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REVIEW

Review of the Potential Therapeutic Effects and Molecular Mechanisms of Resveratrol on Endometriosis

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Abstract: Endometriosis is a hormone-dependent inflammatory disease characterized by the existence of endometrial tissues outside the uterine cavity. Pharmacotherapy and surgery are the current dominant management options for endometriosis. The greater incidence of recurrence and reoperation after surgical treatment as well as the adverse effects of medical approaches predispose patients to potential limitations for their long-term usage. Consequently, it is essential to explore novel supplementary and alternative drugs to ameliorate the therapeutic outcomes of endometriotic patients. Resveratrol is a phenolic compound that has attracted increasing interest from many researchers due to its pleiotropic biological activities. Here, we review the possible therapeutic efficacies and molecular mechanisms of resveratrol against endometriosis based on in vitro, animal, and clinical studies. The potential mechanisms of resveratrol include anti-proliferative, pro-apoptotic, anti-angiogenic, anti-oxidative stress, anti-invasive and anti-adhesive effects, thereby suggesting that resveratrol is a promising candidate for endometriosis. Because most studies have investigated the effectiveness of resveratrol on endometriosis via in vitro trials and/or experimental animal models, further high-quality clinical trials should be undertaken to comprehensively estimate the clinical application feasibility of resveratrol on endometriosis.

Keywords: endometriosis, resveratrol, therapeutic efficacies, molecular mechanisms, clinical application

Introduction

Endometriosis (EMS), a hormone-dependent gynecological inflammatory disease, is defined as the endometrium, including both stroma and glands, presenting at the extrauterine sites, mostly involving pelvic organs and peritoneum.[1] It may also affect external pelvic organs and even the central and peripheral nervous systems.[1] Endometriosis affects 10% of women of reproductive age.[2] Approximately 30–80% of women with this disease experience pelvic pain, and 30–40% of women are accompanied by infertility, representing the two major clinical symptoms.[3,4] In addition to the aforementioned symptoms and phenomena, endometriosis also has adverse effects on the quality of life, such as sleep quality, physical and psychological well-being, sexual function, and interpersonal relationships, resulting in a large economic burden to individuals, the healthcare system, and society.[5,6] Furthermore, some studies have reported that endometriosis is closely correlated with the elevated incidence rate of endometrial and ovarian malignant tumors, which may be implicated as a precursor to epithelial ovarian cancer and may have a tumor-promoting effect on ovarian cancer.[7,8]

At present, pharmacotherapy and surgical resection are the main therapeutic approaches for endometriosis. Pharmacotherapy mainly consists of hormone therapies that induce hypoestrogenism or antagonize estrogen effects,

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such as progestines (including the levonorgestrel-releasing intrauterine system (LNG-IUS), dienogest and medroxyprogesterone acetate), combined oral contraceptive pills (COCs), aromatase inhibitors, danazol, gestrinone, gonadotropin-releasing hormone agonist (GnRH-a) and GnRH antagonist (GnRH-ant), selective estrogen/progestogen receptor modulators (SERMs/SPRMs), and nonhormone therapy for alleviating endometriosis-related pain, such as nonsteroidal anti-inflammatory drugs (NSAIDs).[9] However, the efficacies of conventional medications are limited or discontinuous in the majority of patients, as long-term usage of these drugs will bring about perimenopausal symptoms, breakthrough bleeding and osteoporosis due to the hypoestrogenic status, as well as other adverse effects such as thrombosis, and liver function damage.[10,11] Although surgical management aims to completely destroy or remove visible ectopic lesions, restore normal anatomy, alleviate pain, and ameliorate infertility,[12] the recurrence rate and reoperation rate of endometriosis after surgery are relatively high. It has been shown that the incidence of disease relapse is 21.5% within 2 years after surgery, and 40–50% within 5 years,[13] and the reoperation rate is 27–58%.[13,14] Surgery combined with hormonal maintenance treatment reduces the risk of disease recurrence,[13] but hormonal treatment inhibits follicular development and ovulation, which opposes reproductive requirements in some patients. In recent years, several emerging nonhormonal therapeutic strategies, such as dopamine agonists and bentamapimod, have achieved prospective outcomes and may become complementary treatment options for endometriosis.[15]

Due to the limitations of existing therapeutic strategies, it is necessary to exploit new supplementary and alternative drugs to improve the treatments of endometriosis. In the past few decades, natural compounds mainly obtained from herbs have been increasingly studied. Natural compounds have potential advantages over synthetic drugs that are developed via target-based assays in terms of tolerance, side effects, and cost-effectiveness, promising to be new therapeutic options for endometriosis. Among them, resveratrol has attracted tremendous attention due to its wide range of biological activities, including anti-neoplastic, anti-oxidant, anti-angiogenic, anti-proliferative, anti-inflammatory, antiglycosylated, antiaging, and pro-apoptotic activities.[16–21] Resveratrol (3,5,4′-trihydroxysilbene) is a natural dietary phytochemical mainly found in beans, peanuts, wine, tea, and some fruits,[22–25] and it is also found in several microorganisms, such as Botulinum, Penicillium and Cephalosporium.[26] Structurally, resveratrol belongs to phenols, existing as cis- or trans-isomers, and it is composed of two aromatic rings linked by an ethylene bridge. Trans-resveratrol can be isomerized into cis-resveratrol when exposed to heat, light, or ultraviolet radiation, of which trans-resveratrol is the major natural form,[27,28] and the biological activities of trans-resveratrol are more significant than cis-resveratrol.[29,30] Resveratrol has been confirmed to have pleiotropic properties that significantly depend on its structures, including hydroxyl groups, hydrogen bonds and double bonds.[31] Some researchers have indicated the possible mechanisms by which resveratrol treats cancers, thereby decreasing the incidence rate and inhibiting the development of diseases. Thus, resveratrol is considered a prospective agent for the treatment of various malignant tumors, such as cervical cancer, breast cancer, liver cancer, pancreatic cancer, colorectal cancer and prostate cancer.[17,32–35] Other biological activities of resveratrol have also been reported, including cardioprotective, vasorelaxant, phytoestrogenic and neuroprotective activities.[36–39]

Based on the available in vitro, in vivo, and clinical studies as well as the pathology and pathogenesis of endometriosis, this review generalizes the efficacies of resveratrol against endometriosis and its possible molecular mechanisms, highlighting the underlying efficacy of resveratrol in the treatment of endometriosis. This review also provides a comprehensive overview of the theoretical foundation of resveratrol in clinical trials for endometriosis (Figure 1, Table 1).

Pathogenesis of Endometriosis

Despite research efforts and extensive investigations, the unequivocal etiologies and pathogenesis of endometriosis remain elusive. Currently, several hypotheses have been proposed for endometriosis to illustrate the pathological mechanism as follows: retrograde menstruation, lymphatic and hematogenous dissemination, peritoneal metaplasia, activation of Mullerian residues, and cellular immunity.[40,41] However, none of these theories comprehensively accounts for the mechanism and the different biological and clinical characteristics of endometriosis alone. According to literature, the formation and maintenance of ectopic endometrial lesions at ectopic sites are the most basic characteristics of endometriosis and are strongly correlated with the pathology and pathogenesis, such as inflammation, oxidative stress,

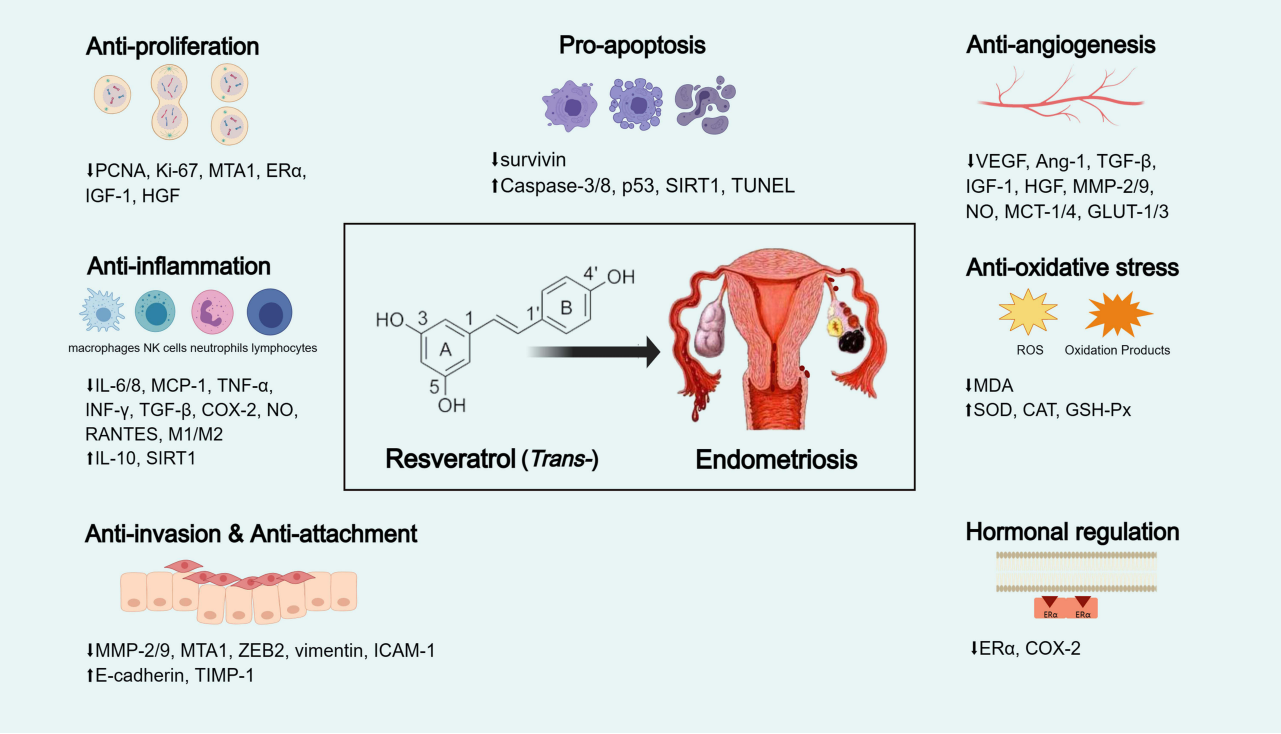

Figure 1 Potential molecular mechanisms of resveratrol on endometriosis. This figure was created with MedPeer (www.medpeer.cn).
Abbreviations: ↑, increase; ↓, decrease; Ang-1, angiotensin-1; CAT, catalase; COX-2, Cyclooxygenase-2; ERα, estrogen receptor alpha; GLUT, glucose transporters; GSH-Px, glutathione peroxidase; HGF, hepatocyte growth factor; ICAM-1, Intercellular cell adhesion molecule-1; IGF-1, insulin-like growth factor-1; IL, interleukin; INF-γ, Interferon gamma; M, macrophage; MCP-1, monocyte chemotactic protein 1; MCT, monocarboxylate transporters; MDA, malonyl dialdehyde; MMP, matrix metalloproteinase; MTA1, metastasis-associated protein 1; NK cell, natural killer cell; NO, nitric oxide; PCNA, proliferating cell nuclear antigen; RANTES, regulated upon activation, normal T-cell expressed and secreted; SIRT1, Sirtuin 1; SOD, superoxide dismutase; TGF-β, transforming growth factor-beta; TIMP, tissue inhibitors of metalloproteinase; TNF-α, tumor necrosis factor-alpha; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; VEGF, vascular endothelial growth factor; ZEB2, zinc finger E-box binding homeobox 2.

proliferation, apoptosis, angiogenesis, immunity, invasion, and adhesion.[42–47] It has also been found that some other factors, such as hormones, heredity, and environment, are implicated in the formation and/or advancement of this disease. Local estrogen augmentation and progesterone resistance are observed in endometriosis, thus promoting the survival, migration, proliferation, and adhesion of ectopic endometrial cells. According to a previous report, first-degree relatives of patients affected by endometriosis have a 7–10 times increased risk of developing endometriosis,[48] and studies in female twins have revealed that the heritability of endometriosis may be up to 50%.[2] Several experimental studies on primates and rodents have shown that exposure to tetrachlorodibenzo-p-dioxin (TCDD) and other organochlorine environments (particularly dioxin-like compounds) during adulthood interfere with hormone regulation and immune function, thereby facilitating endometriosis.[49]

Molecular Mechanisms of Resveratrol Against Endometriosis

Anti-Proliferation

Endometriosis is a proliferative chronic disorder that is mainly characterized by the abnormal endometrial growth at ectopic sites outside the uterine cavity.[42] Previous studies have shown an incremental cell proliferation rate of ectopic endometrium in endometriotic patients, which is conductive to survival and implantation into the ectopic site.[50] Proliferating cell nuclear antigen (PCNA), a sensitive indicator of proliferation and DNA restoration, exists in the G1, S and G2 phases of the cell cycle, while Ki-67 exists in all active phases and is a more specific proliferative marker than PCNA.[51] The proliferative ability of cells is usually be assessed by detecting the expression of proliferative markers.

Bruner-Tran et al firstly evaluated the curative potential of resveratrol on endometriosis in an animal model of endometriosis and endometrial tissues, and they reported that resveratrol reduces the incidence of experimental

Table 1 Researches Investigating the Effects and Potential Molecular Mechanisms of Resveratrol Against Endometriosis

Authors	Year	Study Characteristics and Endometriosis Model	Groups	Intervention Duration	Main Results	Potential Mechanisms
Taguchi et al[112]	2014	IV 1) Human EcESCs from patients with ovarian EMS 2) Human NESCs from patients with benign gynecological diseases	1) Resveratrol (10 μM) 2) Resveratrol (20 μM) 3) Resveratrol (40 μM) 4) Control (sirtinol, 20 μM)	1 hour	↓IL-8 releasing induced by TNF-α dose-dependently No effects in cell proliferation	↓Inflammation (through endogenous SIRT1 activation)
Taguchi et al[59]	2016	IV Human EcESCs from women affected by ovarian EMS	Resveratrol (40–120 μM)	24 hours	↑Proportion of apoptotic cells cultured with TRAIL ↓Survivin mRNA expression	↑Apoptosis (induced by TRAIL)
Arablou et al[81]	2019	IV 1) Human EcESCs and EuESCs from 40 patients with peritoneal EMS 2) Human NESCs from 15 non-endometriotic patients	Resveratrol (100 μM)	6, 24, 48 hours	↓Cell activity with 200 and 400 μM ↓IGF-1 mRNA level in EcESCs, EuESCs and NESCs ↓HGF mRNA level in EcESCs and EuESCs; ↓IGF-1 and HGF protein level in EcESCs and EuESCs	↓EMS advancement (via down-regulating IGF-1 and HGF expression)
Khazaei et al[57]	2020	IV (3D model) 1) Human eutopic endometrium from women were in stage III–IV of EMS 2) Human normal endometrium from women aged 25–40 years	1) Control 2) Resveratrol (10 μM) 3) Resveratrol (50 μM) 4) Resveratrol (100 μM) 5) Resveratrol (200 μM)	21 days	↓Growth score; growth was fully attenuated at 200 μM ↓Bax/Bcl-2 ratio ↓NO level at 100 and 200 μM ↑Bax, p53, caspase-3 and SIRT1 mRNA level	↓Proliferation ↓Angiogenesis ↑Apoptosis
Kolahdouz et al[58]	2020	IV 1) Human EcESCs and EuESCs from 40 women aged 19–45 years with peritoneal EMS stage III–IV 2) Human NESCs from 15 women aged 19–45 years without endometriosis	Resveratrol (100 μM)	6, 24, 48 hours	↓EuESCs viability with 200 μM ↓Bax mRNA level in EcESCs ↑Bax mRNA level in EuESCs at 6 hours ↑Bcl-2 mRNA expression in NESCs and EuESCs ↓Bax/Bcl-2 ratio in NESCs and EuESCs	↑Apoptosis

Arablou et al[80]	2021	IV 1) Human EcESCs and EuESCs from 40 women aged 19–45 years with peritoneal endometriosis stage III–IV 2) Human NESCs from 15 non-endometriotic women aged 19–45 years with benign gynecological diseases	Resveratrol (100 μM)	6, 24, 48 hours	Protein and gene basal expressions of MMP-9 and VEGF were higher in EcESCs than those in EuESCs and NESCs ↓VEGF protein expression in EcESCs and EuESCs ↓VEGF gene expression in EcESCs, EuESCs and NESCs ↓MMP-9 protein and gene expression in EcESCs, EuESCs and NESCs ↓TGF-β protein and gene expression in EuESCs and EcESCs	↓EMS advancement (via undermining the expression of VEGF, MMP-9 and TGF-β)
Kolahdouz et al[86]	2021	IV 1) Human EcESCs and EuESCs from 40 women aged 19–45 years with peritoneal endometriosis stage III–IV 2) Human NESCs from 15 non-endometriotic women aged 19–45 years with benign gynecological diseases	1) Resveratrol (100 μmol/L) 2) Ethanol	6, 24, 48 hours	↓MCP-1 protein expression in EcESCs and EuESCs ↓MCP-1 gene expression in EcESCs, EuESCs and NESCs ↓IL-8 protein expression in EcESCs, EuESCs and NESCs ↓IL-8 gene expression in EcESCs and EuESCs ↓IL-6 protein and gene expression in EcESCs and EuESCs ↓RANTES protein expression in EcESCs	↓Inflammation
Madanes et al[55]	2022	IV 1) Primary endometriotic stromal cells from women aged 19–37 years with endometriosis 2) Endometrial stromal cell line St-T1b 3) Endometriotic epithelial cell line 12Z	1) Resveratrol (50 μM) 2) Resveratrol (100 μM)	24, 48 hours	↓Viability and migration in St-T1b and 12Z ↑Cleaved caspase-3 level and percentage of apoptotic cells in St-T1b and 12Z ↓Ang-1 and VEGF mRNA expression ↓MMP-2/TIMP-1 Alteration stem cell markers mRNA expression: ↑KLF-4, SOX-2, Notch-1 and TERT ↑Snail-1 in St-T1b and 12Z ↑OCT-4 in St-T1b and primary endometriotic stromal cells ↑Vimentin in primary endometriotic stromal cells ↓Nanog and Msi-1 in St-T1b	↓Proliferation ↓Migration ↑Apoptosis Mediation stem cell markers expression

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Table 1 (Continued).

Authors	Year	Study Characteristics and Endometriosis Model	Groups	Intervention Duration	Main Results	Potential Mechanisms
Bruner-Tran et al[51]	2011	IV Human NESCs from 9 women with non-endometriosis aged 18–45 years old AS Peritoneal EMS mice model established by five-week-old female nude mice	IV Resveratrol (10–30 μM) AS 1) Resveratrol (n=20, 6 mg/mouse, gavage) 2) Control (n=16, 25% ethanol, gavage)	24 hours (IV) 10–12 or 18–20 days (AS)	↑PCNA (IV) ↓Ki67 (IV) ↓Number of cells invading matrigel (IV) ↑TUNEL (AS, IV) ↓Proportion of establishing EMS in mice (AS) ↓Number and volume of implants (AS)	↓Proliferation ↓Invasion ↑Apoptosis
Ricci et al[75]	2013	IV 1) Human EuESCs from 16 patients with untreated endometriosis 2) Human NESCs from 15 patients with infertility. AS Mesenteric EMS mice model established by 2-month-old female BALB/c mice	IV 1) Resveratrol (25 μM) 2) Resveratrol (50 μM) 3) Resveratrol (100 μM) 4) Control (DMSO) AS (n=29) 1) Low dose resveratrol (10 mg/kg/d, intraperitoneal) 2) High dose resveratrol (25 mg/kg/d, intraperitoneal) 3) Control (10% ethanol, intraperitoneal)	24 hours (IV) 28 days (AS)	↓Cell proliferation rate (IV) ↑TUNEL (AS, IV) ↓Number and volume of established lesions (AS) ↓PCNA (AS) ↓Vascular density (AS)	↓Proliferation ↑Apoptosis ↓Angiogenesis
Amaya et al[39]	2014	IV Ishikawa cells AS Abdominal EMS mice model established by RAG-2-γ(c) mice	IV Resveratrol (10^{-4}-10^{-12} mol/L) AS 1) E2 (n=4) 2) E2 + P (n=4) 3) E2 + resveratrol (n=4, 6 mg/d) 4) E2 + resveratrol (n=4, 30 mg/d) 5) E2 + resveratrol (n=4, 60 mg/d)	72 hours (IV) 30 days (AS)	Act as estrogen agonist or antagonist in lower or higher concentration, separately (IV), ↓ERα expression (AS) ↓Ki-67 expression (AS)	↓Proliferation (through ERα at high doses)

Kong et al[138]	2020	IV 1) Human ectopic and eutopic endometrium as well as EcESCs from patients with ovarian endometriosis 2) Human normal endometrium and NESCs from patients with benign non-endometrial diseases 3) Ishikawa cells (surrogate of EECs) AS Peritoneal EMS mice model established by female nude mice aged 6–8 weeks	IV Resveratrol (25–50 μM) In AS 1) Resveratrol (n=6, 25 mg/kg/d, intraperitoneal) 2) PBS (n=6, intraperitoneal) 3) Blank (n=6, no medicine)	12, 24 and 48 hours (IV) 4 weeks (AS)	Basal expression of E-cadherin was lower, while vimentin, MTA1 and ZEB2 were higher compared with eutopic and or normal endometrium (IV, AS) MTA1 accelerated proliferation, migration, and invasion of NESCs (IV) ↓Proliferation, migration and invasion (IV) ↓EMT (IV) ↓MTA1, ZEB2 and vimentin expression (IV, AS) ↑E-cadherin expression (IV, AS) ↓Implants volume (AS)	↓Proliferation ↓Migration ↓Invasion ↓EMT (via downregulating MTA1 and ZEB2 expression)
Chen et al[134]	2021	IV 1)Human EcESCs from patients with endometriosis stage III–IV 2) hEM15A cells AS Peritoneal EMS rat model established by 8- to 10-week-old female SD rats weighing 200–250 g	IV 1) Resveratrol (40 μM) 2) Resveratrol (100 μM) AS 1) Control (n=10, 0.9% NaCl + 35% DMSO, intraperitoneal) 2) Medium dose resveratrol (n=10, 15 mg/kg/d, intraperitoneal) 3) High dose resveratrol (n=10, 45 mg/kg/d, intraperitoneal) 4) Sham operation (n=10, 0.9% NaCl + 35% DMSO, intraperitoneal)	48 hours (IV) 28 days (AS)	↓AKT phosphorylation (IV) ↑Sphingolipid (IV) ↓Glycerolipid and major phospholipid (IV) ↑Apoptosis (IV) ↓Proliferation and invasion (IV) ↑Casepase-8 (IV) ↑PPARα expression (IV, AS) ↓Implant sizes (AS) ↓Growth of endometrial epithelial and ducts (AS) ↓HDL and Cholesterol levels in serum (AS) ↓LDL level in medium dose group (AS) ↓ICAM-1 and MMP-2 protein expressions (AS) ↓VEGF, Bcl-2 and MMP-2 gene expressions (AS)	↑Apoptosis ↓Migration ↓Proliferation ↓Invasion (via inducing Lipidomic alterations and PPARα activation)
Ergenoğlu et al[78]	2013	AS Peritoneal EMS rat model established by mature female SD rat weighting 180–260 g	1) Resveratrol (n=6, 10 mg/kg/d, intramuscular) 2) Control (n=6, saline, 1 mL/kg/d, intramuscular)	14 days	↓Implant sizes ↓Vascularization of implants ↓Epithelial scores ↓MCP-1 level in PF ↓VEGF level in PF and plasma ↓VEGF expression in ectopic endometrium	↓Angiogenesis ↓Inflammation

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Table 1 (Continued).

Authors	Year	Study Characteristics and Endometriosis Model	Groups	Intervention Duration	Main Results	Potential Mechanisms
Rudzitis-Auth et al[52]	2013	AS Peritoneal and mesenteric EMS mice model established by female BALB/c mice at 10 to 14 weeks of age weighting 18–20 g	1) Resveratrol (n=10, 40 mg/kg/d, gavage) 2) Control (n=10, 25% ethanol, gavage)	28 days	↓Implant sizes ↓PCNA- and Ki67-positive cell numbers ↓PCNA-positive endothelial cells ↓MVD	↓Angiogenesis (through inhibiting endothelial cell proliferation)
Yavuz et al[127]	2014	AS Peritoneal EMS rat model established by adult female Wistar rat weighting 300–350 g	1) Control (n=9, DMSO, intraperitoneal) 2) Resveratrol (n=9, 10 mg/kg/d, intraperitoneal) 3) Resveratrol (n=9, 100 mg/kg/d, intraperitoneal) 4) Sham operation (n=8, 10%, intraperitoneal)	7 days	↓Endometriotic implant volumes ↓Histological scores and PCNA expression ↑SOD activity in serum and implants dose-dependently ↑CAT activity in implants ↑GSH-Px activity in serum and implants dose-dependently ↓MDA activity in serum and implants	↓Oxidative stress ↓Proliferation
Bayoglu et al[77]	2015	AS Peritoneal EMS rat model established by mature, non-pregnant female SD rat weighting 200–250 g	1) Resveratrol (n=9, 30 mg/kg/d, intramuscular) 2) Leuprolide acetate (n=8, 1 mg/kg, single dose) 3) Resveratrol +leuprolide acetate (n=8) 4) Control (n=8, no medication)	14 days	↓Endometriotic implants volumes and histopathological scores ↓Levels of TNF-α, IL-6 and IL-8in plasma and PF ↓Immunoreactivities of VEGF, MMP-2 and MMP-9 in implants	↓Inflammation ↓Angiogenesis
Cenksoy et al[76]	2015	AS Peritoneal EMS rat model established by female Wistar-Albino rats weighing 200–250 g	1) Resveratrol (n=7, 60 mg/kg/d, gavage) 2) Leuprolide acetate (n=8, 1 mg/kg, single dose, subcutaneous) 3) Control (n=7, no medication)	21 days	↓Histopathological scores and superficial areas of implants ↓MCP-1 level in PF and serum ↓VEGF level in PF and serum, VEGF immunohistochemical staining scores in endometriotic tissues	↓Inflammation ↓Angiogenesis
Bahrami et al[79]	2021	AS Peritoneal EMS rat model established by mature female Wistar rats weighting 220–280g	1) Control (n=6, no treatment) 2) Resveratrol (n=6, 40 mg/kg/d, oral) 3) Atorvastatin (n=6, 5 mg/kg/d, oral) 4) Resveratrol + atorvastatin (n=6, oral)	28 days	↓Endometriotic implants sizes ↓Vascular distribution ↓MCT-1$^+$, MCT-4$^+$, GLUT-1$^+$and GLUT-3$^+$ cells numbers ↓MCT-1, MCT-4, GLUT-1 and GLUT-3 mRNA expression	↓Proliferation ↓Angiogenesis ↓Glycolysis

Wang et al[91]	2021	AS Peritoneal EMS rat model established by 8- to 10-week-old female SD rats weighing 200–250 g	AS 1) Control (n=10, 0.9% NaCl + 35% DMSO, intraperitoneal) 2) Resveratrol of medium dose (n=10, 15 mg/kg/d, intraperitoneal) 3) Resveratrol of high dose (n=10, 45 mg/kg/d, intraperitoneal) 4) Sham operation (n=10, 0.9% NaCl + 35% DMSO, intraperitoneal)	28 days	↓Endometriotic lesion and adipocyte sizes ↑Glucose tolerance; ↓M1/M2 ratio in high dose group ↑IL-10 mRNA levels ↓TNF-α, INF-γ and IL-6 mRNA expressions ↑PPARγ mRNA expression	Anti-inflammation Mediation of immune and lipid-related metabolism
Maia et al[116]	2012	Clinical trial Trial 1 12 patients with EMS aged 22–37 years old Trial 2 42 endometriotic patients suffer from EMS-related pain or sterility aged24-40 years old	Trial 1 1) DRSP/EE (n=12, oral) 2) DRSP/EE + resveratrol (n=12, 30 mg/d, oral) Trial 2 1) DRSP/EE (n=16, oral) 2) DRSP/EE + resveratrol (n=26, 30 mg/d, oral)	Trial 1 1) 6 months 2) 6 months (DRSP/EE) +2 months (DRSP/EE + resveratrol) Trial 2 At least 2 months	↓Pain scores ↓Aromatase and COX-2 expressions in eutopic endometrium	↓Pain
da Silva et al[117]	2017	Clinical trial 44 patients with EMS diagnosed by laparoscopy aged 20–50 years	1) COC+ resveratrol (n=22, 40 mg/day, oral) 2) COC+ placebo (n=22, 40 mg/day, oral)	42 days	No differences for treatment of pain in endometriosis.	
Kodarahmian et al[105]	2019	Clinical trial Women aged 18–37 years with laparoscopic-proven diagnosis of EMS stage III and IV	1) Resveratrol (n=17, 400 mg Bid, oral) 2) Placebo (n=17, oral) (Two groups added COCs in the last three weeks)	12–14 weeks	↓MMP-2 protein and gene expression in endometrial tissue, level in EF and serum ↓MMP-9 protein and gene expression in endometrial tissues, level in EF and serum	↓Inflammation (via down-regulating MMP-2 and MMP-9 expression)
Khodarahmian et al[82]	2021	Clinical trial Women aged 18–37 years with laparoscopic-proven diagnosis of endometriosis stage III and IV	1) Resveratrol (n=17, 400 mg Bid, oral) 2) Placebo (n=17, oral) (Two groups added COCs in the last three weeks)	12–14 weeks	↓Protein and mRNA expressions of TNF-α and VEGF within endometrium	↓Angiogenesis ↓Inflammation

Abbreviations: ↑, increase; ↓, decrease; 3D, three-dimensional; Ang-1, angiotensin-1; AS, animal study; AKT, Protein Kinase B; Bax, BCL2-Associated X; Bcl-2, B-cell lymphoma-2; Bid, twice a day; CAT, catalase; COCs, combined oral contraceptive pills; COX-2, Cyclooxygenase-2; DMSO, dimethyl sulfoxide; DRSP/EE, drospirenone +ethinylestradiol; E2, estradiol; EcESCs, ectopic endometrial stromal cells; EECs, endometrial epithelium cells; EF, endometrial fluid; EMS, endometriosis; EMT, epithelial-mesenchymal transition; ERα, estrogen receptor alpha; EuESCs, eutopic endometrial stromal cells; GLUT, glucose transporters; GSH-Px, glutathione peroxidase; HDL, high-density lipoprotein; HGF, hepatocyte growth factor; ICAM-1, Intercellular cell adhesion molecule-1; IGF-1, insulin-like growth factor-1; IL, interleukin; INF-γ, Interferon gamma; IV, in vitro study; KLF-4, Kruppel-like factor 4; LDL, low-density lipoprotein; M, macrophage; MCP-1, monocyte chemotactic protein 1; MCT, monocarboxylate transporters; MDA, malonyl dialdehyde; MMP, matrix metalloproteinase; Msi-1, Musashi 1; MTA1, metastasis-associated protein 1; MVD, micro-vessel density; NESCs, normal endometrial stromal cells; NO, nitric oxide; P, progesterone; PBS, phosphate buffer saline; PCNA, proliferating cell nuclear antigen; PF, peritoneal fluid; PPARα, peroxisome proliferators-activated receptor alpha; RANTES, regulated upon activation, normal T-cell expressed and secreted; SD, Sprague-Dawley; SIRT1, Sirtuin 1; SOD, superoxide dismutase; SOX-2, SRY-box transcription factor 2; OCT-4, octamer-binding transcription factor 4;TERT, telomerase reverse transcriptase; TGF-β, transforming growth factor-beta; TIMP, tissue inhibitors of metalloproteinase; TNF-α, tumor necrosis factor-alpha; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; VEGF, vascular endothelial growth factor; ZEB2, zinc finger E-box binding homeobox 2.

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endometriosis and also decreases the invasion of normal endometrial stromal cells (NESCs) in vitro.[51] Additionally, they demonstrated that resveratrol attenuates the formation and advancement of endometriosis by suppressing cell proliferation, promoting apoptosis, and reducing invasiveness. However, the efficacy of resveratrol against proliferation in ectopic endometrial lesions remains unclear as they reported to upregulate expression of PCNA but to downregulate expression of Ki-67 in implants.[51]

In peritoneal and mesenteric endometriosis rat model, Rudzitis-Auth et al reported that resveratrol treatment reduces the number of $PCNA^+$ and $Ki\text{-}67^+$ endometrial cells, thereby mitigating the growth rate of endometriotic implants compared to the control group. In addition, they demonstrated that resveratrol suppresses the formation of novel microvasculature in endometriotic implants by inhibiting the proliferative activity of $CD31^+$ endothelial cells.[52]

Pro-Apoptosis

Apoptosis is the process of programmed cell death, that helps sustain intracellular homeostasis by scavenging dysfunctional cells from the endometrium during the menstrual cycle.[43] Compared to healthy participants, patients affected by endometriosis have impaired spontaneous apoptosis of ectopic and eutopic endometrium, leading to growth and implantation of endometrial tissues at ectopic areas.[53] This resistance to apoptosis is associated with increased expression of anti-apoptotic factors (eg, B-cell lymphoma-2 (Bcl-2)) and decreased expression of pro-apoptotic factors (eg, caspase-3, Bcl-2 associated X (Bax)).[53,54]

To date, the effect of resveratrol on cell apoptosis in endometriosis has been evaluated through several animal models and in vitro experiments. Madanes et al investigated the mechanism of resveratrol in endometrial cells, and they reported that this compound remarkably reduces cell viability and induces apoptosis by increasing caspase-3 cleavage in two cell lines, namely, endometriotic epithelial cells (12Z) and endometrial stromal cells (St-T1b).[55] The property of invasiveness depends on the ratio of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs).[56] Furthermore, resveratrol mitigates the ability of invasion and angiogenesis by lowering the gene expression ratio of MMP-2/TIMP-1 and suppressing the mRNA expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1).[55]

In an in vitro three-dimensional culture model of endometriosis, Khazaei et al investigated the effects of resveratrol at various doses on human endometrial overgrowth, neovascularization, and the expression of apoptosis-related genes, and they reported that resveratrol attenuates the growth of endothelial cells, stromal and epithelial cells in a dose-dependent manner.[57] Furthermore, these researchers demonstrated that resveratrol fully inhibits growth and angiogenesis at a concentration of 200 μM. They also reported that resveratrol decreases the level of nitric oxide (NO, a vasodilator and messenger molecule in the process of angiogenesis), and significantly increases the expression levels of pro-apoptotic genes, such as Sirtuin-1 (SIRT1), Bax, caspase-3 and p53, and decreases the ratio of Bax/Bcl-2.[57] Additionally, another study has assessed the influence of resveratrol on Bax and Bcl-2 gene expression within ectopic endometrial stromal cells (EcESCs), eutopic endometrial stromal cells (EuESCs), and NESCs, demonstrating that resveratrol intervention effectively decreases the gene expression ratio of Bax/Bcl-2 in EuESCs and NESCs but not in EcESCs.[58]

In addition to the aforementioned effects of resveratrol on endometriosis, a previous study has demonstrated that pretreatment with resveratrol diminishes the level of the anti-apoptotic protein, survivin, as well as suppresses the apoptosis resistance of EcESCs and accelerates apoptosis induced by tumor necrosis factor-alpha (TNF-α) related apoptosis-inducing ligand (TRAIL).[59]

Anti-Angiogenesis

Angiogenesis, the formation of neovascularization, is a sophisticated multistage procedure that includes the following processes: coordinated expression of genes encoding angiogenic growth factors, disintegration of extracellular matrix, migration and proliferation of endothelial cells, and formation of capillary tubes.[60] Because the implantation, proliferation, and growth of endometriotic lesions require a new blood supply, angiogenesis plays an essential role in the establishment and maintenance of endometriotic lesions.[44] Based on the literature, increased levels of cytokines related to angiogenesis, such as VEGF, MMPs, TNF-α, interleukin-6 (IL-6), IL-8, transforming growth factor-beta (TGF-β), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), angiopoietin, macrophage migration inhibitory factor (MIF), erythropoietin, neutrophil activating factor, and tissue factor (TF),

have been measured in the peritoneal fluid (PF) of endometriotic patients compared to disease-free women.[61–63] Moreover, inflammation, oxygen deficiency, endothelial cell damage, and disturbances in acid-base imbalance also facilitate the formation of new blood vessels.[64,65] These factors are collectively implicated in the angiogenesis of endometriosis.

VEGF, the most prominent angiogenic factor in endometriosis,[63] which is produced by EcESCs, EuESCs, peritoneal macrophages, and neutrophils, triggers endothelial cell proliferation, migration, and survival during the process of angiogenesis, and it increases vascular permeability, thus enhancing the development of endometriosis.[66,67] Compared to the non-endometriotic controls, markedly increased levels of VEGF have been detected in the PF, serum, EcESCs and EuESCs of endometriotic women, and the level is linked to the clinical stage.[68–70] However, there is no distinction in VEGF levels in either blood or urine.[71] TGF-β is involved in mediating numerous cell functions, such as cell proliferation, apoptosis, angiogenesis, inflammation, migration, adhesion, differentiation, tumor inhibition, and immune functions. TGF-β may promote the survival of ectopic endometrial cells, strengthen apoptosis resistance, accelerate invasion, and initiate neoangiogenesis by inducing alterations in cellular metabolism, thereby leading to the progression of endometriosis.[72] Compared to the non-endometriotic controls, the levels of TGF-β in serum, PF, ectopic endometriotic lesions, and peritoneal tissue of endometriotic patients are higher, and it is linked to the degree of inflammation.[73,74]

To evaluate the anti-angiogenic effects of resveratrol, a previous study applied resveratrol to treat endometriosis in a mesenteric endometriosis rat model as well as treated EuESCs and NESCs with resveratrol. Ricci et al suggested that resveratrol diminishes the vascular density and reduces the numbers and volumes of endometriotic lesions.[75] They also reported that resveratrol suppresses cell proliferation and promotes cell apoptosis, further inhibiting the occurrence and development of endometriotic lesions.[75]

Two studies have evaluated the therapeutic efficacy of resveratrol in an experimental rat model and compared this effect to leuprolide acetate, a GnRH analog, demonstrating that the effectiveness of resveratrol on endometriosis is equivalent to that of leuprolide acetate. Both resveratrol and leuprolide acetate have the following effects: significantly decrease the volume and histopathological scores of endometriotic lesions, downregulate the expression of VEGF, MMP-2, and MMP-9 in implants, reduce the levels of monocyte chemoattractant protein-1 (MCP-1) and VEGF in serum and PF, and reduce the levels of TNF-α, IL-6, and IL-8 in plasma and PF. Interestingly, the drug combination of resveratrol and leuprolide acetate represses the anti-angiogenic and anti-inflammatory efficacy compared to treatment with each drug alone.[76,77] Additionally, Ergenoğlu et al reported that resveratrol treatment in a rat endometriosis model minimizes the size of endometriosis lesions and decreases VEGF level in the PF and plasma as well as downregulates VEGF expression in endometriotic lesions.[78]

Bahrami et al reported that resveratrol, atorvastatin alone, and particularly the combination of resveratrol and atorvastatin diminish the size of endometriotic lesions, reduce the number of new blood vessels, and inhibit the expression of glycolysis-related proteins, such as glucose transporters-1 (GLUT-1) and GLUT-3 and monocarboxylate transporters-1 (MCT-1) and MCT-4 in a rat model of endometriosis, suggesting that resveratrol inhibits the establishment and development of ectopic endometrial tissue by suppressing glycolysis and angiogenesis.[79]

In vitro experiments have revealed higher basic gene and protein expression levels of VEGF, MMP-9, IGF-1, and HGF in EcESCs compared to EuESCs and NESCs, and resveratrol intervention significantly reduces the gene and protein expression levels of VEGF, MMP-9, and TGF-β in EcESCs and EuESCs, as well as downregulates the gene expression levels of VEGF and MMP-9 in NESCs.[80,81] Reduced expression of IGF-1 and HGF has also been observed in EcESCs and EuESCs after resveratrol intervention, especially in EcESCs, which are effective promotors of ectopic endometrial lesions, owing to their role in growth, proliferation, invasion, and angiogenesis.[80,81]

Khodarahmian et al conducted a randomized exploratory clinical study, in which endometriotic patients with stage III–IV were treated with resveratrol (400 mg) or placebo for 12 to 14 weeks in addition to COCs.[82] The results show that resveratrol remarkably reduced the protein and gene expression levels of TNF-α and VEGF in eutopic endometrial tissues, compared to the control group and before intervention. Thus, they suggested that resveratrol mitigates angiogenesis and inflammation in the endometrium of endometriotic patients by undermining the expression of TNF-α and VEGF.[82]

Anti-Inflammation

Endometriosis, an inflammatory disease, is relevant to chronic inflammation and immune dysregulation in the peritoneal microenvironment.[45] Several studies have reported that levels of pro-inflammatory cytokines and chemokines, such as IL-1, IL-4, IL-6, IL-8, IL-12, TGF-β, TNF-α, prostaglandin (PG), growth factor, MCP-1, and regulated upon activation, normal T cell expressed and secreted (RANTES), are higher in the PF of women affected by endometriosis compared to disease-free participants.[83–85] These inflammatory mediators may participate in the establishment and advancement of endometriosis, and they are secreted by activated macrophages, lymphocytes, endometriotic lesions, and peritoneal mesothelial cells, thereby promoting the viability, proliferation, adhesion, invasiveness, and angiogenesis of endometrial cells.[86]

Macrophages are the most common member of the immune cell family in endometriosis, and activated macrophages modulate the peritoneal microenvironment through phagocytosis and secretion of immune mediators.[85] M1 and M2 are two main categories of activated macrophages, M1 predominantly participate in the pro-inflammatory response, inhibit cell proliferation, and exacerbate tissue damage, while M2 mainly participate in anti-inflammatory reactions, tissue repair, and angiogenesis.[87,88] Evidences suggest that in endometriotic women, the macrophages in the eutopic endometrium are mostly M1-polarized, while those in the ectopic endometrium are mostly M2-polarized.[89] Macrophages depletion tests have demonstrated that M2 enhance the growth and vascularization of endometriotic lesions, while M1 effectively protect mice from endometriosis.[90] In an experimental endometriosis rat model, Wang et al reported that the number of activated macrophages is increased in the PF, which agreed with other studies. However, they reported that M1/M2 polarization in the PF is increased and resveratrol reduces the M1/M2 polarization, which contradicts other studies.[91] The inconsistent conclusions may be explained by the measurement of different samples. Wang et al detected macrophage polarization in the PF, while other researchers detected macrophage polarization in endometriotic lesions. Additionally, Wang et al reported that resveratrol decreases the mRNA expression levels of the pro-inflammatory cytokines IL-6, TNF-α, and interferon gamma (INF-γ) but increases the mRNA expression levels of the anti-inflammatory IL-10.[91]

MCP-1, also known as chemokine (C-C motif) ligand 2 (CCL2), binds to its receptor, CCR2, and then activates the signaling pathways regulating cell migration, further promoting the migration of inflammatory cells, such as monocytes/macrophages, and infiltration of other cytokines in the inflammatory site.[92] MCP-1 is generated by fibroblasts, macrophages, endothelial cells, epithelial cells, EcESCs, and EuESCs.[86,92] Some studies have demonstrated that the expression level of MCP-1 in the serum, PF, and EcESCs is higher in endometriotic patients than in non-endometriotic controls.[93,94] Heidari et al assessed the effects of resveratrol on endometriosis by isolating EcESCs and EuESCs from endometriotic patients and NESCs from disease-free participants.[87] They demonstrated that the protein and gene expression levels of MCP-1 were higher in EcESCs compared to EuESCs and NESCs under basic conditions, but that resveratrol (100 μM) intervention significantly downregulates the expression of MCP-1 and RANTES in EcESCs.[87] Similarly, other studies have reported that resveratrol reduces MCP-1 level in the PF of endometriotic animal models.[76,78]

IL-6, an inflammatory cytokine, stimulates M2 polarization of peritoneal macrophages, weakens phagocytosis of macrophages, reduces cytotoxicity of natural killer (NK) cells, and facilitates the synthesis of aromatase, consequently promoting the progression of endometriotic lesions.[89,95–97] IL-8, a pro-inflammatory, pro-angiogenic, and growth-promoting cytokine, enhances the expression of various adhesion molecules and neutrophil chemotaxis, and it may also promote the initial adherence of endometrial cells to the peritoneum surfaces.[98] Numerous studies have reported that the levels of IL-6 and IL-8 in the PF and serum of endometriotic patients are significantly higher than those in individuals without endometriosis and they increase correspondingly with the aggravation of endometriosis stage.[93,98,99] Additionally, the levels of IL-6 and IL-8 are higher in EcESCs compared to EuECSs,[100] and the increased expression of IL-6 and IL-8 increases the migration and invasion abilities of EcESCs.[99,101] Using an experimental endometriosis model, Bayoglu Tekin et al revealed that resveratrol reduces the levels of IL-6 and IL-8 in the PF and serum compared to the control group.[77] Consistent with their findings, another study has evaluated the impacts of resveratrol on IL-6 and IL-8 mRNA and protein expression in EcESCs, EuESCs, and NESCs, demonstrating that resveratrol reduces the expression of IL-6 and IL-8 in EcESCs compared to the EuESCs and NESCs groups.[86]

TNF-α is implicated as a pivotal factor in the inflammatory response and immunopathological injury.[102] Previous studies have reported that ectopic endometrial tissue stimulates humoral and cellular immunity, acting as an antigen, which results in an increased number and activity of macrophages and lymphocytes, thereby increasing the expression of TNF-α.[103] The level of TNF-α is increased in the PF and serum of endometriotic women, and it is closely related to the stage of endometriosis, which may contribute to the production of other cytokines and the proliferation, adhesion, and angiogenesis of endometrial cells.[103,104] Similarly, in vitro, animal, and clinical exploratory experiments have demonstrated that resveratrol decreases the levels of TNF-α in the PF and endometrial tissues of the endometriosis groups.[77,91,105] Other studies have reported that resveratrol alleviates TNF-α-stimulated inflammatory injury in late-stage endothelial progenitor cells (EPCs) by reducing the expression of intercellular adhesion molecule 1 (ICAM-1) and MCP-1.[106] Additionally, resveratrol suppresses the invasiveness of human hepatoma cells by inhibiting nuclear factor-kappa B (NF-κB) activity to reduce TNF-α-mediated MMP-9 expression.[107]

SIRT1 is involved in the modulation of inflammation. The increased activity and overexpression of SIRT1 suppresses the production of inflammatory cytokines,[108,109] while SIRT1 deficiency stimulates the inflammatory response.[110] SIRT1 also has a role in oxidative stress. Resveratrol treatment can reverse the experimental induced oxidative stress condition and upregulate SIRT1 expression.[111] Taguchi et al reported that resveratrol ameliorates local inflammation in endometriosis by suppressing TNF-α-induced IL-8 release in a dose-dependent manner via the SIRT1 pathway.[112]

Cyclooxygenase-2 (COX-2), a rate-limiting enzyme of prostaglandin E2 (PGE2) biosynthesis,[113] is an essential part of the positive feedback circulation of estradiol (E2)-COX-2-PGE2-aromatase-E2, and upregulated COX-2 expression decreases apoptosis and promotes proliferation, invasiveness, angiogenesis, endometriosis-related pain, and infertility.[114] The expression of COX-2 in the ectopic and eutopic endometrium of endometriotic women is upregulated compared to the normal endometrium of disease-free individuals.[115] In a clinical trial, Maia et al reported that resveratrol promotes the effectiveness of COCs to alleviate dysmenorrhea by downregulating the expression of COX-2 and aromatase in the endometrium.[116] Nonetheless, another clinical study has reported that resveratrol has no advantage over placebo in treating endometriosis-related pain.[117]

Anti-Oxidative Stress

Oxidative stress is characterized by an imbalance between anti-oxidant defense and oxidation,[118] resulting in the accumulation of ROS and oxidation products as well as causing damage to molecules, cells, and the organisms. ROS mediate cytotoxicity by interacting with lipids, proteins (especially cysteine residues), and nucleic acids.[119] Based on data from previous research, the oxidative stress of endometriosis is associated with increased ROS and oxidation products, reduced anti-oxidant enzymes and detoxifying enzymes, disordered iron metabolism, and elevated number of activated macrophages. An increased level of oxidative stress gives rise to inflammation, angiogenesis, cell proliferation, cell adhesion, and extracellular matrix degradation, resulting in endometriosis and infertility.[47,120,121]

NF-κB, a transcription factor, modulates the expression of a variety of genes encoding angiogenic factors, growth factors, pro-inflammatory factors, chemokines, and adhesion molecules, such as ICAM-1, as well as inducible enzymes, such as inducible nitric oxide synthase (iNOS) and COX-2.[122,139] These gene products facilitate cell proliferation, adhesion, inflammation, angiogenesis, and oxidative stress, thereby implicating the progression of endometriosis.[123] NF-κB initiates gene transcription of gp91-phox, the catalytic subunit of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is implicated in the electron transport chain of oxidative phosphorylation and responsible for donating electrons from NADPH to molecular oxygen to generate superoxide anion, consequently increasing oxidative stress.[119] Another study has reported that NF-κB-mediated transcriptional activation of COX-2 also inhibits apoptosis and promotes cell proliferation in endometriosis.[124] Oxidative stress and iron overload activate the NF-κB signaling pathway and elevate IL-10 levels in the serum and PF of patients affected by endometriosis, leading to MMPs activation, extracellular matrix (ECM) remodeling, and neovascularization.[115] Elevated levels of INF-γ and IL-10 resulting from increased IL-2 and IL-27 are able to collaboratively accelerate the proliferation and invasion of endometrial stromal cells.[125]

The role of oxidative stress in endometriosis is generally assessed by ROS markers, including malondialdehyde (MDA), oxidative products, and enzyme antioxidants, such as glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD).[126] Using resveratrol in experimental endometriosis rats, Yavuz et al showed that resveratrol

increases SOD and GSH-Px activities in ectopic endometrial tissues and serum in a dose-dependent manner as well as increases CAT levels in tissues.[127] And they reported that resveratrol reduces MDA levels in tissues and serum but not to a significant extent compared to the control group. What's more, resveratrol effectively diminishes implant sizes, histological scores, and PCNA expression levels were observed. And they demonstrated that resveratrol inhibits oxidative stress by activating endogenous antioxidant capacity to ameliorate endometriosis.[127] In diazinon (DZN)-induced oxidative stress rat models, Mehri et a reported that DZN inhibits serum acetylcholinesterase (AChE) as well as serum and liver CAT, GSH-Px, and total antioxidant abilities, and they also demonstrated that resveratrol reverses the oxidative stress conditions, improves the activity of antioxidant enzymes, and lower MDA level in the serum and liver.[111]

Anti-Invasion and Anti-Attachment

In view of Sampson's theory, invasion and adhesion are key processes in the establishment of endometriosis.[128] Elevated levels of MMPs, especially MMP-2 and MMP-9, as well as cell adhesion molecules, such as ICAM-1, integrin, and cadherin, have been reported in the PF of endometriotic women, which collectively exert influences on the invasion and adhesion of ectopic endometrium.[46,129,130]

MMPs, a group of zinc-dependent proteolytic enzymes, play an important role in the degradation of ECM, which is a vital step of ectopic endometrial cell implantation and endometriosis formation.[131] A comprehensive analysis of previous studies has revealed that MMPs are implicated in multiple stages associated with endometriosis formation as follows: endometrial cells migrating from the uterine cavity and implanting in peritoneal surfaces, vascular endothelial cells migrating to new blood vessels, macrophages distinguishing and phagocytizing escape cells, and NK cells killing target cells. These stages promote cell migration, cell invasion, angiogenesis, ephemeral mesenchymal transformation (EMT), fibrosis, and regulation of immune cells or autoimmune factors, ultimately inducing endometriosis.[132] ECM protein degradation and tissue remodeling play pivotal roles in ectopic endometrial cell implantation and endometriotic lesion formation, and the extent of which is generally determined by the MMP/TIMP ratio.[133] PGE2 and COX-2 can facilitate angiogenesis indirectly by mediating MMP-2 activity.[113] Chen et al revealed that resveratrol reduces invasiveness and proliferation as well as induces early apoptosis of EcESCs in a dose-dependent manner.[134] Moreover, they reported that resveratrol effectively reduces the gene expression of VEGF, Bcl-2 and MMP-2 as well as the protein expression levels of ICAM-1 and MMP-2. Additionally, they showed that resveratrol corrects aberrant lipid distribution in endometriosis model rats.[134] An exploratory clinical trial has indicated that the gene and protein expressions levels of MMP-2 and MMP-9 are significantly decreased within endometrial tissues, endometrial fluid, and serum after resveratrol intervention compared to controls.[105]

EMT is the trans-differentiation of epithelial cells into mesenchymal cells. Zinc-finger E-box-binding (ZEB) and other transcription factors drive EMT by increasing mesenchymal maker (eg, vimentin) expression and decreasing epithelial marker (eg, E-cadherin) expression, which further degrades the extracellular matrix, promoting invasion ability.[132,135] To the best of our knowledge, metastasis-associated protein 1 (MTA1) induces EMT in a variety of cancers to promote disease progression and metastasis,[136] and it is overexpressed in endometrial cancer to promote carcinoma cell proliferation, migration, and invasion.[137] A thorough exploration of the Gene Expression Omnibus (GEO) database has indicated that the expression levels of MTA1 and ZEB2 are upregulated in ectopic endometrial tissues.[138] Kong et al found that MTA1 interacts with ZEB2 to induce EMT, thus facilitating the proliferation, migration, and invasiveness of NESCs, while resveratrol downregulates the expression of MTA1 and ZEB2 as well as inhibits their promoting function.[138] In an endometriosis mouse model, compared with the eutopic endometrium, the expression of MTA1, ZEB2, and vimentin is increased in endometriotic implants, but E-cadherin expression is decreased, however, resveratrol reverses these phenomena by inhibiting the growth of ectopic endometrium and suppressing the expression of MTA1, ZEB2, and vimentin as well as promoting the expression of E-cadherin.[138]

Hormonal Regulation

Endometriosis is regarded as hormone-dependent as several studies have reported that the endometrium is modulated by steroid hormones, mainly including estrogen and progesterone, which regulate the expression of various genes at diverse stages of the menstrual cycle.[140] The level of estrogen detected in the ectopic endometrium of endometriotic women is

elevated compared to that in the eutopic endometrium or normal endometrium, which depends on local estrogen metabolism rather than circulating levels.[141] Ectopic endometrial tissues can synthesize abundant E2 de novo from cholesterol, resulting from the high expression of aromatase (the key enzyme for estrogen biosynthesis) and steroidogenic acute regulatory protein (StAR), while normal endometrial tissues cannot synthesize estrogen due to the lack of these enzymes.[142] Moreover, some inflammatory factors are also involved in the synthesis of local E2. The elevated level of COX-2 increases the expression of PGE2, which activates the aromatase gene promoter, resulting in aromatase overexpression and accumulation. Furthermore, E2 stimulates the expression of COX-2 by binding to its receptor, estrogen receptor beta (ERβ). Thus, estrogen generation and chronic inflammation form a vicious spiral under the positive feedback cycle of E2-COX-2-PGE2-aromatase-E2.[114]

Because immunoreactive ER and progesterone receptor (PR) exist in ectopic and eutopic endometrium, they show similar histological changes in response to estrogen and progesterone.[143] PR-A and PR-B are the main subtypes of PRs in the endometrium, of which PR-B plays more important biological functions. In EcESCs of endometriotic patients, the methylation of the PR-B transcription factor is enhanced, resulting in progesterone resistance, which is consistent with the report that EuESCs of women with endometriosis are less responsive to progesterone.[144] ERs in the endometrium mainly consist of ERα and ERβ. The expression of ERα is more prominent in healthy endometrial tissues, while the expression of ERβ is more prominent in ectopic endometrial tissues.[145] The ERβ level in EcESCs cultured in vitro is 142 times higher than that in NESCs, while the ERα level in EcESCs is 9 times lower than that in NESCs.[146] ERα and ERβ may be cooperatively responsible for the regulation of proliferation, adhesion, and inflammation in the initiation of endometriotic lesions. Besides, ERα principally triggers angiogenesis, and ERβ exerts a leading role in the pro-invasive capability, anti-apoptotic effects and activation of inflammatory bodies to maintain survival.[147]

Using an experimental animal model, Han et al showed that overexpressed ERβ in ectopic endometrium attenuates TNF-α-induced apoptosis, elevates the level of IL-1β to promote inflammation, and enhances EMT to facilitate invasion and adhesion.[147] Amaya et al suggested that resveratrol is an estrogen agonist or antagonist at lower or higher levels, respectively.[39] Their another study using a recombination activating gene-2 mouse model of endometriosis has demonstrated that the expression of Ki-67 and ERα in the endometrial epithelium is downregulated, and that ERα is reduced to a level similar to that with progesterone treatment. However, progesterone treatment dose not decrease the Ki-67 expression level. Therefore, these researchers proposed that high-dose resveratrol reduces proliferation activity of the endometrial epithelium by inhibiting ERα expression.[39]

Pharmaceutical Properties of Resveratrol Against Endometriosis

Absorption and Metabolism

Resveratrol mostly exists in dietary foods in a glycosylated form, which prevents resveratrol from enzymatic oxidation in the digestive tract, thus preserving its biological activity and overall stability.[148,149] However, intestine cells absorb only resveratrol aglycone via transepithelial diffusion with an absorption rate of approximately 75%. Pharmacokinetics studies have confirmed that resveratrol is rapidly and comprehensively metabolized through the intestine and liver, and the main glucoside and sulfate metabolites of resveratrol are produced through glucuronidation and sulfation.[149,150] Therefore, it has been proposed that improving the content of resveratrol glycosylation and aglycone may increase its absorption rate in foods and beverages.[151] Despite good lipophilicity and a high absorption rate, these coupling reactions (glucuronidation and sulfation) also decrease cell permeability to the drug, increase the polarity of the drug, and promote drug excretion from the body. Evidence suggests that after extensive metabolism of resveratrol in the intestines and liver, nearly 75% of the metabolites are scavenged from the body through urine and feces, ultimately, the oral bioavailability of resveratrol is less than 1%.[149,152] Thus, the limited effect of resveratrol results from its rapid metabolic rate in vivo.[153]

Walle et al reported that the plasma concentration of resveratrol is less than 10 ng/mL following oral administration of 25 mg resveratrol in humans, and the plasma concentration is 500 ng/mL after taking 5000 mg of high-dose resveratrol, indicating that increased or repeated dose of resveratrol does not significantly improve the bioavailability.[149] To date, it is generally believed that the limited bioavailability of resveratrol is largely due to its poor water solubility, thus, a variety of formulations and strategies have been developed, including nanocarriers, liposomes, and synthetic

derivatives (aromatic rings contain different substituents, such as methoxy, hydroxyl, or halogen), to improve the bioavailability.[154–156] Compared to free resveratrol, some studies have reported that resveratrol nanoparticles increase the uptake and sustained release in target cells as well as the toxicity of resveratrol to these cells, thereby improving the bioavailability,[157] and the absorption rate of resveratrol nanoparticles conjugated with polyethylene glycol is increased by 7-fold.[158] Methylation of resveratrol enhances the water solubility and bioavailability of resveratrol, and Summerlin et al proposed that methylated resveratrol synthesized by in vitro metabolic engineering (recombinant Escherichia coli) is superior to chemosynthesis in biological activity.[157] Importantly, in the process of drug research and development, attention should be focused on amending the structure, bioavailability and activity of resveratrol.

Toxicity

Comprehensive testing has indicated that oral administration of resveratrol is considered safe.[159] A previous rat experiment has demonstrated that resveratrol effectively suppresses the growth of ovarian cancer but does not affect normal tissues.[160] Another study has reported that resveratrol regulates the proliferation and apoptosis of cancer cells and epithelial cells in a dose-dependent manner. Resveratrol exerts a time- and concentration-dependent pro-apoptotic impact on cancer cells.[161] Besides, resveratrol protects healthy cells and induces cancer cell death, which may be due to its inconsistent molecular targets and metabolic pathways within these cells.[162] Experimental animal models have shown good tolerance to resveratrol. For instance, CD rats receiving resveratrol at a daily dosage of 200 mg/kg and beagle dogs receiving resveratrol at a daily dosage of 600 mg/kg for 90 days do not show any obvious biological adverse effects.[163] In CD rats, a high daily dose of resveratrol (1000 mg/kg, lasting for 10–13 weeks) increases the level of bilirubin without any gross or microscopic changes associated with liver injury, and the high dose of resveratrol administration reduces the incidence of cardiomyopathy. Notably, elevated bilirubin has not been reported in beagle dogs exposed to any dose level of resveratrol.[163]

By evaluating the potential toxicity of resveratrol, Crowell et al reported that rats fed resveratrol at a high daily dosage (3000 mg/kg, lasting for 4 weeks) show elevated levels of transaminase, bilirubin, creatinine, and blood urea nitrogen (BUN) as well as increased incidence and severity of nephrosis but with no histological changes in the liver.[164] Liu et al used an experimental renal fibrosis mouse model to estimate the impact of resveratrol on renal fibrosis.[165] They found that resveratrol at low dosage (≤25 mg/kg) partially ameliorates kidney function by mitigating unilateral ureteric blockage, while a high dosage (≥50 mg/kg) fails to prevent fibrosis and aggravates renal fibrosis in mice. These researchers also concluded that mice with ureteric blockage are more predisposed to kidney injuries induced by high-dose resveratrol than normal mice.[165] Some researchers have considered that the effective dosage range of this compound in cells is inconsistent with the concentration in the human body, therefore, it is difficult to ascertain the efficacious concentration range of resveratrol in participants.[166] The safety of resveratrol in humans has been assessed at different doses in several clinical studies, and these studies have indicated that resveratrol has no obvious adverse effects.[167–173] Resveratrol is safe and well-tolerated in a disease-free population following a single dose of 500 mg resveratrol tablet.[172] Another study has suggested that resveratrol is considered to be safe at daily doses up to 5000 mg and these slight adverse effects, such as alopecia, nausea, headache, and diarrhea, occur only when taking a high oral dose of resveratrol (>2500 mg, every 4 hours).[173] Since these studies on the toxicity of resveratrol were conducted in endometriosis-free participants, it is possible that the side effects of resveratrol may vary in patients with endometriosis.

As a substitute or supplement treatment for endometriosis, resveratrol is a promising candidate. To date, however, the clinical trials evaluating the role of resveratrol in endometriosis have been small samples and lack an assessment of its side effects. [82,105,116,117] The optimal drug dosage to maximize the health benefits of resveratrol without causing toxicity requires further supporting evidence, suggesting that additional comprehensive studies are needed.[29,166] Furthermore, it is not easy to determine the therapeutic effect of resveratrol at a specific dosage as well as the precise dosage safety range in patients with endometriosis. Thus, the optimum dosage and preparation method of resveratrol need to be further explored.

Conclusion

Botanical therapies (or herbal medicines) have been used to combat diseases for a long time in human history, especially for infectious diseases, cancer, and other chronic ailments. The basis of these synergistic therapeutic effects of the therapies and herbal medicines is bioactive compounds within the mixtures or crude preparations. More precisely and scientifically, compounds found in the natural sources (eg, plants, animals, microorganisms, and minerals) are defined as natural products (NPs). Due to their vast scaffold diversity, structural complexity, and stability, NPs have received much attention in the drug discovery process. To date, many successfully approved drugs have been derived from NPs, such as Taxol (oncology), Fumagillin (antiparasitic), Trabectedin (oncology).

Resveratrol, a natural product, is mainly found in the grapes and red wines, and it also exists in some other plants and several genera of microorganisms. Based on in vitro, animal, and clinical studies associated with endometriosis, resveratrol has been reported to have multiple biological functions, such as anti-proliferative, pro-apoptotic, anti-angiogenic, anti-oxidant, anti-invasive, and anti-adhesive effects. Accumulated evidences confirm that resveratrol is a relatively safe and well-tolerated compound for humans, but it is also an inefficient agent due to its rapid metabolic rate in vivo. Nanocarriers, liposomes, and synthetic derivatives of resveratrol have been explored to increase its biological availability. In the light of existing evidence, resveratrol is effective and potential in endometriosis, we speculate that resveratrol may be a new supplementary and adjuvant drug for the treatment of endometriosis. However, the exact molecular mechanisms are not fully elucidated, and the majority of studies have been conducted on in vitro and rodent animal models, with a few clinical studies. Furthermore, there are distinctions in the reproductive physiology between humans and rodents because rodents never develop endometriosis spontaneously due to a lack of menstruation. Consequently, caution is always warranted when extrapolating results obtained from in vitro experiments or animal models to humans, and further high-quality clinical trials with large sample sizes should be implemented to assess the effectiveness and clinical application feasibility of resveratrol in endometriosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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