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MELATONIN AS A THERAPEUTIC OPTION FOR ENDOMETRIOSIS: A NARRATIVE REVIEW

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ABSTRACT

Endometriosis is a chronic condition in which conventional hormonal suppression and surgical excision are frequently accompanied by high recurrence and risks to ovarian reserve (Q. Li et al., 2024; Y. Li et al., 2024). Melatonin, a pleiotropic neuroendocrine hormone with antioxidant, anti-inflammatory, and antinociceptive properties, has emerged as an adjunctive candidate that targets the oxidative-inflammatory-angiogenic axis without suppressing reproductive function (Li et al., 2022; Mosher et al., 2019). This narrative review synthesizes the available preclinical and clinical evidence, retrieved through a structured search of PubMed, Scopus, and Web of Science (January 2005–May 2025), examining melatonin's therapeutic role across seven mechanistic domains: lesion size, histological characteristics, oxidative stress, inflammatory modulation, matrix metalloproteinase regulation, angiogenesis, and chronic pelvic pain. Across more than a dozen rodent studies at 10–50 mg/kg/day, melatonin consistently reduced lesion volume and weight, restored superoxide dismutase and catalase activity while lowering malondialdehyde and COX-2, downregulated proMMP-9 and elevated TIMP-1/TIMP-2, and suppressed VEGF/VEGFR-2 signaling (Mosher et al., 2019; Yılmaz et al., 2014). Clinically, two randomized controlled trials — Schwertner et al. (n = 40, 10 mg nightly, 8 weeks) (Schwertner et al., 2013) and Esmaeilzadeh et al. (n = 80) (Esmaeilzadeh et al., 2025) — documented analgesic benefit, with the former reducing daily pain by 39.80% and the latter yielding a VAS change of −1.56 (P < 0.001). Melatonin is therefore a mechanistically distinctive, fertility-preserving adjunctive candidate for endometriosis. However, the evidence base remains weighted toward preclinical rodent models and rests on a small number of short-duration randomized trials. Larger Phase III studies with imaging-based endpoints, dose-finding designs, active-comparator arms, and extended follow-up are required before its clinical role can be considered definitive.

KEYWORDS

Melatonin, Endometriosis, Oxidative Stress, Chronic Pelvic Pain, Anti-inflammatory Agents

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Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease characterized by the presence of endometrial glands and stroma outside the uterine cavity (Ou et al., 2025). It is one of the most widespread gynecological conditions: it affects approximately 6–10% of women of reproductive age in the general population and rises to 30–45% among women who present with infertility or chronic pelvic pain (Anderson, 2019; Harlev et al., 2015). Globally, the disease is estimated to affect 176 million women, and despite modest annual declines in age-standardized incidence (−0.21%) and prevalence (−0.29%) between 1990 and 2017, endometriosis remains a leading cause of gynecological disability-adjusted life-years in high-income regions (Ou et al., 2025). It typically presents in the second or third decade of life, peaks between 30 and 40 years of age, and disproportionately affects 5–10% of Western women and approximately 15% of Asian women (Anderson, 2019).

The clinical burden is substantial and multidimensional. Pelvic pain is the leading presenting symptom and is chronic in roughly half of affected individuals, with 70% experiencing it during menstruation (Anderson, 2019). Dysmenorrhea, dyspareunia, dysuria, and dyschezia further dominate the symptomatic picture, and the disease progresses to compromise fertility in approximately 50% of affected women — a consequence of a multifaceted mechanism that includes anatomical distortion, a hostile pelvic microenvironment driven by chronic inflammation and oxidative stress, poor oocyte quality, impaired folliculogenesis, reduced ovarian reserve, and altered endometrial receptivity (Anderson, 2019; Ou et al., 2025). The disease also exacts a significant socioeconomic cost, estimated at roughly 22 billion US dollars per year in the United States alone, accompanied by measurable negative impacts on educational attainment, productive employment, and mental health, including psychological sequelae such as depression, anxiety, and social withdrawal (Ou et al., 2025).

Conventional management rests on two pillars — hormonal suppression of menstruation and surgical excision of ectopic lesions (often by laparoscopy or laparotomy) — yet both interventions are associated with substantial limitations, including high recurrence rates, transient or permanent compromise of the ovarian reserve, and symptom relief that is frequently inadequate (Q. Li et al., 2024; Y. Li et al., 2024). These limitations are particularly consequential for women who wish to conceive, because hormonal suppressants must be discontinued prior to attempting pregnancy, and surgery carries a documented risk of further diminishing follicular reserve (Li et al., 2024). This convergence of high prevalence, substantial personal and socioeconomic burden, and the absence of a curative, fertility-preserving therapy has motivated sustained interest in adjunctive pharmacological strategies that target the disease's underlying oxidative–inflammatory pathophysiology rather than its endocrine output alone (Harlev et al., 2015; Li et al., 2022).

In this context, melatonin — a pleiotropic neuroendocrine hormone synthesized primarily by the pineal gland and also produced in extrapineal reproductive tissues — has emerged as a promising candidate owing to its combined antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, antinociceptive, and circadian-rhythmic properties, with documented efficacy across a wide range of experimental models of endometriosis (Yang et al., 2018). This narrative review critically evaluates the pathophysiological mechanisms underlying melatonin's role in endometriosis, with the primary objective of assessing its efficacy in modulating disease symptoms and mitigating disease progression in both preclinical and clinical settings. By bridging the gap between basic research and potential clinical utility, this analysis provides a robust rationale for investigating melatonin as a potentially well-tolerated, fertility-preserving, and cost-effective therapeutic strategy for patients suffering from this debilitating condition.

Methodology

A structured narrative review search of PubMed, Scopus, and Web of Science was conducted for articles published between January 2005 and May 2025 examining the molecular and clinical interactions between melatonin and endometriotic tissue. The search string was constructed as follows: ("endometriosis" OR "endometriotic implant" OR "endometrioma") AND ("melatonin" OR "N-acetyl-5-methoxytryptamine"). Original research articles, randomized controlled trials, systematic reviews, and narrative review articles were eligible for inclusion. Both preclinical investigations — including rodent models of surgically induced endometriosis and *in vitro* cell-culture work — and clinical studies — including randomized trials and observational cohorts of women with endometriosis — were considered. Eligible studies examined melatonin administered to women with endometriosis or relevant preclinical models, with comparators including placebo, vehicle, or active controls (such as the aromatase inhibitor letrozole), and reported outcomes on lesion volume or histopathology, pain, oxidative-stress markers, inflammatory mediators, matrix metalloproteinase activity, or vascular endothelial growth factor signaling. Studies not published in English, conference abstracts without full-text availability, duplicate publications, and articles not directly related to the therapeutic role of melatonin in endometriosis were excluded. Additional studies were identified through manual screening of the reference lists of the selected articles. All retrieved records were screened by the authors against the inclusion criteria. Title and abstract screening were supported by Scispace, with final inclusion decisions verified manually. Ambiguous records were documented and resolved through structured re-evaluation using the predefined criteria. Seven therapeutic domains — lesion morphology, histopathology, oxidative stress, inflammation, matrix remodeling, angiogenesis, and pain — were pre-specified on the basis of the prevailing mechanistic literature, and the retrieved literature was narratively synthesized within this structure to provide an overview of the current evidence regarding the therapeutic potential of melatonin in endometriosis. A practical access constraint is acknowledged: only articles available in free full-text form or accessible through the authors' institutional subscription at the time of the search were eligible, an inclusion criterion that is discussed in the Limitations of the Current Evidence Base as a potential source of selection bias toward open-access publications.

Results

The accumulated evidence from preclinical and clinical studies indicates that melatonin exerts a broad, multimodal influence on the pathophysiology of endometriosis, disrupting several of the molecular and cellular processes—including abnormal hormone signaling, oxidative stress, chronic inflammation, aberrant extracellular matrix turnover, and pathological angiogenesis—that together sustain ectopic tissue implantation, growth, and survival (Harlev et al., 2015; Li et al., 2022). When examined at the level of phenotypically observable outcomes, as well as at the level of the underlying molecular pathways, this influence can be organized into seven principal domains of therapeutic effect: a reduction in the size and volume of endometriotic implants (Yılmaz et al., 2014); an improvement in the histological characteristics of ectopic tissue (Chuffa et al., 2019; Dymanowska-Dyjak et al., 2024); a mitigation of oxidative stress, reflected by elevated superoxide dismutase and catalase activity and reduced malondialdehyde and cyclooxygenase-2 levels in endometriotic lesions (Li et al., 2022; Yılmaz et al., 2014); a modulation of systemic and peritoneal inflammation, reshaping the microenvironment away from one that favors lesion maintenance (Harlev et al., 2015; Li et al., 2022); a regulation of matrix metalloproteinases, with melatonin downregulating proMMP-9 and elevating its endogenous inhibitor TIMP-1, thereby attenuating matrix degradation required for ectopic implantation (Paul et al., 2008); a suppression of vascular endothelial growth factor signaling and consequent angiogenesis, curtailing a fundamental requirement for the survival and continued growth of ectopic tissue (Yılmaz et al., 2014); and a clinically meaningful attenuation of chronic pelvic pain symptoms reported in controlled clinical trials (Esmaeilzadeh et al., 2025; Schwertner et al., 2013). Each of these domains is detailed in the subsections that follow.

Reduction in Endometriotic Lesion Size

Preclinical investigations, primarily utilizing surgically induced rodent models, consistently demonstrate that daily melatonin administration leads to a significant, dose-dependent decrease in both the total volume and the aggregate weight of ectopic endometrial explants (Çetinkaya et al., 2014; Yılmaz et al., 2014). In oophorectomized rats, intraperitoneal melatonin (10 mg/kg/day) reduced median lesion volume from 239 mm³ to 20 mm³ and median implant weight from 254 mg to 53 mg ($P < 0.05$) (Yılmaz et al., 2014), while dose-ranging experiments showed volumes declining from 98.8 mm³ to 42.8 mm³ under 10 mg/kg/day and from 108.2 mm³ to 32.7 mm³ under 20 mg/kg/day ($P < 0.001$ for both) (Çetinkaya et al., 2014). Comparable reductions have been documented in letrozole-controlled studies in which lesion volumes fell from 99.6 mm³ to 21.5 mm³ ($P < 0.001$) and notably persisted two weeks after melatonin withdrawal without a statistically significant rebound ($P = 0.56$) (Yıldırım et al., 2009).

A particularly informative extension of the lesion-size evidence comes from a SCID-mouse xenograft model, in which human endometriotic cells — collected from patient lesions — were subcutaneously implanted in immunodeficient hosts and the mice were subsequently randomized to receive either melatonin (20 mg/kg/day) or vehicle for 4 weeks (Yeşildağlar et al., 2016). Because the implanted tissue is of human rather than syngeneic origin, this design isolates the effect of melatonin on human endometriotic cells themselves, free from species-mismatch confounders. At necropsy, gross inspection showed that recovered lesions in the melatonin group were smaller and less vascularized than those in controls, and this macroscopic impression was confirmed by blinded histopathological scoring ($P = 0.04$) (Yeşildağlar et al., 2016). The translational value of this finding is considerable: it indicates that the lesion-regression signal is preserved when the cellular target is human endometriotic tissue rather than rodent endometrium (Yeşildağlar et al., 2016).

Mechanistically, this regression has been linked to direct binding and inhibition of EGFR phosphorylation, suppression of the downstream PI3K–Akt–CCND1 pathway, reduced PCNA expression, G0/G1 cell-cycle arrest, and coordinated induction of apoptosis in endometriotic cells (Li et al., 2024). Recent work has clarified the molecular basis of this EGFR interaction: molecular docking and biolayer interferometry demonstrated stable binding of melatonin to EGFR (affinity energy -6.492 kcal/mol; equilibrium dissociation constant $K_D = 300$ μ M) and to the related receptor ERBB2 (affinity energy -5.867 kcal/mol; $K_D = 370$ μ M), with subsequent Western blot confirmation of a significant reduction in phosphorylated EGFR without a comparable change in p-ERBB2 in two independent endometriotic cell lines (Li et al., 2024). Notably, classical MT1/MT2 receptor protein expression was found to be undetectable in endometriotic cells by immunohistochemistry, indicating that the EGFR-mediated mechanism represents a non-classical pathway of melatonin action specific to this disease (Li et al., 2024). A further mechanistic insight comes from the observation that melatonin decreased the RNA expression of cyclins and cyclin-dependent kinases, arresting the cell cycle at the G0/G1 phase in dopaminergic neuroblastoma cells — a precedent that is now reflected in the G1-phase arrest observed in endometriosis models (Li et al., 2024). Collectively, these effects restrict the growth and survival of ectopic implants, and comparative analyses across diverse treatment durations and administration protocols underscore the reliability of melatonin as an inhibitor of lesion expansion (Li et al., 2022).

Improvement of Histological Characteristics

Beyond these macroscopic outcomes, histological examination of ectopic tissue in rodent models shows that melatonin promotes a structural regression of endometriotic explants rather than a simple volumetric shrinkage — an effect reflected in lower histopathological scores and reduced implant weight across 2- to 4-week supplementation protocols spanning doses from 10 to 50 mg/kg/day (Chuffa et al., 2019). At the tissue level, this regression manifests as a reduction of the endometrial-like glandular and stromal components within the implants, with melatonin-replacement experiments in pinealectomized rats documenting a measurable decrease in endometrial and epithelial thickness, fewer and smaller uterine glands and vessels, and a weaker overall proliferative pattern in the recovered tissue (Chuffa et al., 2019). The SCID-mouse xenograft data referenced in the preceding subsection reinforce this histological signal: in melatonin-treated implants of human origin, mean histopathological scores were significantly lower than in vehicle-treated implants, with mean uterine weights comparable between groups, indicating that the histological improvement reflects a

genuine arrest of ectopic tissue activity rather than non-specific weight loss (Yeşildağlar et al., 2016). At the cellular level, the histopathological improvement reflects a coordinated antiproliferative and pro-apoptotic program: reduced mRNA expression of the cell-cycle drivers *Ccnd1* and *Ccne1* and of the proliferation marker PCNA in murine endometriotic lesions, inhibition of both endometrial epithelial and stromal cell proliferation, and active apoptosis induction in the endometriotic region via Bax and caspase-9 activation coupled with downregulation of the anti-apoptotic factor Bcl-2 (Chuffa et al., 2019). Recent work has extended this to a caspase-3-mediated pathway: melatonin-induced regression of ectopic tissue coincides with activation of the effector caspase-3, identifying a specific molecular executioner through which the histological improvement is achieved (Chuffa et al., 2019; Yang et al., 2018). The structural nature of the improvement has clinical relevance: the reduction of nerve fiber density, glandular density, and vascular density within recovered lesions all bear directly on the symptom clusters (pelvic pain, dyspareunia) and on the substrate for recurrence, so the histological effect is not merely cosmetic but translates into a meaningful reduction in disease-burdening tissue characteristics (Yang et al., 2018). In a head-to-head preclinical comparison, this melatonin-induced histopathological improvement has proved comparable to the aromatase inhibitor letrozole — an important benchmark because, unlike letrozole, melatonin achieves this without suppressing ovarian steroidogenesis (Yıldırım et al., 2009). Collectively, these findings indicate that melatonin does not simply shrink ectopic lesions but fundamentally disrupts the cellular and structural mechanisms that sustain their persistence (Yıldırım et al., 2009).

Mitigation of Oxidative Stress

Because endometriosis lesions are characterized by markedly elevated reactive oxygen species generation — women with the disease consistently show higher oxidative stress markers in peritoneal fluid and significantly lower concentrations of the endogenous enzymatic antioxidants superoxide dismutase and glutathione peroxidase than healthy women — this imbalance defines both a mechanistic pathway and a critical therapeutic target (Harlev et al., 2015; Li et al., 2022). Melatonin intervenes at both ends of this balance. As a direct free-radical scavenger it neutralizes hydroxyl radicals, hydrogen peroxide, and nitric oxide derivatives through electron donation, generating the stable metabolite cyclic 3-hydroxymelatonin that itself functions as a scavenger; as an indirect antioxidant it stimulates the synthesis and activity of endogenous antioxidant enzymes, prevents their oxidative inactivation, and up-regulates the glutathione redox cycle (Harlev et al., 2015; Li et al., 2022). The empirical record of pre-clinical effects on the redox balance is unusually consistent across model systems. In the pinealectomy rat model of Koç and colleagues, intraperitoneal melatonin (10 mg/kg/day for 4 weeks) restored explant superoxide dismutase activity from 10.9 ± 1.2 to 15.2 ± 1.7 U/mg ($P < 0.01$), catalase from 1.2 ± 0.17 to 1.6 ± 0.2 U/mg ($P < 0.01$), and reduced malondialdehyde — a stable marker of lipid peroxidation — from 32.6 ± 4.5 to 21.5 ± 2.7 nmol/g ($P < 0.01$) compared with untreated pinealectomized controls, returning these markers to levels indistinguishable from intact animals (Koç et al., 2010). Comparable findings were reported by Yılmaz et al. in 20 Wistar rats receiving the same dose for 4 weeks: SOD activity was significantly higher and MDA significantly lower in the melatonin-treated group than in saline-treated controls, alongside a statistically significant reduction in tissue COX-2 positivity, indicating concurrent downregulation of the pro-oxidant cyclooxygenase-2 pathway (Yılmaz et al., 2014). The SCID-mouse xenograft study extended these redox findings to implants of human origin: mean MDA was significantly lower in melatonin-treated SCID mice (5.0 ± 1.7 nmol/g) than in vehicle-treated controls (8.8 ± 2.6 nmol/g, $P = 0.01$), confirming that the lipid-peroxidation-reduction signal persists when the target tissue is human endometrium rather than syngeneic rodent tissue (Yeşildağlar et al., 2016). Further mechanistic insight comes from studies in senescence-accelerated mouse models, which suggest that melatonin reduces granulosa cell senescence and links the classical redox effect to broader cellular preservation in the reproductive context (Dymanowska-Dyjak et al., 2024).

Aggregating these preclinical signals, the systematic forest-plot meta-analysis of Li and colleagues confirmed that exogenous melatonin (10 mg/kg) consistently elevates SOD after 2 weeks across independent rodent studies, with effect sizes that align with the histopathological and lesion-volume improvements summarized in the preceding subsections (Li et al., 2022). Together, these redox-corrective effects close the vicious cycle between oxidative stress and lesion maintenance: by lowering ROS and restoring enzymatic antioxidant defenses, melatonin removes one of the metabolic conditions that allows ectopic tissue to survive in the peritoneal cavity and to recruit further inflammatory and angiogenic support (Koç et al., 2010; Li et al., 2022).

Modulation of Systemic and Peritoneal Inflammation

Endometriosis is now understood as a chronic inflammatory condition in which ectopic tissue is recognized as antigenic, recruiting macrophages that release pro-inflammatory cytokines (IL-2, IL-4, IL-10, TNF- α , IFN- γ) within a COX-2/CYP19A1-driven feed-forward cycle of prostaglandin and estrogen production, while macrophages themselves release NF- κ B, whose further upregulation amplifies the inflammatory gene program; in deeply infiltrating disease, serum and peritoneal IL-33 are additionally elevated over healthy controls and over patients with superficial endometriosis (Harlev et al., 2015). Melatonin restructures this environment at multiple complementary levels. Systemically, it raises peripheral monocyte and natural killer cell counts after 7 or 14 days of treatment and enhances macrophage–T-lymphocyte antigen presentation — activating a key arm of cytotoxic immune surveillance that is blunted in endometriosis (Li et al., 2022). At the monocyte level, melatonin paradoxically stimulates IL-1, IL-6, and IL-12 production — a profile consistent with its early-phase pro-inflammatory role — while concurrently inhibiting secretion of IL-10, IL-2, and TNF- α from monocytes and suppressing LPS-stimulated TLR3- and TLR4-mediated signaling in macrophages (Yang et al., 2018). The net effect is a "smart" anti-inflammatory behavior: melatonin may favor inflammatory healing processes at early stages while antagonizing pathologically chronic or deregulated inflammation at later stages, which is precisely the type of bidirectional control that is therapeutically desirable in endometriosis (Yang et al., 2018).

The downstream consequences of these cytokine and innate-immune shifts align directly with the lesion pathology at the molecular level. Melatonin suppresses TLR4-mediated NF- κ B and Akt activation in macrophages, thereby damping the central amplification arm of the peritoneal inflammatory response; it downregulates B7-1, iNOS, and COX-2 expression in macrophages; and it blocks LPS-induced production of IL-6, IL-8, IL-10, NO, PGE₂, and PGF₁ α (Harlev et al., 2015; Yang et al., 2018). The COX-2 suppression observed across these immunological assays is congruent with the statistically significant reduction of tissue COX-2 positivity observed in melatonin-treated rodent endometriosis models (Yilmaz et al., 2014), and this point is mechanistically consequential: by lowering COX-2, melatonin simultaneously attenuates prostaglandin-driven inflammation and aromatase-driven estrogen production, interrupting the COX-2/CYP19A1 cycle at a single molecular node (Harlev et al., 2015; Yilmaz et al., 2014). Furthermore, melatonin modulates T-cell dependency and antibody production, with measurable effects that vary according to the stage of the inflammatory response, and autocrine melatonin synthesis — shown to be driven by the RelA/c-Rel NF- κ B dimer in macrophages — adds a fine-tuned paracrine regulatory layer that the exogenous compound can reinforce rather than replace (Yang et al., 2018). Importantly, melatonin's anti-angiogenic and anti-inflammatory actions are reinforced by a direct anti-adhesive effect: in a rat uterine horn model, even a single dose of 10 mg/kg melatonin significantly reduced postoperative intraperitoneal adhesion formation regardless of administration route (intraperitoneal or subcutaneous) and duration (single dose or 5 days), and parallel findings were observed in an experimental pericardial adhesion model in dogs (Yang et al., 2018). This anti-adhesive effect is directly relevant to the peritoneal adhesions that contribute to infertility in endometriosis and to the chronic pain of adhesive disease (Ou et al., 2025; Yang et al., 2018). The cytokine-reduction profile observed in the rodent endometriosis findings above also mirrors broader literature in which exogenous melatonin significantly reduces circulating TNF- α and IL-6 — two cytokines central to lesion maintenance and pain sensitization in endometriosis — indicating that the cytokine-inhibitory profile observed in animal models of this disease is consistent with a more generalizable systemic anti-inflammatory effect of the molecule (Li et al., 2022; Yang et al., 2018). Together, these findings indicate that melatonin converts the peritoneal cavity from a milieu that supports ectopic tissue survival into one in which immune surveillance is reinforced, cytokine amplification is dampened, the inflammatory–estrogenic feed-forward loop is interrupted, and adhesion formation — a structural substrate of chronic pain — is reduced (Li et al., 2022).

Regulation of Matrix Metalloproteinases

Building on the inflammatory microenvironment characterized in the preceding subsection, melatonin also regulates the matrix metalloproteinase system that mediates invasive ectopic implantation, restoring a balance that is markedly shifted toward matrix degradation in untreated endometriosis (Li et al., 2022; Paul et al., 2008). Viable endometrial cells attach to the peritoneal mesothelium through interactions with cell-surface integrins and extracellular matrix components including fibronectin and laminin; once attached, MMP-mediated remodeling of this matrix is required for invasion and for the establishment of an ectopic blood supply (Li et al., 2022). Both eutopic endometrium and ectopic lesions of women with endometriosis express higher MMP-2, MMP-3, and MMP-9 with concordant reductions in TIMP-1, TIMP-2, and TIMP-3 (Li et al., 2022; Paul et al., 2008). In eutopic endometrium, proMMP-9 activity relative to TIMP-1 expression is significantly elevated, a ratio now proposed as a quantitative indicator of disease progression (Paul et al., 2008). In addition, mice kept under different light conditions further display a dose-dependent melatonin modulation of integrin-mediated granulocyte adhesion to ICAM-coated plates via melatonin receptors, suggesting that the inhibitory effect on adhesion events at implantation sites is tightly coupled to MT1/MT2 signaling (Li et al., 2022).

Melatonin shifts the MMP–TIMP balance coherently across multiple compartments. In the murine peritoneal-endometriosis model, 48 mg/kg daily intraperitoneal melatonin downregulated proMMP-9 activity by approximately 45% on day 25 and by approximately 90% on day 35, with a roughly twofold rise in TIMP-1 large enough to invert the MMP-9/TIMP-1 ratio toward physiological homeostasis (Paul et al., 2008). Yılmaz et al. confirmed and extended these findings in 20 Wistar rats receiving 10 mg/kg melatonin intraperitoneally for 4 weeks: implant MMP-9 immunoreactivity was significantly lower (median 1.0 vs. 2.0, $P < 0.001$) and TIMP-2 staining significantly higher (median 2.5 vs. 1.0, $P = 0.001$) than in saline-treated controls (Yılmaz et al., 2014). The early-phase TIMP-3 elevation and MMP-3 suppression — observed in the same strain at the same dose — indicate that melatonin acts on the MMP network at multiple depths rather than against a single target, simultaneously protecting the pericellular TIMP shield (TIMP-1, -2, -3) and dampening three distinct matrix-degrading proteases (MMP-2, -3, -9) (Li et al., 2022). The downstream consequence is twofold: ectopic cells lose part of their invasive capacity, and the structural substrates on which new vessels form become less permissive (Li et al., 2022; Paul et al., 2008). The same network is implicated in a parallel cellular process — epithelial–mesenchymal transition — in which eutopic endometrial cells acquire invasive motility; in an *in vitro* assay using 1 mM melatonin on primary eutopic epithelial cultures, melatonin restored Numb and E-cadherin expression, downregulated the EMT transcription factors Notch1, Vimentin, Slug, and Snail, and decreased cell migration and invasion (Li et al., 2022). Collectively, these data suggest that melatonin attenuates the invasive capacity of ectopic endometrial tissue not solely through anti-proliferative effects but by restoring a coordinated balance between MMPs and their tissue inhibitors, suppressing EMT-related transcription, and reducing integrin-mediated adhesion — complementing the antioxidant, anti-inflammatory, and pro-apoptotic actions summarized in the surrounding subsections (Li et al., 2022; Paul et al., 2008; Yılmaz et al., 2014).

Suppression of Vascular Endothelial Growth Factor Signaling and Angiogenesis

Angiogenesis is required for sustained growth of ectopic lesions, and VEGF — particularly the VEGFC isoform — acts as a key driver: women with endometriosis exhibit elevated VEGF concentrations in both peritoneal fluid and eutopic endometrium, and meta-analytic data show that inhibiting VEGF/VEGFR signaling reduces lesion size in animal models without compromising follicular reserve (Li et al., 2022). VEGFR-2 is the principal receptor mediating VEGF's proliferative, migratory, and tubulogenic effects on endothelial cells, and hypoxia-inducible factor 1 α (HIF-1 α) is the upstream transcription factor driving VEGF transcription under the hypoxic conditions that arise in growing ectopic tissue (Li et al., 2022).

Melatonin interferes with this axis at multiple nodes. In 20 Wistar rats bearing surgically induced implants, intraperitoneal melatonin (10 mg/kg/day for 4 weeks) significantly reduced implant VEGF immunoreactivity (median score 1.0 vs. 2.0, $P < 0.001$) (Yılmaz et al., 2014); in a complementary dose-ranging study in 32 oophorectomized Sprague-Dawley rats, treatment with 10 and 20 mg/kg/day doses of melatonin for 2 weeks significantly reduced endometriotic volume, as assessed over a 6-week observation period ($P = 0.001$) (Çetinkaya et al., 2014). The downstream mechanism is supported by HUVEC and MCF-7 cell-line

data showing that melatonin dose-dependently inhibits VEGFR-2 signaling — extending the breast-cancer xenograft observation that melatonin suppresses VEGFR-2 to significantly reduce vascular density — and interferes with HIF-1 α , lowering the complementary angiopoietins ANG-1 and ANG-2 in co-culture, suppressing endothelial proliferation, migration, and tubular organization required for new vessel formation (Li et al., 2022). Importantly, both ANG-1 and ANG-2 are themselves elevated in the eutopic endometrium of endometriosis patients compared with normal uterine endometrium, indicating that the angiopoietin arm is an additional substrate for melatonin's anti-angiogenic action beyond the VEGF/VEGFR-2 axis (Li et al., 2022). Complementary strand of evidence comes from a renal-cancer mouse model in which melatonin's effect on HIF-1 α and VEGF expression was shown to depend on its antioxidant activity — directly tying the angiogenic pathway to the redox-corrective effect documented in the preceding subsection and lending mechanistic unity to both findings (Li et al., 2022).

Further support comes from in vivo studies in which oral melatonin reduced serum VEGF levels in patients with metastatic cancer, and from MCF-7 hypoxia experiments showing that melatonin suppresses VEGF-C and the ancillary receptors VEGFR-2 and VEGFR-3 under low-oxygen conditions relevant to growing endometriotic lesions (Li et al., 2022). Surgically induced endometriosis animal models further demonstrate that selective suppression of the VEGF-C isoform itself is sufficient to block angiogenesis and lesion growth — implying that melatonin acts on a pathway whose pharmacological relevance has been independently validated by VEGF/VEGFR inhibitors in non-melatonin studies (Li et al., 2022). Together, these findings indicate that melatonin's anti-angiogenic action is multimodal: where present, it reduces local VEGF immunoreactivity in implant tissue, but it also disrupts VEGFR-2–driven downstream signaling, HIF-1 α –mediated transcriptional programs, and angiopoietin-1/2 pathways at complementary nodes — collectively depriving ectopic lesions of the vascular supply required for their persistence while sparing the follicular vasculature that underpins melatonin's fertility-preserving profile (Li et al., 2022).

Attenuation of Chronic Pelvic Pain Symptoms

Beyond its role in molecular and structural modulation, melatonin's most clinically meaningful effect in endometriosis lies in its documented attenuation of chronic pelvic pain (Li et al., 2022; Schwertner et al., 2013). Chronic pelvic pain itself — defined as non-malignant pain perceived in pelvic structures, constant or recurring for at least 6 months — has a population prevalence of approximately 4% overall but rises to 40% in infertility populations, and endometriosis is among its strongest correlates, with lesions producing pain both through direct compression and infiltration of adjacent nerves and through nerve-growth-factor-mediated hyperalgesia and growth of sympathetic and sensory neurons into ectopic tissue (Schwertner et al., 2013). The molecular pathway linking endometriosis to chronic pain is increasingly understood: estrogen elevates brain-derived neurotrophic factor during the estrous cycle, BDNF potentiates N-methyl-D-aspartate receptors in dorsal spinal horn neurons, and BDNF has accordingly received attention as a neuromediator of hyperalgesia and spinal central sensitization in chronic pain states (Schwertner et al., 2013). Macrophage-derived cytokines (TNF- α , IL-1 β , IL-12) and C-fiber-released neuropeptides (substance P, calcitonin gene-related peptide, tachykinins, nitric oxide) integrate this cascade and amplify sensory input to the central pain matrix, while astrocytes sustain the maladaptive neuroplasticity by releasing additional neurotrophic factors, cytokines, and COX-2 (Schwertner et al., 2013).

In the phase II randomized, double-blind, placebo-controlled trial of Schwertner and colleagues in 40 women aged 18–45 with endometriosis-associated chronic pelvic pain, 10 mg melatonin nightly for 8 weeks produced a significant time-by-treatment interaction on visual analogue scale scores for daily pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia ($P < 0.01$ for all); melatonin reduced daily pain scores by 39.80% (95% CI 12.88–43.01%) and dysmenorrhea by 38.01% (95% CI 15.96–49.15%) versus placebo (Schwertner et al., 2013). Analgesic consumption dropped substantially: use occurred in 22.9% of the melatonin group versus 42.2% of the placebo group, yielding a relative risk of 1.80 (95% CI 1.61–2.08) for requiring additional analgesics, meaning the placebo group was 80% more likely to need adjunctive analgesia (Schwertner et al., 2013). Sleep quality improved in parallel: a 42% improvement in how patients felt upon awakening was recorded in the melatonin arm, with a significant time-by-treatment interaction on VAS sleep-quality scores ($P < 0.001$) (Schwertner et al., 2013). Importantly, melatonin also reduced serum BDNF levels — a finding whose mechanistic implications are distinctive: because the BDNF reduction was observed

independently of any measurable effect on pain, this biomarker dissociates melatonin's central neurotrophic effect from its peripheral analgesic effect and points to a direct action on pain pathways or on signaling chemicals that regulate pain (Schwertner et al., 2013). Another triple-blind trial in 80 infertile women with endometriosis and sleep disturbance confirmed these findings ($P < 0.001$) (Esmaeilzadeh et al., 2025), showing a pelvic-pain VAS change of -1.56 in the melatonin arm; while the study calculated a Number Needed to Treat of 2.03, it noted that the observed reduction may not have reached the threshold for clinical significance (Esmaeilzadeh et al., 2025). A large effect on sleep ($\eta^2 = 0.20$; Cohen's $d = 1.00$) accompanied the pain reduction (Esmaeilzadeh et al., 2025).

The analgesic picture is not uniformly supported. In a double-blind, placebo-controlled trial of 40 women randomised to 20 mg melatonin or placebo across two menstrual cycles, between-group pain was 2.9 (SD 1.9) versus 3.3 (SD 2.0) — neither statistically ($p = 0.45$) nor clinically significant (Söderman et al., 2023). The divergence from the significant analgesic effects reported at 10 mg (Schwertner et al., 2013) and comparable lower doses (Esmaeilzadeh et al., 2025) is best explained by lower baseline pain in Söderman's cohort (~ 2.9), where ceiling effects limit detectable benefit, a plausible non-linear dose-response with melatonin signalling saturating at supraphysiological concentrations, and a shorter two-cycle window versus the eight-week durations yielding positive results (Esmaeilzadeh et al., 2025; Schwertner et al., 2013). Evidence therefore remains incompletely characterised, and attenuation of benefit at 20 mg should be read as hypothesis-generating rather than as refutation of the lower-dose signal.

The aggregate picture is consistent with a multi-target analgesic action in which melatonin's effects at the molecular level (BDNF reduction, cytokine dampening, COX-2 suppression), at the tissue level (lesion regression, vascular supply reduction), and at the central level (sleep restoration, modulation of the central pain matrix) together contribute to the clinically documented reduction in endometriosis-associated chronic pelvic pain — without hormonal suppression and without compromising ovarian reserve (Li et al., 2022; Yang et al., 2018).

Discussion

Integrative Mechanistic Architecture

The seven domains of melatonin's therapeutic action catalogued in the preceding Results section are not discrete processes occurring in parallel. They instead converge on a single coherent pathophysiological axis — the oxidative-inflammatory-angiogenic axis — that, when viewed collectively, explains the breadth of the macroscopic (lesion volume, histopathological, pain) and molecular (cytokine, MMP, VEGF) endpoints summarized above. The axis is initiated when peritoneal macrophages recognize ectopic tissue as antigenic, releasing cytokines (IL-2, IL-4, IL-10, TNF- α , IFN- γ) and NF- κ B within the COX-2/CYP19A1 feed-forward cycle of prostaglandin and estrogen synthesis documented by Harlev and colleagues (Harlev et al., 2015). The resulting chronic inflammatory microenvironment elevates reactive oxygen species and depletes endogenous enzymatic antioxidants, shifting the peritoneal redox state toward oxidative stress (Harlev et al., 2015). Oxidative stress in turn promotes MMP-9 activation and disrupts the MMP-9/TIMP-1 balance required for controlled extracellular-matrix turnover, enabling invasive ectopic implantation (Paul et al., 2008), and drives VEGF-VEGFR-2 signaling and HIF-1 α -mediated transcription of angiogenic genes, supplying the vascular niche required for sustained lesion growth (Li et al., 2022). Melatonin intervenes at each of the four levels of this axis—oxidative, inflammatory, matrix-modeling, and angiogenic—providing the molecular basis for the macroscopic lesion regression and clinical pain relief observed in human trials (Li et al., 2022; Schwertner et al., 2013; Yilmaz et al., 2014).

Convergence With the Estrogen-Dependent Pathogenesis Hypothesis

The integrative model above is consistent with the known estrogen-dependent pathogenesis of endometriosis, with Mosher and colleagues (Mosher et al., 2019) demonstrating that melatonin modulates these estrogen-dependent alterations. Because the COX-2/CYP19A1 cycle couples inflammation directly to aromatase-driven estrogen synthesis, suppression of COX-2 simultaneously attenuates both prostaglandin-

driven inflammation and estrogen-driven proliferation. Yılmaz and colleagues documented this dual attenuation in a rat model in which melatonin drove regression of endometriotic implants through anti-angiogenic, antioxidant, and matrix-metalloproteinase activity (Yılmaz et al., 2014). Together these findings position COX-2 as a single molecular node whose pharmacological targeting by melatonin interrupts the disease at two distinct points on the same pathway. This convergence is corroborated by the EGFR-binding work of Li and colleagues, who documented that melatonin suppresses the PI3K–Akt–CCND1 cascade through inhibition of EGFR phosphorylation — a pathway that is itself downstream of estrogen signaling in ectopic endometrial cells (Li et al., 2024). The aggregate effect is therefore not simply additive across independent pathways but multiplicative at molecular nodes (COX-2, PI3K–Akt, EGFR) where the inflammatory and proliferative arms intersect.

Why This Mechanistic Picture Matters Clinically

The clinical relevance of this integrative mechanism is supported by the phase II randomized, double-blind, placebo-controlled trial of Schwertner and colleagues, in which 10 mg oral melatonin administered nightly for 8 weeks reduced overall pain scores by 39.8% and analgesic use by 80% in women with endometriosis (Mosher et al., 2019). The 2025 Esmaeilzadeh triple-blind randomized controlled trial replicated these analgesic findings, with a significant mean reduction in VAS pain ($\Delta = -1.56$; 95% CI: -2.41 to -0.71 ; $P < 0.001$) and a large effect size ($\eta^2 = 0.2$; Cohen's $d = 1.00$). However, the authors explicitly cautioned that this observed mean difference fell below their *a priori* clinical significance threshold of 1.8 VAS units, and accordingly characterized the effect as statistically significant but not necessarily clinically conclusive — a nuance that should be carried forward when interpreting the analgesic magnitude (Esmaeilzadeh et al., 2025). The combined pattern of analgesic benefit coupled with central nervous system effects — without hormonal suppression — is mechanistically distinctive, because hormonal suppressants currently in clinical use achieve pain relief only by suppressing ovarian function and at the documented cost of compromising follicular reserve (Li et al., 2024). The fact that melatonin's multimodal action produces pain relief in two independent randomized trials while appearing not to cause the same follicular reserve impairment is the central reason that the compound has attracted sustained clinical interest despite a limited evidence base (Li et al., 2022; Tesařík & Tesarik, 2025).

Bridging the Preclinical–Clinical Evidence Gap

The preclinical evidence base supporting melatonin's use in endometriosis is now substantial and internally consistent: across more than a dozen independent rodent studies spanning multiple species, melatonin has been shown to reduce lesion volume and weight, improve histopathological scores, restore antioxidant defenses, downregulate proMMP-9, suppress COX-2, and reduce VEGF immunoreactivity at intraperitoneal doses ranging from 10 to 50 mg/kg/day over 2–6 weeks (Li et al., 2024; Yılmaz et al., 2014). The clinical evidence base, by contrast, currently rests on just two published randomized trials — Schwertner 2013 ($n = 40$) (Schwertner et al., 2013) and Esmaeilzadeh 2025 ($n = 80$) (Esmaeilzadeh et al., 2025). Bridging this gap will require Phase III multicenter trials with adequate statistical power to detect changes in lesion size on imaging, rather than relying solely on pain scores; pharmacokinetic studies to define the dose–exposure relationship in eutopic and ectopic endometrium — a relationship Li and colleagues (Li et al., 2022) emphasize as still insufficiently characterized; and head-to-head comparisons against the aromatase inhibitor letrozole, in which rodent comparisons suggest melatonin may offer a lower recurrence rate (Yıldırım et al., 2009). Tesařík and Mendoza Tesarik note that the only combination tested preclinically to date — melatonin with colchicine — reduced ectopic cell adhesion by simultaneously increasing apoptosis and decreasing survival, suggesting that combinatorial strategies may further extend the therapeutic window (Tesařík & Tesarik, 2025).

Pharmacokinetic and Safety Profile of Exogenous Melatonin

Endogenous melatonin is secreted by the pineal gland between approximately 19:30 and 21:30 in adults, with plasma concentrations under tight circadian regulation (Li et al., 2022; Parua et al., 2024). Exogenous melatonin administered during the daytime has a half-life of 35–45 minutes (Parua et al., 2024); more broadly, the plasma half-life is relatively short — approximately 20–50 minutes — with peak plasma concentration

reached approximately 50 minutes after oral intake of an immediate-release preparation and an elimination half-life of 45 minutes for both oral and intravenous routes (Li et al., 2022). Melatonin is highly soluble in both water and lipids, allowing diffusion across cell membranes and the blood–brain barrier (Ferreira et al., 2024; Li et al., 2022), and is mainly metabolized by the hepatic CYP1A2 enzyme to 6-hydroxymelatonin, which is then sulfate-conjugated and excreted in urine (Li et al., 2022).

This short plasma half-life has direct implications for the endometriosis regimens tested clinically to date: 5 mg prolonged-release melatonin for 2 months in the Esmaeilzadeh trial (Esmaeilzadeh et al., 2025), 10 mg oral daily for 8 weeks in Schwertner (Schwertner et al., 2013), and 20 mg oral for two menstrual cycles in Söderman (Söderman et al., 2023). Prolonged-release preparations better approximate the endogenous nocturnal profile than immediate-release preparations, which function primarily as chronobiotic agents (Esmaeilzadeh et al., 2025; Ferreira et al., 2024), and no consensus has yet been reached on the optimal dosage or treatment period for gynecological indications (Ferreira et al., 2024).

On safety, current evidence indicates that exogenous melatonin is safe for short-term use, with only mild adverse effects — dizziness, sleepiness, nausea, and headache — reported even at extreme doses, and no serious adverse events documented (Li et al., 2022). Long-term administration similarly produces only mild adverse effects comparable to placebo (Li et al., 2022). However, safety in children and adolescents, as well as in pregnant and lactating women, requires further investigation (Li et al., 2022). The favorable tolerability profile of supplemental melatonin therefore provides a permissive — though not yet definitive — basis for the doses and durations proposed in future endometriosis trials.

Position Among Adjunctive Antioxidants

Melatonin is one of several antioxidant molecules explored in endometriosis, and contextualizing its evidence base against that of vitamin C, vitamin E, resveratrol, xanthohumol, and epigallocatechin-3-gallate is essential (Harlev et al., 2015). Two recent systematic reviews and meta-analyses have examined this question. Zhong and colleagues' meta-analysis of RCTs concluded that antioxidant supplementation reduces dysmenorrhea pain with substantial heterogeneity driven by compound, stage, and intervention duration, but called for large, phenotype-stratified trials before firm conclusions (Zhong et al., 2025). Esmaeilzadeh and colleagues' 2025 meta-analysis of 15 RCTs reported that four included melatonin trials demonstrated a consistent, significant benefit for dysmenorrhea ($SMD = -1.07$; 95% CI: -1.24 to -0.89), with trim-and-fill analysis showing no missing studies and a stable pooled effect — a signal notably more robust than the parallel Salmeri 2025 review, which restricted inclusion to a single null melatonin trial (Esmaeilzadeh et al., 2025). The wider meta-analytic literature also highlighted that the apparent benefit of antioxidants for chronic pelvic pain is sensitive to methodological rigor and is rated as "very low certainty of evidence," placing melatonin in an evidence landscape that is encouraging but not yet definitive (Esmaeilzadeh et al., 2025; Zhong et al., 2025). Within this spectrum, melatonin has been explored for its antioxidant and free radical scavenging properties in endometriosis (Li et al., 2022).

Limitations of the Current Evidence Base

Five limitations should be made explicit. First, the rodent models on which most inferences rest rely on surgically induced endometriotic implants that do not recapitulate the natural history of human disease, in which lesions arise spontaneously over years under complex hormonal regulation (Yeşildağlar et al., 2016). Second, the dosing extrapolated from rodent studies (10–50 mg/kg/day intraperitoneal) cannot be directly compared to the 10 mg/day oral human dose used in the Schwertner trial without body-surface-area and pharmacokinetic adjustment; the meta-analytic dose-response relationship between rodent efficacy and human clinical benefit has not been formally derived (Li et al., 2022). Third, the existing clinical trials are limited in sample size and short in duration: the pivotal phase II protocol extended just eight weeks of treatment (Schwertner et al., 2013). No published long-term safety data exist for endometriosis patients, so conclusions on safety must rest on the wider melatonin record in pediatric, adolescent, and obstetric populations, where adverse effects are limited to mild dizziness, sleepiness, nausea, and headache at rates comparable to placebo even at extreme doses (Li et al., 2022). The therapeutic durability of melatonin after withdrawal — documented for 2 weeks of treatment in rats (Yıldırım et al., 2009) — also remains unstudied in humans. Fourth, the analgesic evidence base contains a genuine dose-response inconsistency — significant efficacy at 10

mg(Schwertner et al., 2013) and equivalent lower doses(Esmaeilzadeh et al., 2025) versus non-significant pain reduction at 20 mg(Söderman et al., 2023) — which is flagged here as an unresolved question rather than as a representative estimate of the full dose range. Until head-to-head dose-ranging RCTs are conducted, the analgesic magnitude and the upper boundary of the therapeutic window remain uncertain. Fifth, the literature search was practically constrained to articles available in free full-text form or accessible through the authors' institutional subscription at the time of the search, and it is therefore possible that paywalled studies — including important work in subscription-based reproductive medicine and gynecology journals — were inadvertently omitted from the evidence base. This access-driven constraint should be considered alongside the methodological, dose-scaling, and small-sample-size limitations discussed above when interpreting the present review and when designing the next phase of clinical evidence collection for this field.

Future Research Priorities

Five priorities for future investigation emerge from the synthesis above. (i) Reproductive endpoints should be predefined in trials enrolling infertile endometriosis populations—a randomized trial demonstrated large effects on pain and sleep at 5 mg prolonged-release over approximately 2 months (Esmaeilzadeh et al., 2025), while others have investigated different regimens in infertile populations (Khatun et al., 2025), yet did not assess conception or live-birth outcomes, leaving the "fertility-preserving" framing of melatonin as a mechanistic inference rather than a directly demonstrated result. (ii) Large multicenter Phase III trials should incorporate standardized lesion imaging as a co-primary endpoint alongside patient-reported outcomes; published randomized trials have primarily judged efficacy from pain, sleep, and analgesic use (Esmaeilzadeh et al., 2025; Schwertner et al., 2013), so the consistent directionality of lesion-volume reduction documented across the rodent studies summarized above cannot yet be tested directly in humans. (iii) Dose-finding should be embedded within the trial design, given that 5- to 20-mg doses have been clinically tested (Esmaeilzadeh et al., 2025; Söderman et al., 2023) against a rodent range spanning approximately 10 to 50 mg/kg/day (Paul et al., 2008; Yılmaz et al., 2014) with no body-surface-area or pharmacokinetic scaling connecting the two ranges and no internal human dose-response characterized. (iv) Future protocols should include active-comparator arms with the non-steroidal analgesics and opioids currently used to manage endometriosis-associated pelvic pain, so that the analgesic magnitudes recorded in this review—the 39.80% reduction in daily pain at 10 mg over 8 weeks and the 80% greater requirement for additional analgesics in the placebo arm (relative risk 1.80) (Schwertner et al., 2013)—can be benchmarked against real-world standards of care rather than against placebo alone. (v) Finally, the clinical follow-up window should be extended to at least 6 months of continuous exposure with structured post-treatment surveillance, so that the durability of analgesic benefit, the recurrence profile, and the analogue of the post-withdrawal lesion regression documented in rats (Yıldırım et al., 2009) can be characterized in humans rather than projected from the 8-week and 2-month windows of the existing trials (Esmaeilzadeh et al., 2025; Schwertner et al., 2013).

Broader Implication

Viewed from a wider lens, the melatonin–endometriosis evidence base is consistent with a broader recharacterization that has gained traction in the field: endometriosis is increasingly recognized not solely as a surgical or hormonal disease but as one with a substantial chronic inflammatory and redox imbalance component, for which adjunctive nutraceutical and circadian-rhythm strategies merit formal evaluation. This recharacterization, if validated by the larger clinical trials outlined above, has the potential to redirect therapeutic development away from estrogen suppression alone and toward multi-target modulation of the peritoneal microenvironment — an objective for which endogenous and exogenous melatonin modulation may represent one plausible adjunctive strategy, given its documented safety profile, its pleiotropic mechanism, and the upstream epidemiological signal linking melatonin disruption to disease risk (Mosher et al., 2019).

Conclusions

Melatonin emerges from this narrative review as a mechanistically distinctive candidate for the adjunctive management of endometriosis — a profile that stands in clear contrast to the hormonal and surgical interventions that currently constitute the standard of care. Whereas existing therapies achieve disease control primarily through the suppression of ovarian function or through the physical removal of ectopic implants, melatonin's therapeutic action is coordinated across the oxidative, inflammatory, angiogenic, and matrix-remodeling pathways that sustain endometriotic tissue, without requiring suppression of reproductive endocrine activity (Li et al., 2022; Mosher et al., 2019).

Across the seven therapeutic domains examined in this review, the consistent directionality of preclinical findings — reduction in lesion volume and histopathological severity, restoration of antioxidant defenses, restoration of the MMP–TIMP balance, and suppression of COX-2 and VEGF signaling — provides a coherent and biologically plausible basis for the analgesic benefits documented in randomized clinical trials (Esmaeilzadeh et al., 2025; Schwertner et al., 2013). The principal strength of this evidence lies less in any single result than in its internal convergence: independent rodent investigations, employing diverse doses, treatment durations, and induction protocols, have reproduced changes of the same sign across lesion morphology, redox biomarkers, cytokine profiles, protease balance, and angiogenic signaling (Li et al., 2022; Yilmaz et al., 2014). Two independent randomized clinical trials have, in turn, documented analgesic benefits that are consistent with the analgesic and circadian properties predicted by the integrative mechanistic model developed in the preceding Discussion (Esmaeilzadeh et al., 2025; Schwertner et al., 2013).

The convergence of these preclinical and clinical signals within a single pathophysiological axis — the oxidative–inflammatory–angiogenic axis that defines both the disease and melatonin's intervention — supports the credibility of the broader claim that melatonin acts on endometriosis as a multi-target modulator rather than as a single-pathway inhibitor (Harlev et al., 2015; Li et al., 2022). This mechanistic profile carries a particular clinical implication: a candidate therapy that intervenes across the disease axis without suppressing reproductive function opens a therapeutic avenue for the substantial subgroup of patients who either wish to preserve their fertility or derive inadequate relief from hormonal or surgical standard-of-care options (Li et al., 2024; Yang et al., 2018). Melatonin's documented short-term safety and tolerability further reinforce its candidacy as an adjunctive rather than substitutive option, consistent with the positioning recommended by the broader antioxidant literature reviewed here (Harlev et al., 2015; Li et al., 2022).

The current evidence base, however, is weighted substantially toward preclinical rodent studies and rests on a limited number of published randomized trials of limited size and duration (Li et al., 2022; Schwertner et al., 2013). Until these findings are extended through larger, longer-duration multicenter trials with imaging-based endpoints and predefined reproductive outcomes, the clinical role of melatonin in endometriosis remains supportive rather than definitive. Within those constraints, however, the preliminary but converging signals of available mechanistic and clinical evidence position melatonin as a compelling candidate for further development: a compound whose pleiotropic, fertility-preserving profile represents a meaningful conceptual advance over the single-pathway, fertility-suppressive therapeutic paradigm that has historically dominated the management of this debilitating condition (Li et al., 2024; Yang et al., 2018).

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