Advances in Pharmacological Treatment of Endometriosis

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Abstract

Endometriosis is a common estrogen-dependent disease and constitutes one of the primary causes of dysmenorrhea and infertility among women of reproductive age. Both hormonal therapy and surgical intervention represent first-line treatment modalities; however, prolonged use of hormonal agents may impair fertility, whereas surgical treatment is associated with high recurrence rates and can compromise ovarian reserve function. Consequently, refining existing therapeutic strategies and identifying novel pharmaceutical agents is of considerable significance. This review summarizes the pharmacological therapeutic approaches for endometriosis, aiming to provide new perspectives for its clinical management.

Full Text

Advances in Drug Therapy for Endometriosis

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Abstract

Endometriosis is a common estrogen-dependent disease and a leading cause of dysmenorrhea and infertility among women of reproductive age. Both hormonal and surgical interventions represent first-line treatment modalities. However,

long-term hormonal therapy can impair fertility, while surgical treatment is associated with high recurrence rates and may compromise ovarian reserve. Therefore, improving existing therapeutic strategies and identifying novel therapeutic agents is of significant clinical importance. This review summarizes pharmacological treatment approaches for endometriosis to provide new perspectives for clinical management.

Keywords: endometriosis, drug therapy, antioxidants, anti-angiogenic drugs, immunomodulators

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Endometriosis (EM) is defined as the presence of functional endometrial tissue (glands and stroma) outside the uterine cavity. This condition affects approximately 10-15% of reproductive-age women and manifests clinically as pelvic pain and infertility [1]. Based on lesion location, endometriosis can be classified as ovarian, peritoneal, deep infiltrating, or extrapelvic. Despite extensive research, the pathogenesis remains incompletely understood. Local hyper-estrogenic environments, inflammatory responses with fibrosis, oxidative stress, angiogenesis, and immune dysregulation are all implicated in disease development, progression, and recurrence [2,3].

Both surgical and hormonal therapies constitute first-line treatments for endometriosis. Surgical management primarily involves excision of endometriotic lesions but is associated with high recurrence rates and potential impairment of ovarian reserve. Pharmacological therapy typically employs combined oral contraceptives, progestins, and gonadotropin-releasing hormone agonists (GnRH-a) to suppress ectopic endometrial proliferation, though hormone-related side effects including vasomotor symptoms and ovulation inhibition remain problematic [4,5]. Consequently, identifying well-tolerated agents with favorable safety profiles and improved patient compliance is urgently needed. This review discusses pharmacological treatments for endometriosis to provide novel therapeutic insights.

1. Conventional Pharmacological Agents

Conventional medications for endometriosis include nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), high-efficiency progestins, GnRH-a, and aromatase inhibitors.

1.1 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs reduce pain by inhibiting cyclooxygenase and decreasing prostaglandin synthesis but do not halt disease progression. A randomized, double-blind, placebo-controlled trial involving 24 endometriosis patients with dysmenorrhea demonstrated that naproxen significantly improved pain symptoms compared to placebo [6]. However, NSAID use carries risks of renal impairment and gastrointestinal ulceration.

1.2 Progestins and Combined Oral Contraceptives

COCs and high-efficiency progestins suppress the hypothalamic-pituitary-ovarian axis through negative feedback, reducing gonadotropin levels, inhibiting ovulation, and creating a hypoestrogenic environment that suppresses ectopic lesion growth. Progestins also act directly on ectopic endometrium to induce atrophy [7]. COCs further alleviate pain by decreasing prostaglandin production [7] and can prevent or reduce postoperative recurrence of dysmenorrhea and disease [8]. Continuous or extended-cycle COC regimens are more effective than cyclic administration, inducing a pseudopregnancy state through artificial amenorrhea [9]. However, COC use carries thrombotic risks in women over 40 or those with diabetes, hypertension, thrombotic history, or smoking [10]. For these high-risk populations, progestin therapy is preferable. Dienogest (DNG), a new-generation synthetic progestin, offers direct anti-inflammatory, anti-angiogenic, and anti-fibrotic effects on ectopic lesions while increasing progesterone receptor β expression in endometriosis, representing a promising long-term treatment option [11].

1.3 Gonadotropin-Releasing Hormone Agonists and Aromatase Inhibitors

GnRH-a, similar to endogenous GnRH, binds GnRH receptors. Initial administration stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production, but continuous use leads to receptor downregulation, reducing LH and FSH levels and suppressing estrogen production to menopausal ranges, thereby inducing amenorrhea and inhibiting disease progression.

Aromatase inhibitors block estrogen synthesis in peripheral tissues and ovaries, alleviating endometriosis-associated pain, reducing extrauterine lesion size, and improving quality of life. Clinical studies demonstrate that letrozole and anastrozole effectively reduce pain severity. One study reported that letrozole combined with progestin therapy reduced endometrioma volume by 75% after three months while significantly improving pain [12]. However, their use is limited by adverse events including bone and joint pain, myalgia, and fatigue [13].

2. Antioxidants

Endometriosis pathogenesis involves increased reactive oxygen species (ROS) and oxidative products, decreased antioxidants and antioxidant enzymes, and iron metabolism dysregulation. Elevated oxidative stress triggers peritoneal inflammation [14], which increases local aromatase activity and estrogen levels. Similar to cancer, ROS promotes endometriotic cell proliferation [14] and induces vascular endothelial growth factor (VEGF) overexpression and angiogenesis [15,16]. Disease severity often correlates positively with oxidative stress marker levels [17].

A clinical trial evaluating vitamins C and E demonstrated that among 59 patients with endometriosis, infertility, and/or pelvic pain, antioxidant therapy

significantly reduced inflammatory markers (IL-6, CCL5, and CCL2) and alleviated dyspareunia and dysmenorrhea compared to placebo [18]. Another study showed that combined vitamin C and E supplementation for eight weeks significantly reduced pelvic pain, dyspareunia, and dysmenorrhea severity while decreasing pro-oxidant markers malondialdehyde (MDA) and ROS levels [19]. In a non-randomized prospective study, ω-3 fatty acid administration after conservative surgery improved pelvic pain and dyspareunia. An observational cohort study in women with ovarian endometriomas found that three months of N-acetylcysteine (NAC) treatment reduced cyst diameter, while untreated controls showed significant enlargement, possibly through NAC's inhibition of abnormal cell proliferation and inflammatory gene activation [20]. Melatonin treatment reduced protein and lipid oxidation while decreasing matrix metalloproteinase-9 (MMP-9) activity in rats with endometriosis, suggesting oxidative stress reduction through MMP downregulation [21].

Phytochemicals have gained increasing attention. Resveratrol inhibits tumor cell proliferation while exhibiting antioxidant, anti-inflammatory, and anti-angiogenic activities [22]. Curcumin suppresses endometriotic lesion growth and ectopic cell proliferation, with dietary supplementation significantly improving clinical symptoms [23]. Pycnogenol, a plant-derived mixture of polyphenols and proanthocyanidins with antioxidant and anti-inflammatory properties, improves pain in endometriosis patients and enhances oral contraceptive efficacy [24].

3. Anti-Angiogenic Drugs

Neovascularization is critical for endometriosis development and progression. Hypoxia-inducible factor-1α (HIF-1α) and stromal cell-derived factors promote endothelial progenitor cell migration from bone marrow to angiogenic sites [25]. VEGF is a key stimulator of angiogenesis, promoting vascular permeability, extracellular matrix degradation, endothelial cell migration, proliferation, and vessel formation [25]. Animal studies demonstrate that tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib) interfere with lesion formation by inhibiting angiogenic pathways in rats [26]. In endometriosis, dopamine receptor agonists (bromocriptine, cabergoline, quinagolide) downregulate pro-angiogenic pathways in inflammatory, endothelial, and endometrial cells while upregulating anti-angiogenic pathways, suppressing cell proliferation, reducing lesion size, and alleviating pain. Combination therapy with pentoxifylline increases pregnancy rates [27,28]. The complexity of angiogenic factor cross-talk in endometriotic lesions limits single-agent efficacy. Combination therapy with the angiotensin II receptor blocker telmisartan and the selective cyclooxygenase-2 (COX-2) inhibitor parecoxib was more effective than telmisartan alone in treating endometriotic lesions in mice and further inhibited nerve fiber ingrowth [29]. An animal study with 30 rats showed that oral rosuvastatin and intraperitoneal bevacizumab induced more pronounced lesion regression than oral progesterone [30].

4. Immunomodulators

Immune factors play crucial roles in endometriosis pathogenesis, including abnormal immune cell function, cytokine dysregulation, immune cell activation, and potential autoimmune responses [31]. Tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8 are critically involved. 6-Shogaol exhibits antioxidant, anticancer, neuroprotective, and anti-inflammatory effects. Animal studies demonstrate that 6-shogaol significantly reduces endometriotic lesion size by downregulating NF- B signaling, VEGF and VEGFR-2 (Flk-1) expression, and decreasing IL-1β, IL-6, prostaglandin E2 (PGE2), and nitric oxide (NO) production [32-35]. In a randomized controlled animal experiment, tocilizumab (anti-IL-6 antibody) significantly reduced ectopic lesion volume and induced atrophy of ectopic endometrial epithelium in 42.8% of treated rats versus 0% in controls [36]. Long-acting IL-8 antibody (AMY109) significantly reduced lesion volume and improved pelvic adhesions in a monkey model by inhibiting inflammation and fibrosis [37]. Pyrvinium pamoate targets IL-6 and IL-8, suppressing their mRNA expression in vitro [38]. Nobiletin acts on NF- B, IL-6, and IL-1β, reducing lesion size by inhibiting cell proliferation, angiogenesis, and excessive inflammation while decreasing pain levels in mice [39]. Additionally, the antirheumatic agent hydroxychloroquine (HCQ) and its derivatives reduce lesion numbers in endometriosis models, with HCQ treatment increasing interferon-γ-induced protein 10 (IP-10) levels and macrophage populations in mouse peritoneal fluid [40].

Beyond these agents, therapies targeting epithelial-mesenchymal transition (EMT), antibiotics, probiotics, and nanoceria have demonstrated therapeutic potential. EMT is a biological process whereby epithelial cells transform into mesenchymal phenotypes with enhanced migratory, invasive, and anti-apoptotic capacities, which is essential for endometriosis establishment and progression [41,42]. Melatonin and 3,6-dihydroxyflavone block 17β-estradiol-induced migration, invasion, and EMT in normal and ectopic endometrial epithelial cells by reducing Notch pathway activity [43]. Isoliquiritigenin and fucoidan reduce lesion volume and weight [44], decrease inflammatory cytokines and VEGF levels in serum and lesions, and inhibit EMT while inducing apoptosis-related protein expression [45]. Dysbiotic microbiota can promote estrogen disruption and systemic inflammation, facilitating endometriosis progression [46]. Broad-spectrum antibiotics (vancomycin, neomycin, metronidazole, ampicillin) significantly reduce lesion size, slow cell proliferation, and decrease invasiveness [47]. Oral lactobacillus improves endometriosis-related pain in women and reduces lesion volume in mouse models [48]. Cerium oxide nanoparticles attenuate induced endometrial lesions in mice by reducing oxidative stress and inhibiting angiogenesis while protecting oocyte quantity and quality [49,50].

Summary and Outlook

Endometriosis is a chronic disease requiring long-term management. Surgical and hormonal therapies remain first-line treatments, though surgery carries high

recurrence risks and may compromise ovarian reserve, while conventional pharmacotherapy is limited by vasomotor symptoms and reproductive suppression [4,5]. Therefore, identifying well-tolerated agents with minimal adverse effects and improved compliance is paramount. Antioxidants, anti-angiogenic drugs, EMT inhibitors, and immunomodulators show promising therapeutic potential, though most remain in experimental or early clinical trial phases requiring further investigation. Given the heterogeneous clinical manifestations of endometriosis, personalized therapeutic approaches are essential.

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Note: Figure translations are in progress. See original paper for figures.