and resveratrol (RES), have been proven to possess distinct anti-inflammatory properties.

Endometriosis, a common, systemic, inflammatory condition defined as the presence of endometrial glands and stroma outside the uterine cavity, presents an opportunity for the potential utilization of the aforementioned substances in treatment [2]. According to the most widely accepted Sampson’s theory of retrograde menstruation, ectopic endometrial tissues provoke a localized inflammatory response [3], which stimulates cellular adhesion and proliferation with simultaneous vascularization and disruption of the protective immune response.

Omega-3 fatty acids are essential components found in fish oil, encompassing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), alongside alpha-linolenic acid (ALA) derived from plants. These components are not only key building blocks of cell membranes but also, due to their wide range of anti-inflammatory properties, scientifically proven to be beneficial in various diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus [4].

Other nutrient relevant to this topic is RES, which is a nonflavonoid polyphenol, naturally produced by plants in response to environmental stressors. It can be found in fruits such as berries and grapes, as well as in peanuts and red wine. This compound induces anti-inflammatory [5], antioxidant [6] and anti-carcinogenic molecule pathways [7]. The literature provides evidence of the beneficial effects of dietary polyphenol intake on the incidence of inflammatory pathologies.

The aim of this systematic review is to investigate the potential role of the anti-inflammatory dietary compounds – omega-3 fatty acids and RES — on endometriosis and their potential influence on its clinical severity.

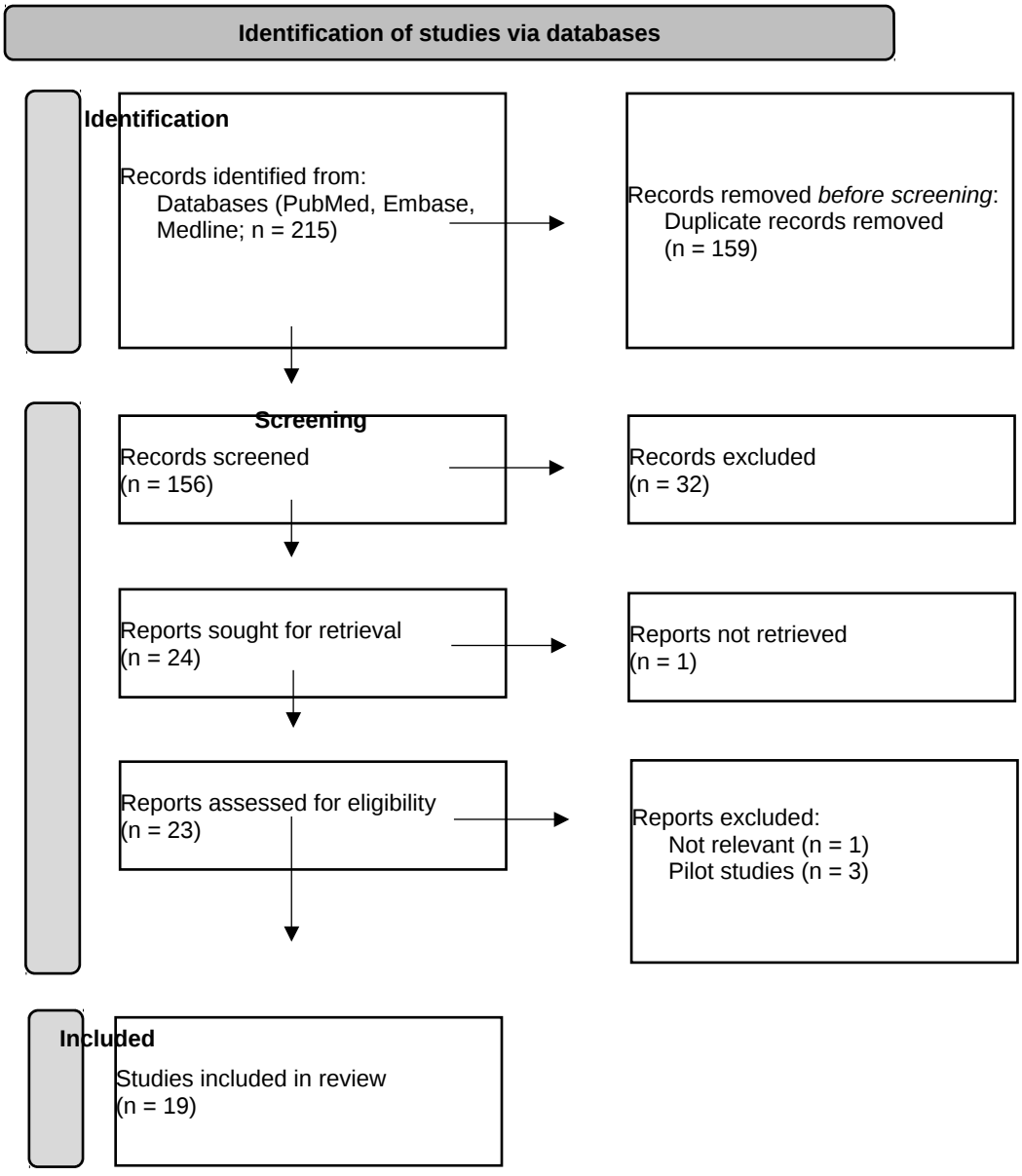

Figure 1. Flow diagram of the selection process of the studies

METHODS

Before initiating the specific literature search, the authors conducted a preliminary screening phase of anti-inflammatory dietary compounds' impact on endometriosis. Based on the highest prevalence, resveratrol and omega-3 were selected as the central focus of this review. The databases searched encompassed PubMed, Medline, and Embase. The search strategy employed terms such as "omega-3" OR "omega 3" OR "resveratrol*" AND "endometrios*" with a publication year limitation of 2008 to the present. The inclusion criteria comprised experimental studies (including human studies and endometriosis cell-cultured models) that investigated the effects of resveratrol and omega-3 on endometriosis. Only papers available in full-text and written in English were considered. Exclusion criteria included review papers, book chapters, abstracts, pre-prints, and editorials, and animal studies. The systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study selection process is depicted in Figure 1.

Figure 1. Flow diagram of the selection process of the studies

RESULTS AND DISCUSSION

Numerous studies have been undertaken to explore the impact of omega-3 and RES on the pathogenesis and treatment of endometriosis. Table 1 summarizes the main information extracted from the studies included in this review.

A variety of effects of polyunsaturated fatty acids (PUFAs) on the endometriosis have been demonstrated through recent studies. The omega-3 and omega-6 fatty acids are suggested to influence the active prostaglandins (PGE2) biosynthesis, leading to the alleviation of pelvic pain and inflammation severity. There are several diseases, such as rheumatoid arthritis, atherosclerosis and asthma, in which the studies have proven the positive effect of omega-3 PUFA dietary intake in alleviating inflammation [4].

In vivo studies — EPA's Anti-Inflammatory role in endometriosis management

Studies considered within this review have indicated a potential anti-inflammatory role of eicosapentaeonic acid (EPA) in endometriosis. EPA, a prominent omega-3 PUFA found in fish oil, exhibits inhibitory effects on the conversion of arachidonic acid (AA) into pro-inflammatory compounds like PGE2 and LTB4, which are associated with pelvic pain in endometriosis. EPA serves as a substrate in the synthesis of PGE3 and LTB5 compounds that exhibit reduced inflammatory activity compared to PGE2 and LTB4 [8].

A study by Hopeman M.M. et al. [9], involving women undergoing IVF, has shown a negative correlation between serum EPA levels and the diagnosis of endometriosis. Women with elevated serum EPA levels demonstrated a 82% reduction in the likelihood of being diagnosed with endometriosis compared to those with lower levels [9].

While both studies by Hopeman M.M. et al. and Khanaki K. et al. [9, 10] conclude that total serum PUFAs levels are not indicative markers for endometriosis, the latter study suggests a potentially significant role for the serum EPA to AA ratio as an indicator of disease severity. Taking into account the effectiveness of dietary interventions in elevating specific PUFA levels, these results, in conjunction with emerging evidence, strongly underscore the need for further research.

In vitro studies — Interplay of Omega-3 Fatty acids and inflammatory proteins in endometriosis

While the primary aim of PUFAs treatment is to reduce the inflammatory aspects of endometriosis symptoms, the omega-3 fatty acids intake can lead to increased levels of specific proteins: secretory phospholipase A2 type IIa (sPLA2IIa) and fatty acid-binding protein 4 (FABP4), both involved in inflammation [11, 12]. Acting as a regulatory enzyme, sPLA2IIa plays a pivotal role in the hydrolysis of PUFA, leading to the synthesis of eicosanoids and AA, precursors essential for PGE2 production [13]. Additionally, it contributes to vascular endothelial cell migration in the angiogenesis process associated with endometriosis [14]. On the other hand, literature findings also highlight the potential anti-inflammatory role of sPLA2IIa in repairing damage to membrane phospholipids induced by oxidative stress [15, 16].

In 2012 in their vitro study, Khanaki K et al. [17] demonstrated that fatty acids, especially those with a high omega-3 to omega-6 ratio, stimulate the secretion of cytokines by ectopic endometriotic cells, subsequently leading to elevated sPLA2IIa levels. Interestingly, they also observed reduced survival of eutopic endometriotic cells under high omega-6 fatty acid treatment. Building upon this, a subsequent study in 2014 by Khanaki K et al. [10] confirmed that omega-3 fatty acid intervention correlates with increased extracellular sPLA2IIa levels. In this investigation, they also observed a comparable effect of omega-3 fatty acid treatment on FABP4, resulting in elevated cellular levels [10]. FABP4 enhances sPLA2IIa activity by facilitating the transmembrane transport of lipid molecules [15].

Moreover, it's noteworthy that both sPLA2IIa and FABP4 are suggested to have the anti-tumorigenic effects through their antiproliferative or pro-apoptotic activities [18], presenting potential benefits for individuals with endometriosis. Both of those proteins seem to impact endometriosis through distinct mechanisms, some of which align partially with the positive effect of omega-3 PUFAs on endometriosis, while others may contradict these beneficial effects [10, 17]. While the primary objective of PUFA treatment remains the attenuation of inflammation in endometriosis, the intricate interplay of sPLA2IIa and FABP4 and their multifaceted effects warrant comprehensive exploration in future research.

Pain relief effects of Resveratrol and Omega-3 Intake

The endometriosis-associated pain is suggested to correlate with the inflammation induced by the release of neurotropic and neuroprotective cytokines following the activation of autonomic nervous system [19]. The potential anti-inflammatory properties of RES and omega-3 intake have prompted investigations into their impact on pain relief. Maia Jr. H et al. [20] have demonstrated promising results after 2 months of incorporating RES into the oral contraceptive treatment containing drosperidone. These findings included a notable reduction in pain scores and a remarkable 82% of patients achieving complete alleviation of pelvic pain and dysmenorrhea.

Nonetheless, the studies conducted by da Silva D.M. et al. [21] and Nodler J.L. et [22] have not demonstrated a significant difference in pain measurements between the studied and control groups, both at baseline and after the treatment duration. The improvements in mean Visual Analog Scale (VAS) scores nn both double-blinded, randomized, placebo-controlled studies were observed following interventions involving RES, omega-3 PUFAs, and placebos.

When considering collective findings from the studies included in this review, the existing evidence suggests that RES might play a role in reducing the growth of endometriotic tissue by affecting various mechanisms, encompassing inflammation, cell viability and apoptosis, proliferation, cell adhesion and invasion, angiogenesis, and lipid metabolism (Tab. 2).

Role of resveratrol in inflammation

Inflammation, oxidative stress and immunological changes are believed to contribute to the development of endometriosis [23, 24]. The literature supports that increased levels of reactive oxygen species (ROS) and pro-inflammatory cytokines are found within the peritoneal fluid of endometriosis patients [25]. In a study by Kolahdouz-Mohammadi et al., RES was shown to reduce the expression of MCP-1, IL-6, IL-8 and RANTES in EcESCs [26]. The presumed mechanism underlying RES's impact on these pro-inflammatory factors involves the regulation of pathways linked to oxidative stress, inflammation, cyclooxygenase-2 (COX-2), and Sirtuin 1 (Sirt1) [26].

Furthermore, in a non-randomized open-label study by Maia et al. [20], patients receiving a combined oral contraceptive pill supplemented with 30 mg/day of RES for two months exhibited decreased COX-2 expression. Increased COX-2 was previously found to regulate survival and invasion of ESCs in humans and its inhibition was able to prevent establishment and maintenance of endometriosis in animal studies.

Another inflammation-associated molecule influenced by RES is Sirt1, which was observed to increase in human endometriotic and endometrial tissue in a 3D culture upon RES incubation in a study by Khazaei et al. [27]. RES-induced activation of Sirt1 notably suppressed TNF-α-induced IL-8 release from ESCs. Conversely, inhibition of Sirt1 by sirtinol, a Sirt1 inhibitor, enhanced IL-8 secretion [28]. Sirt1 is recognized for its ability to inhibit NF-κB activity, consequently reducing the production of inflammatory cytokines.

These findings highlight RES's potential to counteract inflammation, oxidative stress, and cytokine dysregulation, which are integral to endometriosis pathogenesis. By targeting key molecular pathways, such as COX-2 and Sirt1, RES holds promise as a therapeutic agent in endometriosis management.

Role of resveratrol in cell viability and apoptosis

The studies included in this review have demonstrated that RES has the ability to decrease the cell viability of both ectopic (EcESCs) and eutopic (EuESCs) endometrial stromal cells derived from endometriotic lesions from patients [29–31]. Notably, the effect of RES varied between these two cell types, with EcESCs showing greater susceptibility to its cytotoxicity [31]. RES induced apoptosis, as evidenced by morphological changes and increased expression of genes associated with apoptosis, including P53, Bax, Bcl2 and caspase-3 [27, 29, 30, 32]. Conversely, the research conducted by Taguchi et al. demonstrated that RES alone did not induce apoptosis in ESCs. However, it did reduce the expression of survivin mRNA [33]. Survivin is a molecule that is known to contribute to preventing apoptosis in endometriosis, therefore it could be inferred that RES, which was shown to suppress survivin expression, holds potential as a treatment option for endometriosis. In conclusion, the studies examined in this review highlight the ability of RES to induce apoptosis through various molecular mechanisms, suggesting its potential as a therapeutic intervention targeting the aberrant growth of endometriotic tissue.

Role of resveratrol in cell proliferation

The effect of RES on cell proliferation is also noteworthy. RES has been observed to diminish the proliferation capacity while decreasing the gene and protein expressions of IGF-1 and HGF in both EuESCs and EcESCs. [31, 32, 34]. Notably, Arablou et al.'s study highlighted a more pronounced effect on EcESCs compared to normal ESCs and EuESCs [31]. This difference could potentially be attributed to variations in inflammatory conditions and microenvironments of these cells.

In the context of literature, IGF-1, particularly released from EcESCs, monocytes, and macrophages, is recognized to prevent apoptosis and promote proliferation by suppressing activation of multiple IGF-1 signaling pathways [35]. Conversely, HGF, a pivotal growth factor linked to endometriosis, is secreted by mesenchymal cells, macrophages, and EcESCs, and has been shown to increase the growth of endometriotic lesions [36]. RES's suppressive effect on IGF-1 and HGF expression is likely mediated through the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase pathways, both integral to inflammatory responses.

Furthermore, RES treatment led to the downregulation of two additional molecules, MTA1 and ZEB2. MTA1, an oncogene implicated in various cancers, promotes epithelial-mesenchymal transition in epithelial cells [37]. Considering the parallels between endometriosis and cancer traits, Kong et al. investigated MTA1's role in endometriosis and found that RES-induced reduction in MTA1 expression inhibited cell proliferation [34]. This process was reversed by MTA1 overexpression. Moreover, RES was shown to counteract EMT triggered by MTA1-ZEB2 in endometrial cells, suggesting MTA1 as a target of RES. RES exerts a multifaceted influence on cell proliferation, involving the modulation of key molecules such as IGF-1, HGF, MTA1, and ZEB2. These findings highlight RES's potential as a targeted strategy for curbing abnormal cellular growth in endometriosis. The intricate interplay between RES and these molecular pathways underscores its promising role in addressing the complex pathogenesis of this condition.

Role of resveratrol in angiogenesis

It is widely acknowledged that angiogenesis, the process of new blood vessel formation, plays a pivotal role in the advancement of endometriosis. According to the findings from studies encompassed in this review, RES demonstrates anti-angiogenic properties by influencing the expression of genes associated with angiogenesis. Specifically, it downregulates the expression of MMP-2 and -9, enzymes implicated in tissue remodelling and angiogenesis, while concurrently upregulating the expression of TIMP-1, an inhibitor of MMP-2. Additionally, RES was found to downregulate the expression of VEGF, Ang-1, and TGF-β [23, 24, 38]. The mechanisms underlying RES's effects on VEGF, TGF-β, and MMP-9 are not fully elucidated, but evidence points to the inhibition of the NF-κB pathway, among other potential mechanisms [39].

LIMITATIONS

There are several limitations of the studies exploring the role of RES and omega-3 in endometriosis, which affect the overall reliability of the research conclusions.

The most important limitation is the scarcity of clinical trials. Among the 14 papers included in this review, merely two were randomized, double-blind, placebo-controlled clinical trials and one was a non-randomized open-label study. This represents a notable limitation. While laboratory studies provide valuable insight into the mechanistic aspects of interventions like RES in endometriosis, their controlled environment does not fully mirror the complexity of endometriosis. Clinical trials offer a more comprehensive way of evaluating the efficacy, and safety of interventions like RES. Despite our deliberate focus on studies conducted with human cells to enhance relevance and applicability, the predominance of laboratory studies limits the direct translation of the findings into clinical setting and restricts our ability to draw robust conclusions in terms of treatment strategies for endometriosis.

Another noteworthy limitation is the variety of RES concentrations used across the studies included in this review. Most studies used a concentration of 100 μM of RES, which is considerably higher than what we could expect to be found in the bloodstream after oral consumption of RES. This raises concerns about the translatability of the results to clinical scenarios. While RES is generally regarded as safe, its use at concentrations like 100 μM could increase the likelihood of adverse effects. Furthermore, the individual variability in

how people respond to RES introduces an additional layer of complexity, potentially impacting the consistency of the outcomes.

It's important to recognize the complex nature of pain and the potential for recall bias in the studies measuring it. It highlights the need for a comprehensive and holistic approach to interpreting the implications of these studies. While the current evidence does not conclusively establish a significant difference in pain relief, the observed trends warrant further investigation into the nuanced relationship between resveratrol, omega-3 intake, and pain management.

CONCLUSIONS

Omega-3 fatty acids, EPA, and RES hold potential as therapeutic options for patients with endometriosis. EPA is suggested to be an anti-inflammatory factor and a possible marker for illness severity, while RES offers diverse advantages, including reducing inflammation, suppressing angiogenesis, inhibiting proliferation, and inducing apoptosis. While RES has shown promise in alleviating endometriosis-related pain, the outcomes of studies on omega-3 and RES in this area have been inconsistent. Although this systematic review has revealed a statistically significant impact of the studied molecules on vital pathogenetic processes associated with the development of endometriosis, the clinical utility of these findings remains uncertain. Considering the complexity of endometriosis and the aforementioned limitations of reviewed studies, further research and clinical trials are required to thoroughly evaluate the safety and effectiveness of these anti-inflammatory nutrient dietary supplements as therapeutic tools.

Table 1. Summary of the main findings extracted from the studies included in this review

Authors, year	Study design	Sample size	Dosage/ intervention/ duration	Outcome	Results	p value
Omega-3						
Nodler J.L. et al., 2020 [22]	Double-blind, randomized, placebo controlled, mulitiarm parallel study	n = 69 VAS score ≥ 3 for their worst pain in the preceding month	- 6 m of receiving 2000 IU vit. D3 (n = 27), 1000 mg fish oil (720 omega-3, including 488 mg EPA and 178 mg DHA)(n = 20) or placebo (n = 22) daily	- primary: pain measure with VAS - secondary: quality of life (SF-12)	- mean VAS scores improving from baseline to 6 m in the placebo: 6.0 to 4.4** and fish oil: 5.9 to 5.2*** - no consistent patterns in changes in physical or mental quality of life (SF-12) - improvement in catastrophic thinking score (all 3 study arms), with a statistically significant mean score only in the vitamin D arm	**p = 0.07 ***p = 0.39
Hopeman M.M. et al., 2015 [9]	Cross-sectional study	n = 205 (24 with endometriosis)	PUFA's analysis in serum extracted from the whole blood, collected the morning of oocyte retrieval after COH	associations between serum PUFAs and endometriosis	- no association between total PUFAs, total n-3 PUFAs, or total n-6 PUFAs and endometriosis - lower serum levels of EPA (1.6 × 10−2 ± 0.006) in women with a previous diagnosis of endometriosis than women without the diagnosis (2.0 × 10−2 ± 0.01)* - women with the highest serum EPA levels were 82% less likely to have a diagnosis of endometriosis compared to women with the lowest levels (95% CI)	*p=.009
Khanaki K. et al., 2014 [10]	Experimental study	EcESCs and EuESCs (n = 15)	- 8 days incubation - culture media: balanced ω-3/ω-6, high ω-3 and high ω-6 PUFAs ratio	sPLA2IIa and FABP4	- EcESCs: increased FABP4 level in high ω-3:ω-6 group (260.35%±77.33% of control value*), balanced (187.04%±46.49 %) and high ω-6:ω-3 group (224.99%±80.92%); sPLA2IIa level increased in high ω-3 group (139.3%±17.411 %**) - EuESCs: FABP4 level was similar in each of groups; increased SPLA2IIa in both ω-3:ω-6 and ω-6:ω-3 PUFAs ratio (114.56%±9.4% and 127.28%±23.4%**)	*p =.014 **p < 0.05
Khanaki K. et al., 2012	Cross-sectional study	n = 138 (64 with endometriosis)	phospholipid extraction from the blood serum samples	Fatty acid composition of the phospholipid fraction	- no significant differences in the level of serum total phospholipid fatty acids, except stearic acid (12.46 ± 2.29*) - only EPA/AA ratio showed a direct correlation with severity of the disease	*p = 0.030 **p = 0.006
Khanaki K. et al., 2012	Experimental study	EcESCs and EuESCs (n = 15)	- 8 days incubation - culture media: balanced ω-3/ω-6, high ω-3 and high ω-6 PUFAs ratio	- cell survival - sPLA2IIa	- survival did not show significant differences between EcESCs and EuESCs - EuESCs: decreased cell survival after high ω-6 intervention* - EcESCs: increased sPLA2IIa level after each of three PUFAs treatments (balanced*, high ω-3** and high ω- 6*)	*p < 0.05 **p < 0.01
Resveratrol						
Golabek-Grenda A. et al., 2023 [29]	Experimental laboratory study	EECs and ESCs	- 48 h incubation - 50/100 µM RES	- Cell viability (MTT assay) - Microscopic detection of cell apoptosis - Apoptosis (Annexin-V/PI staining assay) - DNA fragmentation (TUNEL assay) - Caspase-3/7 activity	- Decreased cell viability: IC10 = 8.99 ± 4.29* (µM), IC50 = 49.32 ± 11.4* (µM) - Morphological apoptosis of cells - Dose-dependent decrease in the population of live cells - Dose-dependent DNA fragmentation (at 100 µM TUNEL-positive cells = 42.8%**) - Dose-dependent caspase-3/7 activation in cells (at 100 µM, 10.3-fold increase**)	*p < 0.05 **p < 0.001

Authors, year	Study design	Sample size	Dosage/ intervention/ duration	Outcome	Results	p value
Madanes D. et al., 2022 [30]	Experimental laboratory study	EECs and ESCs	- 24 and 48 h incubation - 50 and 100 μM RES	- Cell viability (MTT assay) - Apoptosis (FITC Annexin V assay) - Caspase-3 cleavage - Cell migration (wound healing assay) - Gene expression of angiogenesis-related genes and stem cell phenotype markers	- Decreased cell viability after 48h of treatment, but not after 24h: at 50 μM and 100 μM, 58 ± 6.6%* and 45.4 ± 6.2%**, respectively - Decreased cell migration - Increased number of apoptotic cells: at 50 μM and 100 μM, 165 ± 29,9%^ and 327,9 ± 86,1%, respectively - Increased caspase-3 levels: at 50 μM and 100 μM, 447.4 ± 91.4%' and 725.7 ± 208.7%'', respectively - Reduced expression of angiogenesis-related genes (MMP-2, VEGF, Ang-1) - Increased expression of stem cell phenotype markers (Notch-1, OCT-4, KLF-4, Snail-1, SOX-2, TERT, and Vimentin)	*P = 0.0180 **P < 0.001 ^P = 0.0450 ^^P = 0.0059 'P = 0.0440 ''P = 0.0026
Chen Z. et al., 2021 [32]	Experimental laboratory study	EcESCs from n = 8 patients	- 48h incubation - 100 μM and 40 μM RES	- Cell proliferation (BioTek) - Cell invasiveness assay - Cell apoptosis assay - PPARα expression	- Decreased proliferation capacity: 36.30%* and 57.78%** at 40 μM and 100 μM, respectively - Decreased invasiveness: 35.00%* and 61.72%** at 40 μM and 100 μM, respectively - Increased proportion of early apoptosis: 25.00%* and 29.58%* at 40 μM and 100 μM, respectively - Increased expression of PPARα	*p < 0.01 **p < 0.0001
Arablou T. et al., 2021 [23]	Experimental laboratory study	EuESCs, n = 13; EcESCs, n = 8; CESCs, n = 11	- 6, 24 and 48h incubation - 100 μM RES	- Gene and protein expression levels of VEGF, TGF-β, and MMP-9	- Decreased VEGF and MMP-9 expression in EuESCs, EcESCs and CESCs* and TGF-β gene and protein expression in EcESCs and EuESCs	*p < 0.0–0.01 and p < 0.05–0.01 respectively **P < 0.0–0.01
Khodarahmian M. et al., 2021 [24]	Placebo-controlled, parallel, randomized, double-blind exploratory clinical trial	patients, n = 34; treatment (n = 17) and control (n = 17) groups	- RES and placebo (400 mg) for 12–14 weeks, respectively	- Endometrial tissue collection from both groups before and after the intervention in the mid-secretory phase - Gene and protein expression levels of VEGF and TNF-α	- Decreased VEGF protein levels in the treatment group when compared with before RES* and with the control group** - Decreased TNF-α protein levels in the treatment group when compared with before RES^ and with the control group^^	*p = 0.016 **p = 0.012 ^p = 0.011 ^^p = 0.19
Kolahdouz-Mohammadi R. et al., 2021 [26]	Experimental laboratory study	EuESCs, n = 13; EcESCs, n = 9 from n = 11 patients, CESCs	- 6, 24 and 48 h incubation - 100 μM RES	- Gene and protein expression levels of MCP-1, IL-6, IL-8 and RANTES	– Decreased MCP-1, IL-6, and IL-8 gene and protein expression in EuESCs and EcESCs compared with CESCs* – Decreased RANTES protein expression in EcESCs**	*P < 0.05–0.001, P < 0.05–0.001 and P < 0.05–0.01, respectively **P < 0.05
Khazaei M.R. et al., 2020 [27]	Experimental laboratory study	human endometriotic and endometrial tissue in 3D culture	- 21 days incubation - 0 (control), 10, 50, 100 and 200 μM RES	- Tissue growth - Angiogenesis - NO secretion - Gene expression levels of apoptotic genes (P53, Bax, Bcl2 and caspase 3) and Sirt1	- Dose dependent inhibition of growth scores in both tissues* - 200 μM concentration completely inhibited growth and angiogenesis in both tissues - Dose dependent decrease in NO production at 100 and 200 μM of RES* - Increased expression of P53, Bax, caspase 3 and Sirt1 in both tissues*	*P < 0.05
Kong X. et al., 2020 [34]	Experimental laboratory study	EcESCs from n = 33 patients, CESCs from n = 20 normal samples	- 25 and 50 μM RES	- Cell proliferation (CCK-8 and colony formation assay) - Cell migration (wound assay) - Cell invasion (transwell assay) - Cell transfection with downregulated / overexpressed plasmid of MTA1 - MTA1 and ZEB2 expression levels	- Suppressed proliferation*, migration* and invasion* in EcESCs after RES - Reduced MTA1 and vimentin and increased E-cadherin expression in EcESCs after RES, reversed by transfection of pCDH-MTA1* - Reduced expression of ZEB2 in EcESCs after RES, reversed by MTA1 overexpression*	*P < 0.01
Kodarahmian M. et al., 2019 [38]	Placebo-controlled, parallel, randomized, double-blind exploratory clinical trial	endometriosis patients (n = 34): treatment (i = 17) and control (n = 17) groups	- RES and placebo (400 mg) for 12–14 weeks, respectively	- Endometrial tissue, fluid and blood sample collection from both groups before and after the intervention - MMP-2 and -9 gene	- Decreased MMP-2 and -9 mRNA* and protein** levels in the endometrial tissue and fluid of treatment group after RES compared to control group - Decreased MMP-2 and -9 mRNA and protein levels in serum and endometrial fluid after surgical removal of	*P < 0.05 **P < 0.001 ***P < 0.01

Authors, year	Study design	Sample size	Dosage/ intervention/ duration	Outcome	Results	p value
				and protein expression levels	endometriotic lesions***	
Arablou T. et al., 2019 [31]	Experimental laboratory study	EcESCs and EuESCs from n = 40 patients, CESCs from n = 15 normal samples	- 6, 24 and 48 h incubation - 100 µM RES	- Cell viability (MTT assay) - IGF-1 and HGR gene and protein expression levels	- Decreased cell viability at 200 and 400 µM RES at 48 h to about 50% and 5%, respectively - Basal expression levels of IGF-1 and HGF higher in the EcESCs compared with EuESCs and CESCs* - Decreased gene expression of IGF-1 by 100 µM RES in EuESCs at 24 and 48 h, in EcESCs at 6, 24, and 48 h, and in CESCs only at 48 h* - Decreased gene expression of HGF by 100 µM RES in EuESCs and EcESCs at 24 and 48 h and in NESCs at 48 h* - Decreased IGF-1** and HGF* protein production by 100 µM RES in EuESCs and EcESCs at 48 h - Reduction of IGF-1 and HGF expression more evident in EcESCs compared with CESCs and EuESCs	*P < 0.05 **P < 0.01
da Silva D.M. et al., 2017 [21]	Randomized, double-blind, placebo-controlled clinical trial	n = 44 (treatment n = 22, control group n=22)	- 40 mg/d RES with COC (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) and COC with placebo - 42 days of treatment	- primary: VAS scale for pain scores at day 42 - secondary: CA-124 and prolactin	- Day 0: mean (95% CI) pain scores 5.4 (4.2 to 6.6) in the placebo group and 5.7 (4.8 to 6.6) in RES groups. - Day 42: pain scores 3.9 (2.2 to 5); n = 22 and 3.2 (2.1 to 4.3); n = 22 in the placebo and RES groups, respectively* - Median (95% CI) difference between groups was 0.75 (−1.6 to 2.3)	*P = 0.7
Taguchi A. et al., 2016 [33]	Experimental laboratory study	ESCs	- 24 h incubation - RES (unknown concentration)	- Cell apoptosis (annexin V–PI staining) - Survivin mRNA expression - TRAIL-induced apoptosis	- RES alone did not induce apoptosis in ESCs (proportion of apoptotic cells to total cells 5.03±0.52% in control and 6.25 ± 1.55% in treatment*) - RES reduced survivin mRNA expression (10% ± 5.7%**) - Enhanced TRAIL-induced apoptosis (8.13 ± 0.83% (control) vs 29.19 ± 7.39% (pre-treated with RES)**	*P > 0.05 **P < 0.05
Taguchi A. et al., 2014 [40]	Experimental laboratory study	ESCs and CESs from n = 5 patients	- 24 h incubation - 0, 20 and 40 µM RES or sirtinol	- SIRT1 expression -TNF-α-induced IL-8 release (mRNA and protein expression)	- SIRT1 expression in ESC and CES, without difference in expression between those cells - Dose-dependent suppression of IL-8 mRNA and protein expression in ESC after RES in the presence and in the absence of TNF-α stimulation* - Enhanced IL-8 secretion from ESC after sirtinol only in the absence of TNF-α	*P < 0.05
Maia Jr. H. et al., 2012 [20]	Non-randomized open-label study	First arm, n = 12 Second arm, n = 42 (treatment n=26, control group n= 16)	- 30 mg/d RES with COC (drospirenone 3 mg + ethinylestradiol 30 µg) and COC with placebo - First arm: 6m of COC alone, then 2m of COC + RES - Second arm: 2 m treatment	- First arm: Pain scores on a 0-3-point scale - Second arm: Aromatase and COX-2 expression in eutopic endometrium rated as positive/negative and on a 0-3 scale, respectively	- Day 0: mean pain score 3 - After COC: 2.1 ± 0.5 (mean ± SD) - After COC + RES: 0.2 ± 0.4 (mean ± SD) - 82% of the patients reporting complete resolution of dysmenorrhea and pelvic pain - Decreased aromatase expression in the eutopic endometrium in treatment group compared with control (% of positive aromatase, treatment group 5/26 (19%)*, control 11/16 (68%); mean COX-2 scores, treatment group 0.9 ± 0.8**, control 2.3 ± 0.7) - Decreased COX-2 expression	*P = 0.0013 **P < 0.0001

Ang-1 — Angiopoietin-1; Bax — Bcl-2-associated X protein; Bcl2 — B-cell lymphoma 2; CA-125 — Cancer antigen 125; CCK-8 — Cell Counting Kit-8; CESCs — Control endometrial stromal cells; CI — Confidence interval; COC — Combined oral contraceptive pill; COH — Controlled Ovarian Hyperstimulation; DHA — Docosahexaenoic Acid; DF-12 — Deficiency of Folate-12; EcESCs — Ectopic endometrial stromal cells; EECs — Endometriotic epithelial cells; EPA — Eicosapentaenoic Acid; ESCs — Endometrial stromal cells; EuESCs — Eutopic endometrial stromal cells; FITC — Fluorescein isothiocyanate; FABP4 — Fatty Acid-Binding Protein 4; H — Hour; HGF — Hepatocyte growth factor; IGF-1 — Insulin-like growth factor 1; IL-6 — Interleukin-6; IL-8 — Interleukin-8; KLF-4 —

Krüppel-like factor 4; m — Month; MCP-1 — Monocyte chemoattractant protein-1; MMP-2 — Matrix metalloproteinase-2; MMP-9 — Matrix metalloproteinase-9; MTA1 — Metastasis-associated protein 1; MTT — 3-(4 —5-Dimethylthiazol-2-yl)-2 —5-diphenyltetrazolium bromide; NO — Nitric oxide; Notch-1 — Notch receptor 1; OCT-4 — Octamer-binding transcription factor 4; P53 — Tumor protein 53; PPARα — Peroxisome proliferator-activated receptor alpha; RANTES — Regulated on Activation — Normal T Expressed and Secreted; RES — Resveratrol; Sirt1 — Sirtuin 1; SIRT1 — Silent Information Regulator 1; Snail-1 — Snail family transcriptional repressor 1; SOX-2 — Sex-determining region Y-box 2; TERT — Telomerase reverse transcriptase; TGF-β — Transforming growth factor beta; TNF-α — Tumor necrosis factor-alpha; TRAIL — Tumor necrosis factor-related apoptosis-inducing ligand; TUNEL — Terminal deoxynucleotidyl transferase dUTP nick-end labeling; VAS — Visual analogue scale; VEGF — Vascular endothelial growth factor; ZEB2 — Zinc finger E-box binding homeobox 2; COX-2 — Cyclooxygenase-2

Table 2. Molecular mechanisms of resveratrol

	Molecular changes	References
Apoptosis	↑ caspase 3	)
	↑ caspase 7	[29]
	↑ P53	[27]
	↑ Bax	[27]
	↓ Survivin	[33]
	↑ Morphological apoptosis	[29]
	↑ DNA fragmentation	[29]
	↑ Early apoptosis	[32]
	↑ TRAIL-induced apoptosis	[33]
Proliferation	↓ IGF-1	[31]
	↓ HGF	[31]
	↓ MTA 1	[34]
	↓ proliferation rate	[32, 34]
Angiogenesis	↓ MMP-2	[30, 38]
	↓ MMP-9	[23, 38]
	↓ VEGF	[23, 24, 30]
	↓ Ang-1	[30]
	↓ NO	[27]
	↓ IGF-1	[31]
	↓ HGF	[31]
	↓ TGF-β	[23]
Inflammation	↓ TNF-α	[24]
	↓ MCP-1	[26]
	↓ IL-6	[26]
	↓ IL-8	[26, 40]
	↓ RANTES	[26]
	↑ SIRT-1	[27]
	↓ COX-2	[20]
Cell adhesion and invasion	↓ ZEB2	[34]
	↓ vimentin	[34]
	↑ E-cadherin	[34]
	↓ MTA 1	[34]
	↓ epithelial–mesenchymal transition	[34]
	↓ IGF-1	[31]
	↓ HGF	[31]
	↓ MMP-2	[30, 38]
	↓ MMP-9	[23, 38]
Lipid metabolism	↑ PPARα	[32]

Ang-1 — Angiopoietin-1; Bax — Bcl-2-associated X protein; COX-2 — Cyclooxygenase-2; HGF — Hepatocyte growth factor; IGF-1 — Insulin-like growth factor 1; IL-6 — Interleukin-6; IL-8 — Interleukin-8; MCP-1 — Monocyte chemoattractant protein-1; MMP-2 — Matrix metalloproteinase-2; MMP-9 — Matrix metalloproteinase-9; MTA 1 — Metastasis-associated protein 1; NO — Nitric oxide; P53 — Tumor protein 53; PPARα — Peroxisome proliferator-activated receptor alpha; RANTES — Regulated on Activation — Normal T Expressed and Secreted; SIRT-1 — Sirtuin 1; TGF-β — Transforming growth factor beta; TNF-α — Tumor necrosis factor-alpha; TRAIL-induced apoptosis — TRAIL-induced apoptosis; ZEB2 — Zinc finger E-box binding homeobox 2

Article information and declarations

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