Journal of Clinical and Nursing Research, 2026, Volume 10, Issue 5
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Protective Effects of Melatonin on the Female Reproductive System

Ziqi Fan, Minghui Hao, Tongtong Wei, Chongran Liu, Wanjing Wang, Yihang Song*

College of Veterinary Medicine, Gansu Agricultural University, Lanzhou 730000, Gansu, China

***Corresponding author**: Yihang Song, 284132319@xbmu.edu.cn

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Abstract: Melatonin (MT) is an indoleamine hormone secreted predominantly by the pineal gland and exhibits diverse biological activities, including antioxidant, anti-inflammatory, anti-apoptotic, immunomodulatory, and mitochondrial-protective effects. In recent years, increasing attention has been paid to the role of MT in the regulation of female reproductive function and in the prevention and treatment of disorders of the female reproductive system. Accumulating evidence indicates that MT is involved in follicular development, oocyte maturation, sex steroid secretion, embryonic development, and pregnancy maintenance by scavenging reactive oxygen species, improving mitochondrial function, and modulating the hypothalamic–pituitary–gonadal axis and related signaling pathways. This review summarizes the biological properties and principal mechanisms of action of MT, with a focus on recent advances in its roles in ovarian function preservation, maintenance of oocyte quality, improvement of embryonic development, and intervention in pregnancy-related disorders.

Keywords: Melatonin; Female reproductive system; Oxidative stress; Follicular development; Embryo quality; Mitochondrial protection

Online publication: May 31, 2026

1. Introduction

Melatonin (MT) is an indoleamine hormone predominantly synthesized and secreted by pinealocytes, and as an endogenous free-radical scavenger, it has excellent radical-scavenging activity and thus exerts potent protective effects against oxidative damage. While MT is classically recognized for its role in regulating seasonal and circadian rhythms, it is now unequivocally established that MT has active, diverse functions in female reproduction, innate immunity, radioprotection, antitumor defense, and anti-ageing processes. Therefore, this section will present a focused, systematic review of the protective actions of MT in the female reproductive system, including its relevant biological properties and functional significance.

2. Biological properties of melatonin

Melatonin (N–acetyl–5–methoxytryptamine, molecular weight 232 Da) was first isolated from bovine pineal glands in 1957 by Aaron B. Lerner, a dermatologist at Yale University, and thereafter thoroughly characterized by him [1]. From a structural point of view, melatonin can be described in a clear, elegant manner: it consists of three distinct and well-defined elements, namely a 5–methoxy group, a 3–position acetamidoethyl side chain, and an indole ring core (**Figure 1**).

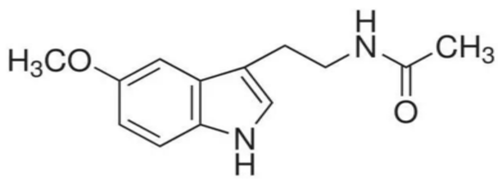

Figure 1. Molecular structure of melatonin.

Tryptophan is the classic, well-established precursor for MT biosynthesis, first being converted to serotonin (5-hydroxytryptamine, 5-HT) by tryptophan hydroxylase (TPH), then decarboxylated, followed by acetylation catalyzed by arylalkylamine N-acetyltransferase (AANAT) to form N-acetylserotonin, which is finally methylated to give MT. Although the pineal gland is the principal site of MT production, it is now unambiguously clear that MT can also be synthesized and secreted by several extrapineal tissues, including the retina, bone marrow, thymus, gastrointestinal tract, and ovary [2,3].

Pineal AANAT activity has a well-established, robust circadian rhythm that is inhibited by light; therefore, MT secretion rises sharply during the dark phase. Even more importantly, MT plays an essential role in the synchronization of reproduction in photoperiodic animals [4]. In the ovary, MT can reach the tissue either through the systemic circulation or be synthesized locally by granulosa cells, including cumulus granulosa cells. The text first makes clear that MT is present not only in oocytes, but then goes on to report that MT concentrations in human preovulatory follicular fluid are markedly higher than those in peripheral blood, with follicular-fluid MT levels in large follicles being approximately threefold the serum levels [5,6]. Most importantly, hamster ovaries actively take up and retain circulating tritium-labeled MT (^3H–MT), thus providing direct, unambiguous evidence that ovarian MT can be derived from the bloodstream and likely has a genuine physiological role in follicular development and ovulation [7].

3. Physiological activities and mechanisms of action of melatonin

3.1. Antioxidant effects of melatonin

Melatonin (MT) is an endogenous, direct free-radical-scavenging antioxidant that protects cells against oxidative injury by attenuating oxidative stress (OS) through clear, well-characterized multiple mechanisms: it directly neutralizes endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anion ($O_2 \bullet -$), hydroxyl radicals ($\bullet$ OH), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2) [8,9]. More importantly, MT and its metabolites, such as N^1–acetyl–5–methoxykynuramine (AMK), initiate a potent antioxidant cascade that dramatically lowers intracellular ROS levels and thereby actively maintains cellular redox homeostasis [10].

MT exerts indirect antioxidant effects by promoting the expression and activation of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH–Px), and by inhibiting the expression of pro - oxidant enzymes such as nitric oxide synthase (NOS) [10]. More specifically, SOD catalyzes the dismutation of $O_2 \bullet -$ into peroxide and molecular oxygen, and the generated H_2O_2 is then promptly and effectively scavenged by GSH–Px. Since this enzymatic cascade is so fundamental for maintaining intracellular redox balance and dealing with oxidative stress, it is quite logical to state that NOS is the main enzyme responsible for nitric oxide (NO) synthesis, and that oxidative stress can induce NOS uncoupling, thereby increasing superoxide generation [11,12]. Therefore, MT may restore the balance between NO and superoxide production, thus ameliorating oxidative stress-induced cellular injury [13].

OS is defined by the excessive generation of ROS, which damage cellular lipids, proteins, and DNA, and thus lead to a variety of pathological changes, including enzyme inactivation, DNA strand breaks, and cell death [14]. Mitochondria are not only the major intracellular source of ROS but also the primary targets of ROS-mediated damage [15]. Therefore, it is particularly important to note that MT protects mitochondrial morphology and function, the ion acts through several clearly defined and logically related mechanisms to inhibit mitochondrial permeability transition, regulate mitochondrial electron flux, reduce mitochondrial electron leakage, enhance the activity of uncoupling proteins (UCPs), and therefore modulate adenosine triphosphate (ATP) production in a way that limits ROS generation. In addition, MT promotes mitochondrial biogenesis, directly favoring mitochondrial integrity and function [16].

OS causes oxidative DNA damage, and 8–Oxo–2'–deoxyguanosine (8–oxo–dG), a major product of DNA oxidation, is now widely accepted as the most reliable and unequivocal biomarker of oxidative DNA damage and oxidative stress [17,18]. Moreover, several by-products of lipid peroxidation are themselves direct inducers of DNA damage [19]. Most importantly, the free-radical-scavenging activity of MT and its protective effect against oxidative DNA damage have been amply demonstrated. Liang et al were the first to clearly and convincingly show that MT protects somatic-cell nuclear transfer-derived porcine embryos from oxidative-stress-induced DNA damage, and subsequent work has nicely extended this finding: continuous MT supplementation for 90 days increases the total antioxidant capacity of semen and reduces oxidative DNA damage in sperm [20,21]. Most importantly, the literature now contains very strong, well-characterized evidence that MT inhibits oxidative-stress-induced DNA damage in mammalian oocytes: MT decreases ROS accumulation and DNA damage in oocytes from aged cows, and in mouse oocytes, it lowers ROS levels and directly suppresses 8-oxo-dG formation, thereby offering direct protection to DNA against oxidation [22,23].

3.2. Anti-apoptotic effects of melatonin

MT inhibits apoptosis in various biological processes mainly by downregulating the expression of pro-apoptotic proteins, as elegantly demonstrated by its ability to protect hippocampal neurons from radiation-induced injury by suppressing the apoptosis-related protein caspase 3 [24]. But even more importantly, MT exerts clear, well-characterized anti apoptotic effects via autophagy: it promotes the degradation of intracellular autophagosomes, thereby correcting cellular injury caused by dysregulated autophagy and offering potent neuroprotection in neurodegenerative diseases [25].

3.3. Anti-inflammatory effects of melatonin

since mT can ameliorate cognitive impairment by promoting activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby increasing cellular antioxidant capacity and protecting tissues against oxidative, inflammatory damage, it is even more significant to note that a large and growing body of evidence now supports the idea that MT modulates the immune system both directly, by acting on leukocytes with melatonin receptors, and indirectly, by affecting other hormones, opioids, or cytokines [26–28].

3.4. Endocrine-regulatory effects of melatonin

Since MT modulates the hypothalamic–pituitary–gonadal (HPG) axis, it has direct, well-defined regulatory effects on female reproductive function, including follicular development, pregnancy, and lactation, which is why MT holds considerable therapeutic promise for a number of pregnancy-related syndromes and reproductive disorders, such as preeclampsia, polycystic ovary syndrome, and endometriosis [29]. Because MT supplementation has been unequivocally shown to lower androgen levels, improve ovulatory function in polycystic ovary syndrome (PCOS), and also promote proper pancreatic development and regulation of physiological rhythms, it is now well established that MT can ameliorate sodium-propionate-induced circadian rhythm disruption and impaired pancreatic development by modulating the thyroid system [30].

4. Protective effects of melatonin on the female reproductive system

4.1. Protective effects of melatonin on follicular development and ovarian function

Follicular development from primordial, primary, and secondary follicles to mature oocytes is a highly intricate process that is superbly regulated by endocrine, paracrine, and autocrine mechanisms. More importantly, steroid hormones secreted by granulosa cells into the follicular fluid are not only necessary for follicular growth and maturation but also exert direct regulatory effects on the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The text provides a very clear, logical overview of how MT affects follicular development, beginning with the original report by Adriaens et al that treatment of mouse preantral follicles with MT for 12 days dramatically increased progesterone and androstenedione secretion, and then proceeds to discuss the well-established functions of MT in antral follicles: regulation of sex steroid production, LH mRNA expression, Bcl-2 and caspase-3 expression, and sex-steroid-related insulin-like growth factor (IGF) and transforming growth factor-β (TGF- β) signaling [31,32]. More importantly, it presents two distinct, beautifully delineated mechanisms:

(1) MT enhances follicular responsiveness to LH by increasing LH receptor mRNA expression in human granulosa cells, and
(2) MT protects granulosa cells from endoplasmic-reticulum-stress-induced apoptosis [33].

Because reactive oxygen species (ROS), reactive nitrogen species (RNS), and other oxidants generated during follicular development regulate molecular and biochemical pathways of folliculogenesis, they have a direct and clear effect on mature follicle development as well as follicular atresia. In female animals, ovarian ageing occurs with age, and oxidative stress is a well-established cause of follicular atresia. MT present in follicular fluid reduces both oocyte number and quality, but far more importantly, it attenuates oxidative stress and therefore protects oocytes and granulosa cells [34]. Moreover, MT delays ovarian ageing and preserves oocyte quality by activating the SIRT1 signaling pathway [35]. As a potent antioxidant, MT provides direct and robust protection against free-radical-induced oxidative damage: it lowers ROS levels in oocytes, improves the oxidative-stress status of oocytes, decreases early apoptosis, restores mitochondrial integrity, facilitates proper spindle assembly and chromosome alignment, and ultimately promotes meiotic maturation [36].

MT has well-documented, clearly defined protective effects against chemotherapy-induced ovarian injury, namely that MT protects ovarian tissue from cisplatin- and cyclophosphamide-induced damage by reducing ROS generation and inhibiting apoptosis [37]. Even better, the combination of MT with growth hormone has been convincingly shown to prevent chemotherapy-induced follicular damage more effectively and to preserve normal ovarian function [38].

4.2. Protective effects of melatonin on oocyte quality and embryonic development

Since fertilization leads to high circulating concentrations of MT, which in turn stimulate progesterone secretion by luteal cells, activate oocyte maturation-promoting factors, and promote blastocyst hatching, all of which are conducive to successful pregnancy, it is now firmly established that MT has an unequivocally important role in embryo implantation and early embryonic development [39]. More importantly, during *in vitro* embryo culture, Since MT protects embryos from oxidative-stress-induced injury by suppressing ROS production and experimental data unambiguously demonstrate that MT lowers ROS levels in embryos, it follows logically that MT improves developmental competence and embryo quality [40]. Therefore, MT not only increases the rate of oocyte maturation but also greatly enhances embryonic developmental capacity, raising both cleavage and blastocyst formation rates [41].

Because MT has very clear, well-documented effects on the regulation of mitochondrial function, and since mitochondria are the principal sites of cellular energy metabolism whose functional integrity directly determines oocyte quality and developmental potential, it is straightforward to conclude that MT improves oocyte quality and developmental competence by increasing mitochondrial membrane potential and properly distributing mitochondria [42]. More remarkably, under oxidative stress, MT restores mitochondrial bioenergetic function by reducing ROS accumulation and elevating intracellular glutathione levels, thereby directly enhancing oocyte maturation and blastocyst formation rates [43].

MT has a thoroughly documented, important role in regulating ovarian function and delaying ovarian ageing because it scavenges excessive free radicals, thereby protecting oocytes from oxidative injury and thus directly regulating ovarian function while simultaneously attenuating ovarian senescence [38]. More remarkably, MT enhances oocyte developmental competence by modulating relevant gene expression and signaling pathways, as elegantly shown by its ability to reverse mycotoxin-induced abnormal embryonic development in mice via the BMP4/MAPK signaling pathway [44].

MT has a well-established, thoroughly documented role in female reproductive health: human preovulatory follicular fluid contains MT at concentrations approximately threefold higher than those in peripheral blood, and MT levels are higher in large follicles than in small ones [5]. Soares et al. provided clear, elegant evidence that pinealectomy increases the number of atretic follicles, raises estrogen levels, and lowers progesterone levels [40]. More crucially, they demonstrated that progesterone concentrations in human preovulatory follicular fluid are directly and positively correlated with MT levels, and progesterone itself regulates LH secretion [5]. Hence, it is now unequivocally established that MT is involved not only in follicular development but also in pregnancy and lactation.

4.3. Effects of melatonin on pregnancy and placental function

Since the placental metabolic pathways of MT have such clear and important implications for pregnancy outcomes, it is quite natural and logical to propose that placental tryptophan metabolism produces several bioactive metabolites, including MT, which regulate immune tolerance, vascular function, oxidative balance, and fetal neurodevelopment [45]. More importantly, MT promotes endometrial receptivity and therefore increases embryo implantation rates by reducing oxidative stress and directly activating its membrane receptors, MT1 and MT2 [46].

MT has clear potential as an adjuvant therapy for gestational hypertension and pre-eclampsia because it reduces maternal and neonatal complications, and there is now robust evidence that MT and other antioxidants can ameliorate placental oxidative injury and improve selected perinatal outcomes [47]. More importantly, its protective effects are not restricted to the placenta but may directly benefit fetal neurodevelopment. This is because the balance of placental metabolic pathways during early pregnancy directly determines the fetal exposure to neuroactive metabolites [45].

4.4. Potential roles of melatonin in female reproductive disorders

MT has therapeutic promise in several gynecological and reproductive disorders, namely gestational hypertension, polycystic ovary syndrome (PCOS), and endometriosis, and moreover, there is now well-established, convincing evidence that MT supplementation protects pregnant women from hypertension by improving endothelial function and decreasing oxidative stress, both of which are key factors in gestational hypertension. A well-conducted study on the effects of MT in hypertensive pregnancy clearly established that MT promotes vasodilation and blood-pressure regulation via Ca^{2+}-activated K^+ channels, hence MT supplementation improved the hypertensive phenotype, restored uterine artery endothelial function, increased uterine blood flow, and ameliorated hypertension-induced vascular dysfunction [2,48]. Building directly on these findings, a subsequent study showed that MT administered during pregnancy prevents hypertension in offspring by modulating the gene expression of the renin–angiotensin system, thereby providing robust evidence that MT has both immediate maternal blood pressure benefits and long-term protective effects for offspring.

Because MT is a robust antioxidant and anti-inflammatory agent, it is both logical and well supported to consider that MT can ameliorate many metabolic and reproductive manifestations of PCOS. Indeed, MT has been clearly shown to reduce hyperandrogenism and restore menstrual regularity in women with PCOS, thereby directly and favorably affecting reproductive health [49]. More strikingly, MT inhibits endometriosis development by interfering with mitochondrial function and regulating transfer-RNA-derived small RNAs, specifically tRNA-derived RNA fragments (tiRNAs), which are known to promote ectopic endometrial cell proliferation [50].

5. Conclusions and perspectives

Melatonin has well-documented, multifaceted protective effects on the female reproductive system mediated by antioxidant, anti-apoptotic, anti-inflammatory, mitochondrial-protective, and endocrine-regulatory mechanisms, which is why its potential applications in reproductive medicine are extremely promising. However, a prudent and necessary caution is that most of the existing evidence comes from basic experimental studies and animal models, so high-quality, large-scale randomized controlled clinical trials are still lacking. Consequently, the optimal dose, timing of administration, and long-term safety of MT in different populations remain to be determined.

Because future studies can easily employ multi-omics approaches to construct complete regulatory networks of MT action, it is both logical and highly desirable to develop sustained-release formulations and combination therapies in parallel, which would therefore greatly accelerate the clinical application of MT in ovarian function preservation and in the prevention/treatment of female reproductive disorders.

Funding

2024 National College Students' Innovation and Entrepreneurship Training Program (Project No.: 202410742005)

Disclosure statement

The authors declare no conflict of interest.

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