

Oxidative stress in endometriosis: Sources, mechanisms and therapeutic potential of antioxidants (Review)

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Abstract. Endometriosis affects ~15% of women of reproductive age worldwide, impacting ~190 million individuals. Despite its high prevalence, the precise pathogenesis of endometriosis remains unclear. Emerging evidence has highlighted oxidative stress as a pivotal factor in the initiation and progression of this disease. The present review comprehensively summarizes the sources of oxidative stress in endometriosis, including redox imbalance characterized by increased oxidative markers and diminished antioxidant defenses, mitochondrial dysfunction leading to excessive production of reactive oxygen species (ROS), and aberrant iron metabolism that further amplifies ROS generation. The accumulation of ROS disrupts cellular redox homeostasis, thereby exacerbating oxidative stress and activating key cell proliferation signaling pathways, such as the Raf/MEK/ERK and mTOR pathways. Activation of these pathways promotes the survival and proliferation of ectopic endometrial cells, contributing to lesion development and disease progression. The present review also discusses how oxidative stress induces epigenetic modifications that may further drive the pathological features of endometriosis. Finally, the recent advances in the application of antioxidants as therapeutic agents for endometriosis are highlighted, underscoring their potential to mitigate oxidative stress and ameliorate disease symptoms. Understanding the intricate relationship between oxidative stress and endometriosis may pave the way for novel diagnostic and therapeutic strategies aimed at improving patient outcomes.

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1. Introduction

Endometriosis affects ~15% of women of reproductive age worldwide, with an estimated 190 million women affected by the disease (1). Endometriosis is a chronic, estrogen-dependent inflammatory condition characterized by the ectopic growth of endometrial tissue, including glands and stroma, outside the uterine cavity (2). Based on the location of the lesions, endometriosis can be classified into peritoneal implants, ovarian cysts and deep infiltrating endometriosis, where endometrial tissue deeply invades surrounding tissues or organs. Commonly affected areas include the parametrium, anterior rectal wall, colon, ureters, bladder and posterior vaginal fornix. Clinically, the condition presents primarily with pelvic pain and infertility (3), often coexisting in affected patients. Research suggests that endometriosis is diagnosed in 30–45% of women with infertility and pelvic pain (4). Additionally, some patients experience dyspareunia (5) and dysmenorrhea (6).

The precise pathogenesis of endometriosis remains unclear. Currently, the most widely accepted theory is the theory of retrograde menstruation (7). This theory proposes that during menstruation, some menstrual blood flows back through the fallopian tubes into the pelvic cavity, carrying endometrial tissue outside the uterus. This displaced endometrial tissue then implants, proliferates and forms ectopic lesions (7). However, retrograde menstruation occurs in 76–90% of women, but only a minority develop endometriosis (8). Moreover, endometriosis has been reported in premenarchal girls (9), suggesting that retrograde menstruation alone cannot fully explain the etiology of the condition. Signorile *et al* (10) found ectopic endometrial tissue in human female fetuses, supporting the theory of embryonic origin. This theory posits that endometriosis arises from small defects during embryonic development, wherein tissue destined to form the endometrium is erroneously distributed outside the uterine cavity during fetal development (10,11). This theory also explains the occurrence of endometriosis

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in premenarchal individuals. Despite the differences among theories, current research agrees that epigenetic alterations and hormonal dysregulation, leading to inflammation, are central features of endometriosis (12), with reactive oxygen species (ROS) serving a key role in this inflammatory response (4). The activation of inflammatory cells, such as macrophages and eosinophils, promotes ROS generation. Elevated oxidative stress induces the secretion of chemokines and stimulates the proliferation of endometrial cells, further exacerbating the progression of endometriosis (13,14). Moreover, components of retrograde menstruation, including heme, iron ions and apoptotic endometrial cells, are known to induce oxidative stress, intensifying the inflammatory response (15). Under normal physiological conditions, cells maintain a balance between ROS production and clearance, as ROS are typical byproducts of cellular metabolism. Cells possess antioxidant systems to neutralize ROS (16); however, once the balance between ROS production and clearance is disrupted, excessive ROS generation can lead to heightened oxidative stress (17).

The relationship between ROS and endometriosis has been widely studied. For example, Cacciottola *et al* (16) provided a comprehensive review on the aberrant ROS metabolism observed in patients with endometriosis and the contributory role of ROS in disease progression. However, compared with previous reviews (4,16,18), the present study distinguishes itself by offering an in-depth examination of oxidative stress in endometriosis, focusing on the disruption of oxidative balance and the increased production of ROS resulting from mitochondrial dysfunction and abnormal iron metabolism. In addition, this review provides a systematic analysis of how enhanced oxidative stress can activate signaling pathways associated with cell proliferation and elucidates their contribution to the progression of ectopic endometrial lesions. The present review also discusses the potential association between ROS and epigenetic modifications, focusing on their involvement in endometriosis, and its malignant transformation through chromatin structure dysregulation and inactivating mutations of the tumor suppressor gene AT-rich interactive domain-containing protein 1A (*ARID1A*). Finally, recent advancements in the use of antioxidants, particularly vitamins and plant extracts, in the treatment of endometriosis are summarized, with the goal of encouraging further research into the role of oxidative stress in the disease and expanding the therapeutic potential of antioxidants in its management.

2. Sources of oxidative stress in endometriosis

As shown in Fig. 1, the sources of oxidative stress in patients with endometriosis include an imbalance in the reductive system, alterations in mitochondrial quantity and structure, and abnormalities in iron metabolism. These oxidative stresses lead to a further increase in ROS, thereby promoting the progression of endometriosis.

Redox imbalance: Elevated oxidative markers and impaired antioxidant defenses. ROS are oxygen-containing compounds with unpaired electrons, including singlet oxygen, superoxide anions and hydroxyl radicals (19). Under normal physiological conditions, ROS are byproducts of cellular metabolism, which have roles in regulating vascular tone and signal

transduction (20). Studies have shown an increase in oxidative stress markers and a compromised antioxidant defense system in patients with endometriosis (21-23) (Table I). This indicates a redox imbalance in these patients, where disruption of the oxidative balance leads to excessive ROS production and elevated oxidative stress.

In patients with endometriosis, antioxidants have been found to be significantly reduced. For example, Prieto *et al* (22) demonstrated that serum levels of vitamin C were notably lower in patients with endometriosis compared with in the controls. Notably, thiol-containing compounds, such as glutathione, react with ROS to neutralize them. In endometriosis, both total and free thiol levels have been reported to be significantly reduced, reflecting a decline in extracellular antioxidant capacity (23). Beyond small-molecule antioxidants, antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) are critical components of the body's defense system. SOD catalyzes the dismutation of superoxide anions into hydrogen peroxide, which is subsequently converted into water and oxygen by CAT or glutathione peroxidase (GPx). Research has shown that the levels of SOD and GPx are significantly reduced in the plasma of women with endometriosis (22,24). Notably, one study reported that the combined sensitivity and specificity of plasma SOD and GPx as biomarkers for preoperative screening of endometriosis reached 68.75 and 80.77%, respectively (24). By contrast, CAT expression has been reported to be significantly elevated in patients with endometriosis compared with in healthy individuals (23). A similar study found that, in healthy women, CAT expression fluctuates with the menstrual cycle, being lower during the early proliferative phase and higher in the later stages. By contrast, patients with endometriosis were shown to exhibit consistently elevated CAT levels throughout the menstrual cycle without any cyclic variation, suggesting that these patients are chronically dealing with oxidative damage, leading to sustained CAT activity (25). Another antioxidant enzyme, paraoxonase 1 (PON-1), is associated with high-density lipoprotein (HDL), detoxifies lipid peroxide (LOOH) and prevents low-density lipoprotein oxidation, thereby protecting tissues from oxidative damage (26). It has been shown that LOOH levels are significantly elevated in patients with endometriosis, whereas PON-1 activity is markedly reduced. Furthermore, PON-1 activity was demonstrated to decrease as disease severity increases (27). The elevation of LOOH indicates substantial lipid peroxidation in endometriosis, which generates additional free radicals, and exacerbates ROS production and oxidative stress (28). This finding aligns with reports of increased levels of lipid peroxidation markers, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal, in patients with endometriosis (29,30). Furthermore, elevated ROS levels can damage DNA, leading to oxidative DNA damage. Increased levels of 8-hydroxy-2'-deoxyguanosine, a marker of DNA oxidation, have also been observed in patients with endometriosis (31,32).

Mitochondrial dysfunction and excessive ROS production in endometriosis. Mitochondria serve as the primary energy factories of the cell and are also a central source of ROS. Mitochondrial ROS are mainly produced through the electron transport chain (ETC) during oxidative phosphorylation (33). This process takes place primarily in the mitochondrial

Table I. Alterations in oxidative stress markers in endometriosis.

A, Antioxidants			
First author, year	Specific marker	Alterations	(Refs.)
Prieto, 2012	SOD	Decreased in patients with endometriosis	(22)
Ekarattanawong, 2017	GPx	GPx plasma activity in patients with endometriosis is significantly reduced to 1.72% of the control group	(24)
Turkyilmaz, 2016	CAT	Increased in patients with endometriosis	(23)
Verit, 2008	PON-1	PON-1 activity is significantly lower in patients with endometriosis, with a further decline detected as disease severity increases	(27)
Prieto, 2012	Vitamin C	Levels of vitamin C are reduced in patients with endometriosis	(22)
Turkyilmaz, 2016	Thiols	Serum native thiol and total thiol level are significantly reduced in patients with endometriosis	(23)
B, Oxidative markers			
First author, year	Specific marker	Alterations	(Refs.)
Verit, 2008	LOOH	Levels of LOOH are increased in patients with endometriosis	(27)
Mier-Cabrera, 2011	MDA	MDA levels are significantly higher in the peritoneal fluid of patients with endometriosis compared with in a control group	(29)
Hayashi, 2020	4-HNE	Significantly increased at each stage of the follicles in patients with ovarian endometriosis	(30)
Da Broi, 2016	8-OHdG	Elevated in the follicular fluid of patients with endometriosis	(32)

4-HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; CAT, catalase; GPx, glutathione peroxidase; LOOH, lipid peroxide; MDA, malondialdehyde; PON-1, paraoxonase 1; SOD, superoxide dismutase.

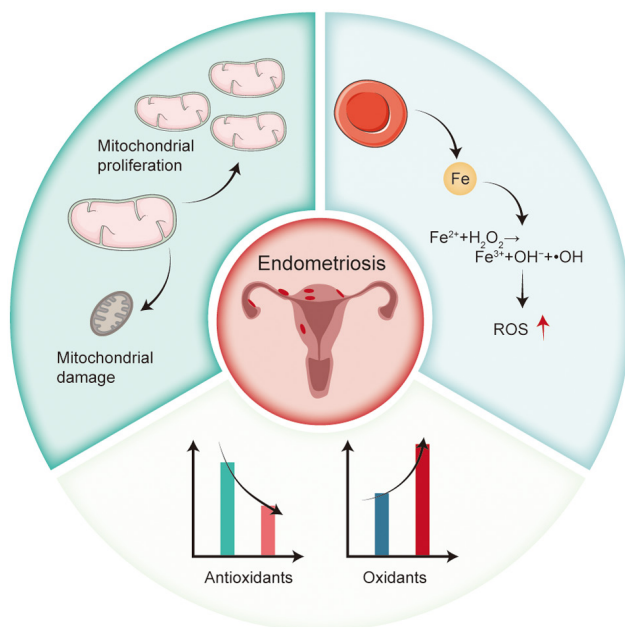


Figure 1. Redox imbalance in patients with endometriosis. In patients with endometriosis, oxidative stress markers such as lipid peroxides are elevated, while antioxidant enzymes are reduced, indicating a significant redox imbalance. Additionally, mitochondrial proliferation and mitochondrial damage, along with increased iron levels, are observed in endometriosis. These changes further promote the production of ROS. H₂O₂, hydrogen peroxide; ROS, reactive oxygen species.

cristae, and when electrons leak from the ETC, they react with oxygen to form superoxide anions, a key source of mitochondrial ROS (34). These superoxide anions are highly reactive and require detoxification by mitochondrial SOD2, which converts them into hydrogen peroxide (35). Notably, SOD2 has been shown to be upregulated in patients with endometriosis (36,37), thus indicating elevated superoxide levels. However, despite the upregulation of SOD2, its ability to fully mitigate ROS appears limited, as ROS levels remain significantly higher in ectopic endometrial tissue compared with in eutopic tissue (37). This may be due to the fact that hydrogen peroxide, the product of SOD2 activity, is also a ROS. The overall mitochondrial ROS burden thus surpasses the neutralizing capacity of the increased SOD2, rendering these tissues more susceptible to oxidative stress.

As shown in Fig. 2, mitochondrial dynamics, including processes such as fission and fusion, are regulated by ROS such as hydrogen peroxide, which alters mitochondrial morphology and quantity in response to cellular energy demands and ROS levels (38). Chen *et al* (37) revealed that ectopic endometrial stromal cells harbor significantly greater numbers of mitochondria compared with eutopic cells, with elongated structures, increased cristae and higher electron density within the matrix. These mitochondrial alterations, including increased number and elongation, enable cells to better meet metabolic demands by providing more oxidative

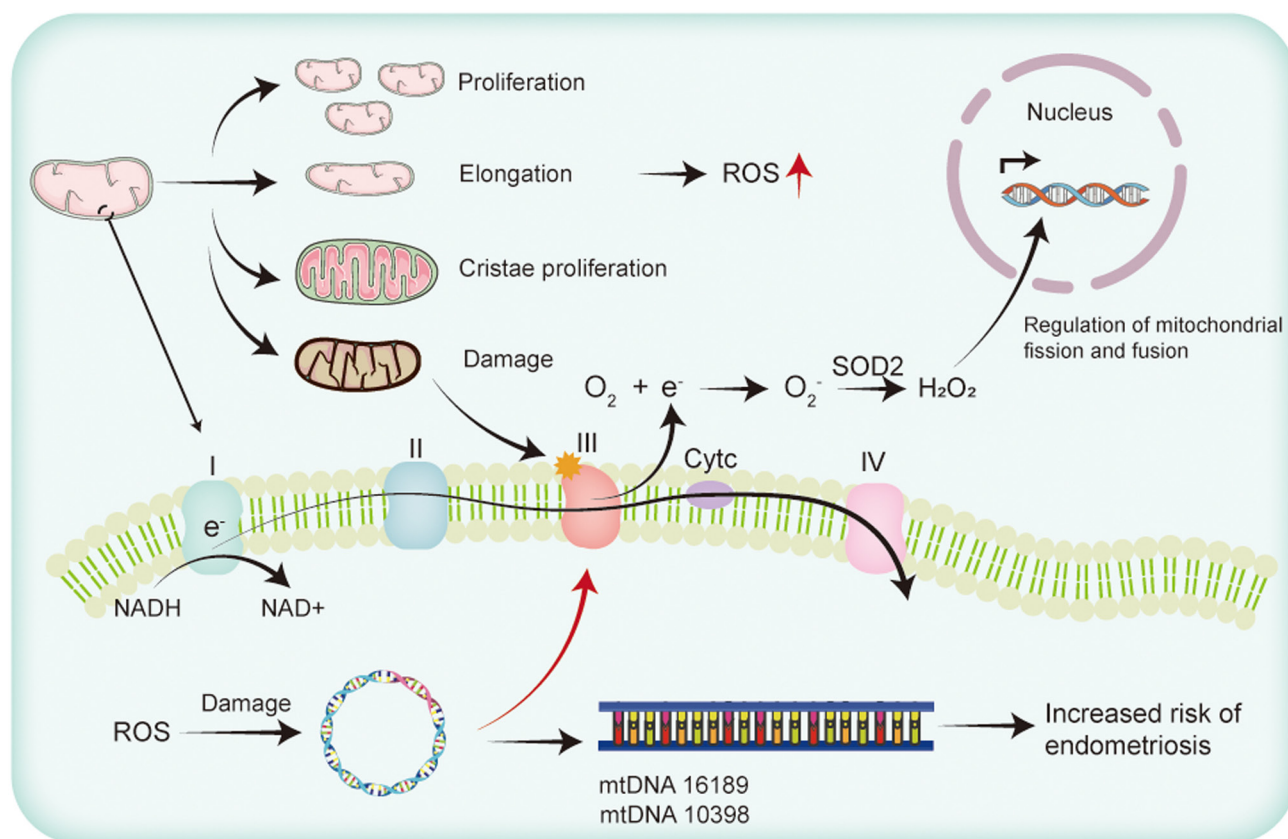


Figure 2. Mitochondrial dysregulation and ROS production in endometriosis. In patients with endometriosis, mitochondria are found to exhibit increased quantity, elongated morphology and deeper cristae curvature, creating more sites for oxidative phosphorylation and thereby promoting the production of reactive oxygen species. Moreover, an increase in three types of mitochondria with structural damage is observed, leading to enhanced electron leakage. ROS, such as H₂O₂, can regulate nuclear signaling to further promote mitochondrial proliferation. Additionally, ROS can attack mtDNA, impairing the assembly of the mitochondrial electron transport chain and increasing the risk of endometriosis. H₂O₂, hydrogen peroxide; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; SOD2, superoxide dismutase 2.

phosphorylation sites (39). However, this metabolic adaptation also places greater stress on the ETC, further exacerbating ROS production (40). Additionally, a higher proportion of type III mitochondria, characterized by irregular cristae and evident mitochondrial damage, has been observed in ectopic stromal cells compared with in eutopic cells (37). The presence of these damaged mitochondria is associated with reduced membrane potential (41), which further impairs ETC efficiency and elevates ROS production (42). Disrupted cristae architecture also contributes to mitochondrial dysfunction, promoting electron leakage and superoxide formation, thereby amplifying mitochondrial ROS levels (43).

As discussed, the limited capacity to neutralize ROS makes the mitochondria in ectopic endometrial tissues particularly vulnerable to oxidative damage. Excessive ROS can induce mutations in mitochondrial DNA (mtDNA) (44). Cho *et al* (45) identified notable mtDNA mutations in patients with endometriosis, with the mtDNA 16189 variant being notably more prevalent in these patients than in controls. Additionally, the combined presence of mtDNA 16189 and mtDNA 10398 variants was reported to be strongly associated with an increased risk of endometriosis ($P=0.015$). mtDNA encodes 13 protein subunits essential for the assembly of electron transport complexes I, III, IV and V (46). Govatati *et al* (47) sequenced genes encoding mitochondrial complex I and identified 72 mutations associated with endometriosis, with the

haplotype '10398A/10400C/13603AG' linked to an elevated risk of the disease. Moreover, this previous study demonstrated that mitochondrial complex I expression was significantly higher in eutopic endometrial tissue than in ectopic tissue (47). These findings suggested that mtDNA mutations can impair mitochondrial respiratory function, further enhancing ROS production (48).

Iron metabolism dysregulation and enhanced generation of ROS. In healthy individuals, iron binds to transferrin, a protein that can carry two iron ions to form diferric transferrin (49). Diferric transferrin binds to transferrin receptors on the cell surface, facilitating internalization and release of iron ions into the cell (50). Once inside the cell, iron participates in various cellular processes or is stored in ferritin (51). Studies have shown a significant increase in ferritin levels in the ectopic endometrial tissue of patients with endometriosis (52,53). Additionally, the breakdown of red blood cells releases iron, and elevated levels of ferritin and hemoglobin have been observed in the peritoneal cavity of patients with endometriosis compared with in healthy individuals (4). Similarly, Van Langendonck *et al* (54) demonstrated iron deposits in endometriotic lesions, and experiments in mice revealed that injecting menstrual effluent containing red blood cells into mice led to substantial iron accumulation in lesions, whereas iron deposits were less prominent in injections containing only

endometrial cells or serum. This suggests that red blood cells are a key factor in iron deposition within lesions.

Beyond red blood cells, enhanced iron metabolism has been observed in the macrophages of patients with endometriosis (55). The detection of hemosiderin-laden macrophages in the peritoneal fluid has been reported to improve the diagnostic specificity for endometriosis (56). In addition, Lousse *et al* (57) demonstrated that peritoneal macrophages from patients with endometriosis exhibit significantly higher ferritin levels and iron concentrations than those from control subjects. Furthermore, an increase in transferrin receptor expression has been identified in the peritoneal macrophages of patients with endometriosis (49). These findings suggest that iron storage may be significantly elevated in the peritoneal macrophages of individuals with endometriosis. Ectopic endometrial tissue stimulates the immune response, prompting macrophages to degrade red blood cells and release hemoglobin, thus contributing to the elevated iron levels observed in these patients (58). Kondo *et al* (59) revealed that macrophages have a limited capacity to phagocytose red blood cells; when the phagocytic index is <1.5 red blood cells per macrophage, iron is slowly released over 24 h; however, as phagocytic activity increases, iron release becomes significantly more pronounced.

These studies collectively highlight a substantial increase in iron levels in patients with endometriosis. Notably, iron serves a key role in the Fenton reaction, in which it catalyzes the conversion of hydrogen peroxide into highly reactive hydroxyl radicals, thereby increasing ROS production (60). This is consistent with findings by Woo *et al* (52), which showed that iron stimulation of 12Z human endometriotic cells can lead to a marked elevation in ROS levels.

3. Role of ROS in the progression and therapeutic targeting of endometriosis

Ectopic endometrial tissue in patients with endometriosis often displays a proliferative phenotype reminiscent of cancer cells, characterized by unchecked growth, local invasion, angiogenesis, distant metastasis and the presence of multiple lesions (61). ROS are known to activate key cell proliferation pathways, including the Raf/MEK/ERK and mTOR signaling cascades, while also inducing chromatin alterations. This suggests that ROS may act as signaling molecules that drive the transformation of ectopic endometrial tissue into a more proliferative phenotype (16).

ROS-mediated activation of the Raf/MEK/ERK signaling pathway. The Raf/MEK/ERK pathway is a pivotal intracellular signaling cascade involved in regulating cellular proliferation, migration and apoptosis (62). In both mouse models of endometriosis and human endometriotic stromal cells, inhibition of the Raf/MEK/ERK pathway has been shown to induce apoptosis, effectively suppressing the proliferation and migration of endometriotic cells (63). The ability of ROS to activate ERK has been widely reported across various cell types (64,65). For example, in human endometrial stromal cells treated with di(2-ethylhexyl) phthalate, an increase in both ERK activity and ROS levels was observed, implicating ROS in the activation of ERK in these cells (66). The ERK family includes

two isoforms, ERK1 (44 kDa) and ERK2 (42 kDa) (67), both of which are activated by MEK, a key upstream kinase that phosphorylates threonine and tyrosine residues on ERK (68). MEK1 and MEK2, the primary subtypes involved in ERK activation, are regulated by the RAF family of proteins, which includes A-Raf, B-Raf and C-Raf (69,70). RAF proteins are, in turn, activated by RAS, a GTP-binding protein that undergoes a GDP-to-GTP transition in response to extracellular stimuli, directly interacting with RAF to initiate the Raf/MEK/ERK cascade (71). Additionally, intracellular calcium levels regulate ERK activation, and elevated calcium concentrations have been shown to enhance ERK signaling. ROS activate the Raf/MEK/ERK pathway through multiple mechanisms (72). ROS increase epidermal growth factor receptor phosphorylation, providing binding sites for the Grb2-SOS complex, which activates RAS signaling (73). ROS also activate Src kinase, which subsequently activates phospholipase C, leading to the hydrolysis of phosphatidylinositol 4,5-bisphosphate and the generation of inositol triphosphate (IP3) and diacylglycerol (DAG) (74). IP3 promotes intracellular calcium release, further activating ERK (75), while DAG activates protein kinase C (PKC), which directly phosphorylates and activates C-Raf (76,77). Moreover, ROS can inhibit protein phosphatase PP2A by oxidizing cysteine residues at its active site, thereby reducing its catalytic activity (78). Since PP2A dephosphorylates ERK, its inhibition sustains ERK in an active, phosphorylated state (79).

The activation of ERK serves a critical role in anti-apoptotic processes (80). Chen *et al* (81) demonstrated that ubiquitin-specific protease 10 activates the Raf-1/MEK/ERK pathway, promoting proliferation and migration of endometrial stromal cells in endometriosis while inhibiting apoptosis. Leconte *et al* (82) revealed that cells from patients with deep infiltrating endometriosis exhibit a significantly higher proliferation rate than controls, a phenomenon linked to increased endogenous oxidative stress and ERK activation. These findings highlight the role of ROS-mediated ERK activation in driving the progression of endometriosis.

ROS-induced activation of the mTOR signaling pathway. mTOR activation involves multiple interconnected signaling pathways. Within the PI3K/AKT pathway, mTOR activation is initiated by the upstream activation of PI3K. When growth factors bind to receptor tyrosine kinases (RTKs), it triggers receptor dimerization and autophosphorylation, recruiting and activating PI3K (83). Activated PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which functions as a second messenger, recruiting AKT and PDK1 to the plasma membrane. PDK1 then phosphorylates AKT at the Thr308 site, activating it (84), with mTORC2 also contributing to AKT activation (85). Activated AKT phosphorylates tuberous sclerosis complex 2 (TSC2), causing it to dissociate from the membrane, thus relieving the inhibition of Rheb by the TSC1/2 complex (86). Activated Rheb subsequently activates mTORC1 (87), promoting mRNA translation by releasing the inhibition on eIF4E (88) and stimulating protein synthesis via the phosphorylation of ribosomal protein S6 (89). The mTOR pathway is also modulated by AMPK; when cellular energy is sufficient, mTORC1 is activated to drive cell proliferation (90), whereas low ATP levels activate AMPK, which

phosphorylates TSC2, stabilizing the TSC complex and inhibiting mTORC1 (91).

ROS can activate the mTOR pathway through several mechanisms. ROS can directly interact with the β subunit of PI3K, enhancing its activity and promoting the conversion of PIP2 to PIP3 (92). Additionally, ROS can oxidize catalytic cysteine residues in protein tyrosine phosphatases (PTPs), leading to their inactivation (93). Normally, PTPs dephosphorylate RTKs, dampening RTK-mediated signaling. By inactivating PTPs, ROS sustain RTK phosphorylation, thereby amplifying RTK signaling (94). PTEN, a key negative regulator of the PI3K/AKT pathway, dephosphorylates PIP3 back to PIP2, thus inhibiting AKT activation (95). However, ROS can oxidize cysteine residues within PTEN, forming intramolecular disulfide bonds that inhibit PTEN activity (96). For example, Lee *et al* (97) demonstrated that hydrogen peroxide can oxidize cysteine residues in PTEN, forming a disulfide bond between Cys124 and Cys71, leading to PTEN inactivation. This inactivation prevents PTEN from dephosphorylating PIP3, resulting in elevated PIP3 levels and enhanced AKT activation (98). Additionally, ROS can inhibit PP2A, a phosphatase that dephosphorylates AKT at Thr308, preventing the deactivation of AKT (99,100).

The mTOR signaling pathway is crucial in regulating the cyclical proliferation, migration, adhesion and invasion of endometrial cells throughout the menstrual cycle (101). Endometriosis, an estrogen-dependent disease, is significantly influenced by estradiol-17 β (E2), which promotes uterine epithelial cell proliferation through the activation of the mTOR pathway. E2, one of the primary ovarian sex hormones, drives cyclic proliferation of uterine epithelial cells (102). It activates the PKC signaling pathway, leading to ERK1/2 activation, which ultimately activates mTOR and promotes epithelial cell proliferation, an effect that can be blocked by rapamycin, an mTOR inhibitor (103), indicating the involvement of mTOR in the proliferation of ectopic endometrial cells. Additionally, elevated AKT phosphorylation has been observed in ectopic endometrial tissues compared with in eutopic tissues in patients with endometriosis, indicating significant AKT activation in ectopic lesions (104). This previous study also revealed that this phosphorylation is driven by E2 and is not inhibited by estrogen receptor antagonists (104), suggesting a potential alteration in AKT signaling in endometriosis, making it more responsive to estrogen or resistant to conventional antagonism. Similarly, Laudanski *et al* (105) detected increased expression of AKT, an upstream activator of mTOR, and 4EBP1, a downstream effector of mTOR, in endometriotic tissues using microfluidic gene chips in patients with endometriosis. Zhang *et al* (106) demonstrated that hyperactivation of the PI3K/AKT pathway contributes to the overproliferation of epithelial cells in endometriotic lesions, while endometriotic stromal cells lose the regulatory control over epithelial growth, as indicated by elevated AKT phosphorylation.

ROS and epigenetic alterations driving disease progression. Previous studies have emphasized the importance of epigenetic changes, such as DNA methylation, histone modifications and chromatin remodeling, in the development of endometriosis (107-109). Chromatin remodeling, which influences gene transcription by regulating DNA accessibility, has been linked

to the progression of endometriosis through structural changes in specific chromosomes (110,111).

The *ARID1A* gene, a tumor suppressor, encodes a key subunit of the SWI/SNF chromatin remodeling complex, which regulates gene expression by altering chromatin structure (112). Loss of *ARID1A* disrupts chromatin organization, activates the p53 pathway and inhibits apoptosis, enhancing cellular survival (113). *ARID1A* mutations have been identified in various types of cancer (114). Endometriosis-related ovarian neoplasms often arise from ectopic endometrial cysts due to oncogenic mutations, with oxidative stress serving a key role in driving these mutations. (115) *ARID1A* inactivation is a common alteration, contributing to tumorigenesis and decreased *ARID1A* expression in endometriosis (116). *ARID1A* mutations, primarily nonsense or frameshift types, are more common in endometriotic epithelial cells and lead to reduced or absent ARID1A protein (108). These mutations are often linked to malignant transformation, as normal *ARID1A* expression is retained in non-cancerous endometriotic tissues (117). Wilson *et al* (118) further demonstrated that ARID1A maintains epithelial characteristics in endometrial cells by binding to open chromatin regions of epithelial-mesenchymal transition (EMT)-related genes. This binding prevents the upregulation of EMT genes, thereby inhibiting the EMT process. When ARID1A is inactivated, endometrial epithelial cells undergo EMT, acquiring invasive properties. Moreover, ARID1A has been shown to colocalize with the progesterone receptor in the endometrium, and its specific deletion disrupts hormonal signaling and the regulation of epithelial cell proliferation, leading to hyperproliferation of epithelial cells (119,120).

Therapeutic approaches targeting oxidative stress. Endometriosis is frequently associated with elevated oxidative stress (121), which arises from an imbalance between ROS production and the antioxidant defenses of the body (122). In this condition, oxidative stress contributes to inflammation and pain in the affected lesions (123). Antioxidants, by neutralizing excess ROS, can mitigate oxidative damage and alleviate the symptoms of endometriosis (124). Table II summarizes the antioxidants recently explored in the treatment of endometriosis. The present review has categorized these agents into three groups: Vitamins, plant-derived extracts and experimental therapies, to present a more structured overview of their potential therapeutic roles.

Vitamin supplementation in endometriosis management. Vitamins, as key antioxidants, have been extensively studied for their therapeutic potential in endometriosis. Pelvic pain, a primary symptom of endometriosis, severely impacts the quality of life for patients (125). A study involving 135 patients with endometriosis revealed that their levels of 25-OH vitamin D were significantly lower than those of healthy controls, with this deficiency potentially linked to pelvic pain (126). Supplementation with 50,000 IU vitamin D every 2 weeks over 12 weeks has been shown to reduce high-sensitivity C-reactive protein levels, increase total antioxidant capacity, improve the total cholesterol/HDL ratio and relieve pelvic pain (127). However, another study reported that similar vitamin D supplementation following

Table II. Application of antioxidants in the treatment of endometriosis.

First author, year	Antioxidant	Type of study	Therapeutic effects	(Refs.)
Mehdizadehkashi, 2021	Vitamin D	Clinical trial	Reduces hs-CRP levels, increases TAC concentration, improves total cholesterol/HDL cholesterol ratio and alleviates pelvic pain	(126)
Almassinokiani, 2016	Vitamin D	Clinical trial	Shows no significant difference in reducing dysmenorrhea or pelvic pain compared with a placebo group	(127)
Mier-Cabrera, 2008; Santanam, 2013	Vitamin C and vitamin E	Clinical trial	Improves inflammatory and oxidative stress markers in plasma and peritoneal fluid, and reduces chronic pain	(128,129)
Bayu, 2024	Vitamin C and vitamin E	Meta-analysis	Shows a higher proportion of patients reporting reductions in chronic pelvic pain, dysmenorrhea and dyspareunia	(130)
Swarnakar, 2009	Curcumin	Animal study	Reduces lipid peroxidation and protein oxidation levels in endometriotic tissue, decreases MMP-9 activity and inhibits the progression of endometriosis in a dose-dependent manner	(133)
Matsuzaki, 2014	EGCG	Clinical trial	Reduces proliferation, migration and invasion of endometriotic cells	(135)
Matsuzaki, 2014	EGCG	Animal study	Inhibits fibrosis of ectopic endometrial cells, with stronger inhibitory effects than NAC	(135)
Wang, 2021	Resveratrol	Animal study	Activates PPAR γ and regulates the PI3K/Akt signaling pathway to alleviate the progression of endometriotic lesions	(137)

EGCG, epigallocatechin gallate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NAC, N-acetylcysteine; TAC, total antioxidant capacity.

surgery did not significantly reduce dysmenorrhea or pelvic pain in patients with endometriosis (128). The discrepancies in these findings could be partially attributed to differences in sample size, with the latter study involving a smaller cohort of only 39 participants. Furthermore, the latter study did not assess participants' serum vitamin D levels prior to the intervention. Given the high prevalence of vitamin D deficiency in the study region, it is likely that a substantial proportion of the participants had pre-existing vitamin D deficiency. As a result, the observed outcomes may reflect the effects of correcting vitamin D deficiency rather than the therapeutic efficacy of vitamin D in treating endometriosis. Additionally, vitamins C and E have been used to manage pelvic pain in endometriosis. Mier-Cabrera *et al* (129) demonstrated that combined supplementation of vitamins E and C reduced oxidative stress markers, such as MDA and LOOH, in the plasma and peritoneal fluid of patients with endometriosis, although no improvement in pregnancy rates was observed. Santanam *et al* (125) further showed that daily supplementation with vitamin E (1,200 IU) and vitamin C (1,000 mg) for 8 weeks significantly decreased chronic pain and lowered inflammatory markers in the peritoneal fluid of patients with endometriosis. Similarly, a meta-analysis conducted by Bayu and Wibisono (130) reported that patients who supplemented

with vitamins C and E reported significant reductions in chronic pelvic pain, dysmenorrhea and dyspareunia.

Plant-based extracts in endometriosis treatment. In addition to vitamins, plant extracts, due to their unique bioactive compounds, have been widely discussed in the context of antioxidant and endometriosis treatment (131). Therefore, understanding the role of plant extracts as active agents in the treatment of endometriosis may further enhance the application of antioxidant strategies in managing this condition. In particular, polyphenolic compounds have shown strong antioxidant and anti-inflammatory properties, making them promising candidates for endometriosis therapy (132). Curcumin, a polyphenol from turmeric, has been shown to inhibit the progression of endometriosis in mouse models in a dose-dependent manner by reducing lipid peroxidation, protein oxidation and MMP-9 activity in endometriotic tissues (133). Epigallocatechin gallate (EGCG), a potent antioxidant flavonoid from tea, has also shown promise in endometriosis management (134). A clinical study involving 45 patients with endometriosis demonstrated that EGCG effectively inhibited the proliferation, migration, and invasion of endometriotic cells (135). Animal studies further confirmed that EGCG can suppress fibrosis in ectopic endometrial cells, with a stronger inhibitory effect than the commonly used antioxidant N-acetylcysteine (135).

Experimental therapies. Plant-based extracts show strong antioxidative and anti-inflammatory properties, making them promising agents for endometriosis treatment. Nevertheless, experimental therapies are being developed to address the complex mechanisms of oxidative stress at a molecular level. Resveratrol, a plant-derived stilbene with multiple pharmacological activities, including antioxidant properties, has been studied for its therapeutic potential in endometriosis (136). Wang *et al* (137) demonstrated that resveratrol attenuated the development of endometriotic lesions, and transcriptomic analysis revealed activation of PPAR γ and modulation of the PI3K/Akt signaling pathway after resveratrol treatment in a mouse model. PPAR γ , a nuclear receptor transcription factor, enhances cellular antioxidant capacity by regulating antioxidant enzyme expression and reducing ROS levels (138). Given the close association between the PI3K/Akt pathway, increased ROS and the progression of endometriosis (92,106), resveratrol may exert therapeutic effects by restoring redox balance and modulating ROS-driven signaling pathways.

4. Conclusion and future perspectives

Endometriosis is a complex and multifactorial disease with a pathogenesis that remains incompletely understood. A hallmark of endometriosis is redox imbalance, leading to increased oxidative stress markers and a weakened antioxidant defense system, including decreased levels of antioxidants and antioxidant enzymes. Mitochondrial dysfunction contributes to excessive production of mitochondrial ROS and mutations in mtDNA, further exacerbating oxidative stress. Additionally, abnormal iron metabolism in endometriosis results in increased iron accumulation, which generates large quantities of hydroxyl radicals via the Fenton reaction, amplifying ROS generation. ROS not only serve as a source of oxidative stress but also serve a pivotal role in disease progression; they promote the proliferation, migration and survival of endometriotic cells by activating signaling pathways such as Raf/MEK/ERK and mTOR. Moreover, oxidative stress-induced epigenetic alterations, including mutations and inactivation of the *ARID1A* gene, may lead to chromatin remodeling and dysregulated gene expression, accelerating disease advancement.

While antioxidants have shown promising effects in the treatment of endometriosis, inconsistent findings exist for certain agents such as vitamin D. Furthermore, the precise molecular mechanisms underlying antioxidant therapy, the optimal timing for intervention, and the interactions between antioxidants and existing hormonal or anti-inflammatory treatments remain to be elucidated. Therefore, large-scale, multi-center randomized controlled trials are needed to evaluate the efficacy and safety of specific antioxidants in diverse patient populations. These trials should prioritize determining the optimal dosages, administration protocols and the effects of combination therapies. Additionally, basic research should further investigate ROS-related signaling pathways and abnormalities in iron metabolism in endometriosis to facilitate the development of novel targeted therapies. Addressing these challenges will pave the way for more effective and personalized treatment strategies, ultimately improving the quality of life for women affected by this debilitating condition.

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Authors' contributions

LH, XY and XJ reviewed the literature and wrote the manuscript. ML collected the information. LS was responsible for constructing the figures and tables in this review, and conceptualized the review. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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