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# Roles of melatonin in the field of reproductive medicine

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ABSTRACT

Melatonin, mostly released by the pineal gland, is a circadian rhythm-regulated and multifunctional hormone. Great advances in melatonin research have been made, including its role in rhythms of the sleep-wake cycle, retardation of ageing processes, as well as antioxidant or anti-inflammatory functions. Melatonin can scavenge free radicals such as reactive oxygen species (ROS), a key factor in reproductive functions. Melatonin plays an important role in oocyte maturation, fertilization and embryonic development as well. The concurrent use of melatonin increases the number of mature oocytes, the fertilization rate, and number of high-quality embryos, which improves the clinical outcome of assisted reproductive technology (ART). This review discusses the relationship between melatonin and human reproductive function, and potential clinical applications of melatonin in the field of reproductive medicine.

## 1. Introduction

Reproduction is a complex and delicate process. In the natural state, human reproduction mainly includes gamete production and transportation, fertilization, and intrauterine development. Any abnormality in the reproductive process may affect individual's reproductive ability and leads to infertility. Infertility is a major health problem worldwide and is estimated affecting 8–12% of couples in the reproductive age group [1]. A Global Burden of Disease survey reported that between 1990 and 2017, the age-standardized prevalence of infertility increased annually by 0.370% in women and by 0.291% in men [2]. The application of assisted reproductive technology (ART), a technology for obtaining new life by manipulating gametes, embryos or genetic material in vivo and in vitro, including artificial insemination (AI), in vitro fertilization-embryo transfer (IVF-ET) and its derivative technologies, has substantially improved the ability of couples with infertility to have biological children [3].

Produced by the pineal gland, melatonin is an ancient molecule that has been retained throughout the evolution of all organisms [4,5]. In animals, tryptophan is initially hydroxylated to 5-hydroxytryptophan which is then decarboxylated with the formation of serotonin. Serotonin is either acetylated to N-acetylserotonin or it is methylated to form 5-methoxytryptamine; these products are either methylated or acetylated, respectively, to produce melatonin [6]. Melatonin has a wide range of physiological effects, which are related to the high lipophilicity of melatonin itself. It has a direct or indirect physiological regulatory effect on the central nervous system and a protective effect on nerve cells. It not only affects the growth and development of immune organs, but also regulates humoral immunity, cellular immunity and cytokines. It has effects on pulmonary resistance, compliance, bronchial and respiratory rhythms. It has regulatory effects on urine formation, renal tubular concentration and dilution, electrolyte excretion and reabsorption, and renin secretion. It affects the function of the digestive tract, gastrointestinal motility and the digestion and absorption of cholesterol. It also regulates the endocrine system, cardiovascular system and metabolic system [7–15]. It can quickly enter various body fluids of the organism and directly play a role [16]. In addition, there are melatonin receptors in many cells, such as melatonin receptor type 1 (MT1) and melatonin receptor type 2 (MT2), and melatonin can also function through its receptors [17–24]. However, recent findings on melatonin functions in the field of reproductive medicine has not received much attention. In this review, our aim is to summarize and discuss roles of melatonin in the field of reproductive medicine.

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**Table 1**
Roles of reactive oxygen species in the maturation and development of oocytes.

| Authors | Subjects | Results | Reference |
|---|---|---|---|
| Blondin et al. 1997 | bovine oocytes | ROS may be beneficial to gamete function under specific conditions | [43] |
| Attaran et al. 2000 | humans | Pregnant women had a high ROS level in their follicular fluid | [44] |
| Oyawoye et al.2003 | humans | ROS play a role in female reproductive function | [45] |
| Iwata et al. 2003 | oocytes | It was beneficial for embryo production to use antioxidants at oocyte aspiration | [46] |
| Kitagawa et al. 2004 | porcine embryos | A low $O_2$ concentration improved developmental ability | [47] |
| Dalvit et al. 2005 | bovine embryos | A gradual increase in ROS production was observed up to the late morula stage | [48] |
| Poleszczuk et al. 2007 | bovine embryos | A physiological role of melatonin in embryo protection. | [49] |
| Goud et al. 2008 | mice oocytes | $O^{2-}$, $H_2O_2$, and HOCl each augment oocyte aging | [50] |
| Koo et al. 2008 | porcine embryos | A combination of electrical activation with antioxidant could be used to improve development of porcine embryos | [51] |
| Stanley et al. 2013 | rat | Lactational exposure accelerated follicular atresia by altering the ratio of ROS in the ovary | [52] |
| Tiwari and Chaube. 2016 | rat | A moderate increase of ROS in the ovary is beneficial for meiotic resumption | [53] |
| Xu et al. 2019 | bovine Oocytes | SIRT2 regulated ROS levels by activating the FoxO3a–Sod2/Cat axis | [54] |
| Li et al. 2021 | porcine Oocytes | Meiotic defects caused by SIRT6 inhibition might result from the excessive ROS | [55] |

## 2. Antioxidative effects of melatonin

Oxygen free radicals are produced in the process of energy metabolism in all cells. If the host lacks an adequate defense system to remove its toxicity, accumulated free radicals will cause widespread cell death. In 1993, melatonin was discovered as a very potent and efficient endogenous radical scavenger [25,26]. The fact that not only melatonin but many of its related metabolites likely work in sequence or in concert to neutralize ROS/RNS, making this group of molecules highly efficient in reducing oxidative stress [27–30]. The antioxidative actions of melatonin and its metabolites are extremely wide, including the ability to neutralize superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), single oxygen ($^1O_2$), hydrogen peroxide ($H_2O_2$), hypochlorous acid (HOCl), nitric oxide (NO), and peroxynitrite anion ($ONOO^-$) [31,32]. Cyclic 3-hydroxymelatonin (C3OHM) is the main product of the melatonin reaction with two ˙OH, and it has been identified as a product of the reactions between melatonin and other oxidants [33–35]. Further transformation of C3OHM yields N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK) [36,37].

## 3. Reactive oxygen species (ROS) and reproduction

ROS is a natural metabolic product in the body, including superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), hydroxyl radical (•OH), hypochlorous acid, and peroxynitrite ($ONOO^-$). As an essential factor in regulating a variety of physiological functions of living organisms, the intrinsic biochemical properties of ROS underlie the mechanisms necessary for the growth, fitness, or aging of living organisms [38–42]. Several reports show that ROS affect the maturation and quality of the oocytes (Table 1). On the other hand, ROS is a double-edged sword. Excessive ROS are considered to be a common cause of poor oocyte quality and poor reproductive results. Mitochondria are a vulnerable target of ROS. Attack originated from free oxygen radicals can damage the mitochondrial DNA of oocytes and then leads to the loss of their intrinsic mitochondrial function, which plays a major role in controlling fertility aging [56,57]. By accumulating ROS in porcine oocytes, peroxynitrite leads to the obstruction of spindle assembly, actin depolymerization, and decreased polar body extrusion, which greatly inhibits the oocyte maturation [58]. Studies have shown that the accumulation of ROS in the ovary decreases the quality of oocytes, causes granular cell (GC) apoptosis, and accelerates degeneration of the corpus luteum. In addition, it weakens the interaction between oocytes and GCs and affects the maturation of oocytes before ovulation. Ovarian oxidative damage is generally caused by the lipid peroxidation cascade, which severely affects follicular development, meiosis and ovulation, and ultimately affects reproductive function [59–65].

## 4. Melatonin and the reproductive function

The pineal gland affects the reproductive function of many species through the release of melatonin. The regulating effect of melatonin on reproductive function varies greatly among different species, and is related to factors such as age, light cycle and menstrual cycle. In some animals, the change in melatonin secretion is a key point in mediating reproductive activities. For example, in the seasonal reproductive animal hamster, a longer night time (increased melatonin secretion) can inhibit reproductive function, thereby causing the male hamster's testicles to degenerate, and the female hamster is in the autistic phase [66]. Although humans do not reproduce seasonally, there are seasonal differences in human reproduction. Environmental factors also affect human conception, among which photoperiod and temperature are more important. Like other mammals, melatonin affects human reproduction and plays an important role in determining conception. Increase of light exposure to women with extremely irregular menstrual cycles at the expected ovulation time can regulate their ovulation cycle and promote ovulation. Since melatonin has the ability to affect the synthesis and secretion of pituitary and gonadal hormones, gonadotropins and gonadal steroid hormones change significantly during the human menstrual cycle [67,68].

Studies on the role of melatonin in the reproductive process has mainly focused on its direct role in the ovaries. Melatonin can penetrate all cell membranes and enter all tissues because of its lipophilic nature, but once entering the system, melatonin is particularly concentrated in the ovaries [69,70]. It is reported that the melatonin concentrations in follicular fluid (FF) in the morning (58.9 ± 3.8 pmol/L) was significantly higher (P less than 0.005) than that in the daytime (23.2 ± 0.8 pmol/L), but its concentrations in morning were not different between the light and the dark seasons of the year, whereas the daytime values were higher (P less than 0.005) during the dark season (27.1 ± 2.1 pmol/L) than that during the light season (21.1 ± 2.1 pmol/L), indicating that melatonin interferes with the regulation of reproductive functions in humans at the follicular level. [71]. Studies have shown that the beneficial effects of melatonin on oocytes are mediated through the MT1 receptor and AMPK pathway. After that, MT1 knockout (MT1-KO) was produced, and the number of oocytes and litter size were significantly reduced. The expression of SIRT 1, C-myc and CHOP was down-regulated in the ovaries of MT1-KO mice, while the protein levels of SIRT 1 and p-NF-kB increased due to the disorder of redox balance, suggesting that melatonin may delay ovarian aging through the MT1/AMPK pathway and improves the fertility [72,73].

## 5. The clinical application of melatonin in the field of reproductive medicine

Melatonin, a neuroendocrine hormone secreted by the pineal gland, transmits information about the environmental light cycle (circadian rhythm and seasonal rhythm) to related tissues and organs in the body

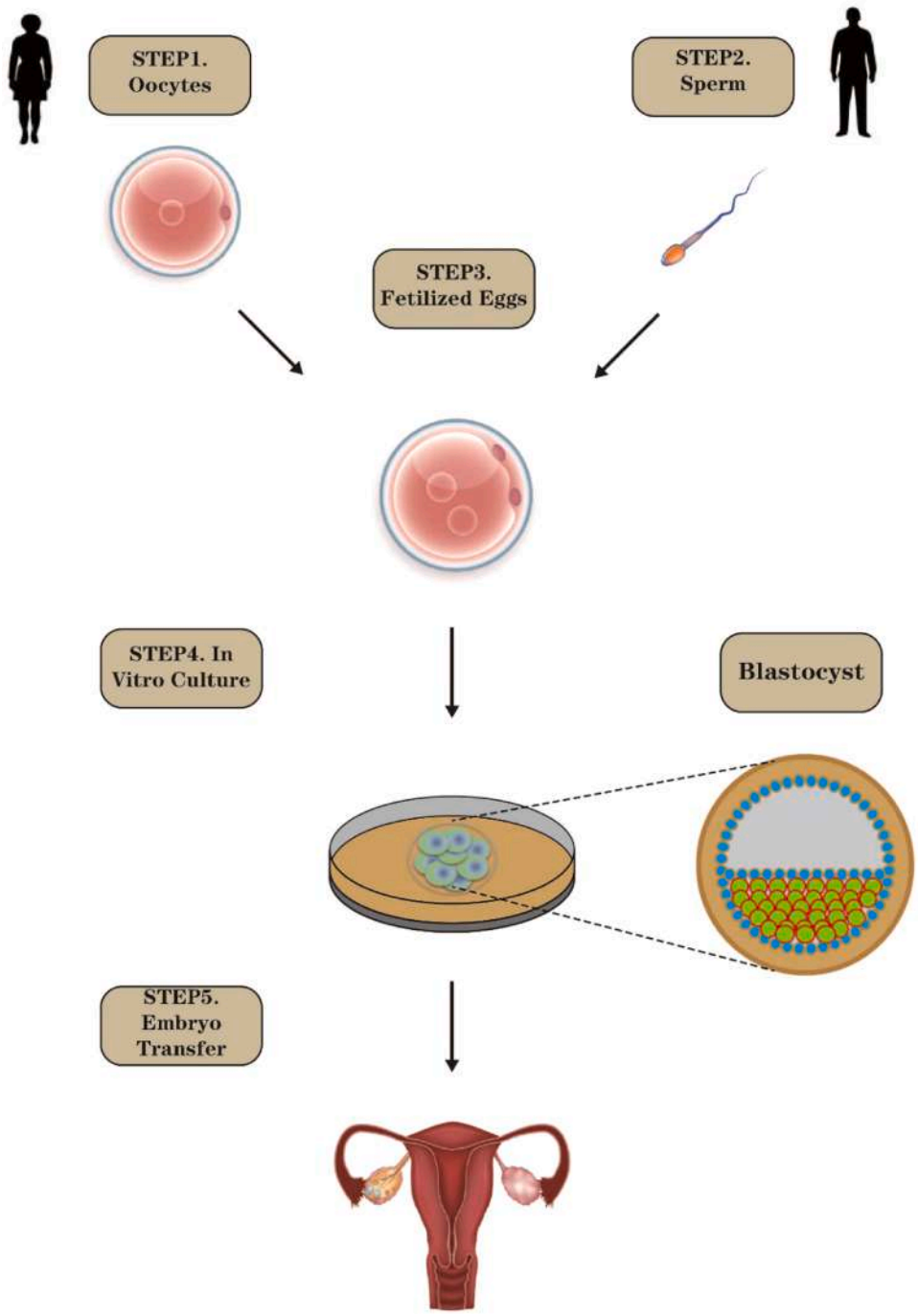


**Fig. 1.** The process of IVF-ET includes: Step1. After taking drugs to induce the development of multiple follicles, the puncture needle is inserted into the follicles to collect the eggs under the guidance of vaginal ultrasound. Step2. Screen out sperm with good quality and high activity from the sperm provided by the male partner. Step3. 4–6 h after egg retrieval, the sperm is cultured together with the egg, and then sperm enters the egg to form a fertilized egg. Step 4, Fertilized eggs can develop into 8–16-cell stage embryos after 48–72 h in vitro culture. At this time, the number of embryos to be transferred is determined according to the age of the patient, whether they have been pregnant or not, and the quality of the embryos. The excess embryos can be frozen and stored. Step5. Transplant the embryos that have developed to a certain period into the woman's uterine cavity to make them implant and develop into a fetus.

by changing the secretion level, so that their functional activities can adapt to external changes. It is mainly used in sedation, hypnosis, immune stimulation, anti-tumor, and anti-oxidation. It has not received much attention in the field of reproductive medicine. However, a growing number of studies have shown that it has great potential in reproductive medicine.

### *5.1. Melatonin in assisted reproductive technology (ART)*

Due to many factors, such as environment, lifestyle and age, the number of infertility patients is increasing. The emergence of assisted reproductive technology (ART) has brought dawn to many infertile families. With the continuous improvement of ART, the global ART birth population has exceeded 6 million. In some developed countries, the population of ART children born every year accounts for 1%−3% of all newborns. The success of ART depends largely on the quality and quantity of oocytes [32,73]. ART is a technology that uses medical aids to make infertile couples pregnant, containing artificial insemination (AI), in vitro fertilization-embryo transfer (IVF-ET) and its derivative technologies. IVE-ET, commonly known as "test-tube baby technology", takes out eggs from the woman's ovary, combines it with her husband's sperm in vitro and fertilizes it for a certain period of time, and then embryos that have developed to a certain period are transplanted into the woman's uterine cavity to develop into a fetus (Fig. 1).

Tamura et al. found that with 56 patients using melatonin treatment (3 mg/day) and 59 patients using no melatonin treatment, the fertilization rate in the melatonin treated subjects was approximately 50% (vs. approximately 20% for the control group) and the pregnancy rate

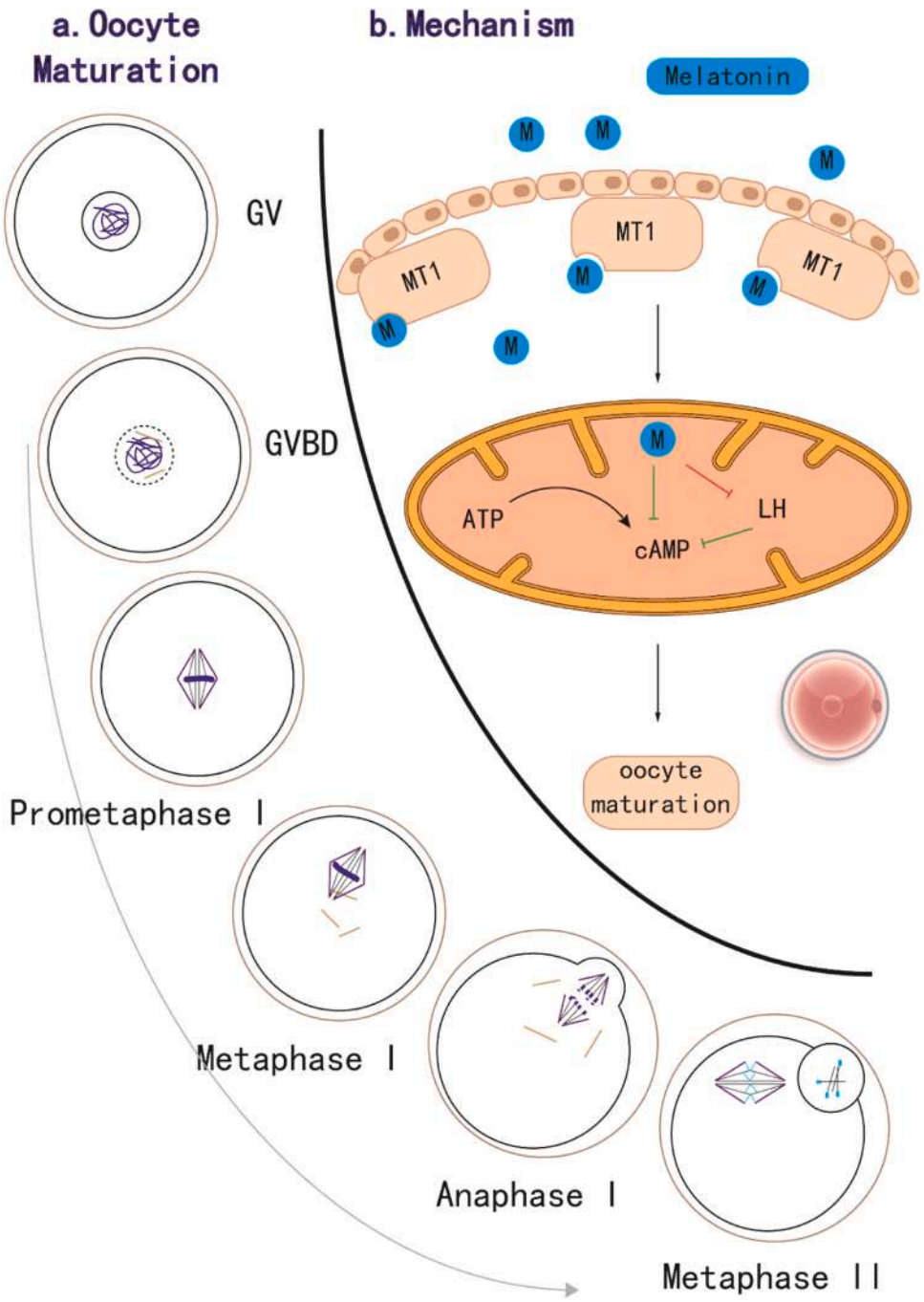


**Fig. 2.** Melatonin and Oocyte Maturation.a. The process of oocyte maturation includes germinal vesicle (GV), germinal vesicle breakdown (GVBD), prometaphase I, Metaphase I, Anaphase I and Metaphase II. b. The mechanism underlying the effect of melatonin on oocyte maturation is that the melatonin can reduce the intracellular level of cyclic adenosine monophosphate (cAMP) in oocytes via promoting the generation of luteinizing hormone (LH).

was roughly 20% (vs. approximately 10% for the control group), suggesting that melatonin is able to increase the success rate of IVF-ET [74]. In a systematic review and meta-analysis, it was found that melatonin treatment significantly increases the clinical pregnancy rate and increases the number of oocyte collected, maturated oocyte, and good quality embryo [75]. Other reports have also found that by increasing the number of mature oocytes, the fertilization rate, and the number of high-quality embryos, melatonin treatment can improve the clinical results of IVF-ET [76–81]. Therefore, it is reasonable to recommend patients to take melatonin in order to improve the outcome of IVF-ET.

### 5.2. *Melatonin and oocyte maturation*

Oocyte maturation is a multi-factor regulated process and has always been a focus in the research of female reproductive development. During the development of oocytes into mature eggs with fertilization ability, oocytes undergo the following key steps: First, they enter meiosis during the embryonic period and are blocked in the double-line phase of the first meiosis. Second, after the follicle is activated, the oocyte starts to grow. Third, when the oocyte grows to its full size, it undergoes meiosis recovery and re-arrest before and after ovulation, and fertilizes to form a zygote after the final ovulation (Fig. 2a). The oocytes in the primordial follicles are blocked in the prophase of the first meiosis and form

primary oocytes. When the oocyte grows to a certain size, it gains the ability to restore meiosis. At this time, the oocyte has a large nucleus, highly loose chromatin, and complete nuclear membrane, which is called germinal vesicle (GV). If fully grown oocytes are out of the control of the follicles, spontaneous meiotic recovery can occur, which is called germinal vesicle breakdown (GVBD). After the occurrence of GVBD, the oocyte completes the first meiosis, homologous chromosomes are separated, and then the first body is discharged. Subsequently, the spindle is assembled again and the oocyte enters the second metaphase of meiosis until fertilization [82–86].

Melatonin promotes oocyte maturation, but the mechanism is not fully understood. Since melatonin reduces reactive oxygen species and oxidative stress due to its direct antioxidant function, it benefits oocyte maturation and embryo development [59,60,62,64]. Another possibility is the potential involvement of melatonin in regulation of certain cellular signaling pathways which positively affects the maturation of oocytes (Fig. 2b). MT1 is the mediator of melatonin activity. Melatonin can reduce the intracellular level of cyclic adenosine monophosphate (cAMP) in oocytes and promote the generation of luteinizing hormone (LH), which can lower the concentration of cAMP within the oocyte by acting on MT1 in oocytes [87]. The effect of melatonin on oocyte maturation may also relates to mitochondrial function, antioxidative enzymes, apoptosis, cumulus cell expansion, oocyte maturation factors, DNA methylation and histone acetylation [88–99].

In recent years, with the development of cryobiology, embryo vitrification technology has gradually attracted attention. This technology is simple to operate, does not require expensive equipment, has a high freezing success rate, and the effect is significantly better than slow freezing. However, the blastocyst rate and the clinical pregnancy rate of cryopreserved oocytes are still lower than those of the fresh oocytes. Zhang et al. found that melatonin can improve the effect of cryopreservation on human oocytes by suppressing oxidative stress and maintaining the permeability of the oolemma, indicating that melatonin may be used as a cryoprotectant additive for the cryopreservation of human oocytes [100]. In conclusion, melatonin can be added to in vitro culture to promote oocyte maturation.

### 5.3. Melatonin and ovarian aging

Not only the ovary can secrete sex hormones to promote and maintain women's secondary sexual characteristics, but also has functions in gamete production and reproduction of offspring. Ovaries are directly controlled by hypothalamus and pituitary to form a mutually restrictive hypothalamic-pituitary-ovarian axis; it secretes sex hormones to regulate the cyclical physiological changes of the uterus, vagina, fallopian tubes and breasts. Therefore, routine activities of women's reproductive organs are carried out under the control of the ovaries. If ovarian dysfunction or disease occurs, it will undoubtedly lead to other parts of women's reproductive organs and even systemic physical or psychological disorders, and ovary aging is an important factor affecting the normal function of the ovary. Ovarian aging occurs earlier than the aging of most other organs such as the uterus, the pituitary gland or pancreas, which is also the major contributor to infertility and failure in ART [101].

Current understanding of mechanisms of ovarian aging includes the theory of free radicals, apoptosis, telomere shortening, mitochondrial dysfunction, and inflammation [102–112]. Free radical theory believes that oxidative stress caused by elevated ROS levels is the most important factor leading to aging of mammalian cells. Telomeres are most vulnerable to oxidative damage, and oxidative stress is considered to be the main cause of telomere shortening. Mitochondrial DNA damage and mutagenesis are directly responsible for a gradual impairment of the respiratory chain function and thus increase electron leakage. ROS may induce the activation of nuclear factor kappa B, a crucial mediator of inflammatory responses and the inflammatory agents interferon (IFN)-γ and lipopolysaccharides (LPS) synergistically increase ROS production.

**Table 2**
Possible mechanisms related to the anti-ovarian aging effects by melatonin.

| Authors | Subjects | Mechanisms* | Reference |
|---|---|---|---|
| Tamura et al. 2017 | mice | elongated the telomere length; reduced follicle atresia through the activation of *SIRT1* and *SIRT3* signaling; contributed to the translational process by regulating ribosomal function; enhanced indirect action of enhancing the antioxidant enzyme activity; bound to G protein-coupled membrane receptors which mediates numerous physiological effects via several signal transduction pathways | [113] |
| Zhang et al. 2019 | mice | via MT1/AMPK pathway | [73] |
| Batnasan et al. 2020 | humans | prevented protein PARylation and translocation of AIF into the nucleus | [114] |
| Hao et al.2020 | hens | activated the mTOR pathway of mTORC1 | [115] |
| Yang et al. 2021 | mice | inhibited the activation, growth, and atresia of follicles in PreOR and DOR | [116] |

* SIRT1, SIRT3: aging-related sirtuin genes; PAR: poly [ADP-ribose]; AIF: apoptosis-inducing factor; mTOR: the signal pathway of mammalian target of rapamycin; MT1: melatonin membrane receptor 1; AMPK: AMP-activated protein kinase; PreOR: pre-established ovarian follicle reserve; DOR: dynamic ovarian follicle reserve.

Other possible mechanisms are summarized in Table 2. Based on these notions, alleviating oxidative stress in the ovaries is of great importance to improve ovarian aging. Given that melatonin can effectively defend against oxidative stress, melatonin has great potential to delay ovarian aging.

### 5.4. Melatonin and early embryonic development

The development of mammalian early embryo, which includes the stages from zygote to blastocyst and undergo important morphological changes such as cell proliferation, compaction and blastocyst formation, is a complex and orderly biological process. And the quality of early embryo development is one of the prerequisites for the success of embryo implantation. Until now, the role of melatonin in earlier embryonic development has began to be investigated. Studies show that the direct free radical scavenging activity, the enhancement of endogenous glutathione levels, and the anti-apoptotic capacity of melatonin may account for its protective effects on vitrified embryonic development [117]. It also has been reported that melatonin supplementation could significantly ameliorate zearalenone-induced oxidative stress, aberrant mitochondria distribution and DNA damage during early porcine embryonic development [118,119]. Qu et al. found that melatonin ameliorated DNA methylation reprogramming; rescued the disrupted gene expression patterns, nuclear remodeling, and apoptosis; and resulted in the high developmental competence and quality of cloned embryos [120]. Niu et al. found that the beneficial effects of melatonin on early porcine embryos are dependent on two key aspects. Melatonin decreased oxidative stress, preventing excess mitochondrial biogenesis induced by a high-oxygen environment in sub-physiological conditions. On the other hand, beyond its antioxidant properties, melatonin promoted mitochondrial biogenesis by activating the SIRT1/PGC-1α pathway to compensate for the mitochondrial depletion and energy deficiency due to environmental toxin exposure, indicating that melatonin can be used to rescue early embryonic development from mitochondrial deficiency conditions [121]. Overall, melatonin, largely by reducing apoptosis, saving mitochondrial damage and enhancing DNA methylation reprogramming, is beneficial to the development of early embryonic.

## 6. Conclusion

A growing number of evidence has suggested that melatonin plays an important role in in the field of reproductive medicine. These recent findings indicate that it is beneficial for patients to take melatonin to improve outcomes for IVF-ET and delay ovarian aging. In addition, melatonin can be added to in vitro culture to promote oocyte maturation. New findings also reveal that melatonin can protect against mitochondrial injury in granulosa cells of polycystic ovary syndrome (PCOS) [122,123]. Hence, melatonin has great potential to become a magic weapon in treating reproductive diseases.

## CRediT authorship contribution Statement

Wei Yong: Investigation, Writing – original draft. Haiying Ma: Writing – review & editing. Man Na: Investigation. Teng Gao: Investigation. Ye Zhang: Investigation. Liying Hao: Writing – review & editing. Hang Yu: Writing – review & editing. Huazhe Yang: Writing – review & editing. Xin Deng: Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have or could be perceived to have influenced the work reported in this article.

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## References

[1] M. Vander Borght, C. Wyns, Fertility and infertility: definition and epidemiology, Clin. Biochem. 62 (2018) 2–10, https://doi.org/10.1016/j.clinbiochem.2018.03.012.
[2] H. Sun, T.T. Gong, Y.T. Jiang, S. Zhang, Y.H. Zhao, Q.J. Wu, Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990-2017: results from a global burden of disease study, 2017, Aging 11 (23) (2019) 10952–10991, https://doi.org/10.18632/aging.102497.
[3] A. Agarwal, S. Baskaran, N. Parekh, C.L. Cho, R. Henkel, S. Vij, M. Arafa, M. K. Panner Selvam, R. Shah, Male infertility, Lancet (London, England) 397 (10271) (2021) 319–333, https://doi.org/10.1016/S0140-6736(20)32667-2.
[4] L.C. Manchester, A. Coto-Montes, J.A. Boga, L.P. Andersen, Z. Zhou, A. Galano, J. Vriend, D.X. Tan, R.J. Reiter, Melatonin: an ancient molecule that makes oxygen metabolically tolerable, J. Pineal Res. 59 (4) (2015) 403–419, https://doi.org/10.1111/jpi.12267.
[5] S.A. Pshenichnyuk, A. Modelli, D. Jones, E.F. Lazneva, A.S. Komolov, Low-energy electron interaction with melatonin and related compounds, J. Phys. Chem. B 121 (16) (2017) 3965–3974, https://doi.org/10.1021/acs.jpcb.7b01408.
[6] D. Zhao, Y. Yu, Y. Shen, Q. Liu, Z. Zhao, R. Sharma, R.J. Reiter, Melatonin synthesis and function: evolutionary history in animals and plants, Front. Endocrinol. 10 (2019) 249, https://doi.org/10.3389/fendo.2019.00249.
[7] G. Favero, E. Moretti, F. Bonomini, R.J. Reiter, L.F. Rodella, R. Rezzani, Promising antineoplastic actions of melatonin, Front. Pharmacol. 9 (2018) 1086, https://doi.org/10.3389/fphar.2018.01086.
[8] R.J. Reiter, S.A. Rosales-Corral, D.X. Tan, D. Acuna-Castroviejo, L. Qin, S.F. Yang, K. Xu, Melatonin, a full service anti-cancer agent: inhibition of initiation, progression and metastasis, Int. J. Mol. Sci. 18 (4) (2017) 843, https://doi.org/10.3390/ijms18040843.
[9] E.J. Sanchez-Barcelo, N. Rueda, M.D. Mediavilla, C. Martinez-Cue, R.J. Reiter, Clinical uses of melatonin in neurological diseases and mental and behavioural disorders, Curr. Med. Chem. 24 (35) (2017) 3851–3878, https://doi.org/10.2174/0929867324666170718105557.
[10] J. Cipolla-Neto, F.G. Amaral, S.C. Afeche, D.X. Tan, R.J. Reiter, Melatonin, energy metabolism, and obesity: a review, J. Pineal Res. 56 (4) (2014) 371–381, https://doi.org/10.1111/jpi.12137.
[11] G. Favero, L. Franceschetti, F. Bonomini, L.F. Rodella, R. Rezzani, Melatonin as an anti-Inflammatory agent modulating inflammasome activation, Int. J. Endocrinol. 2017 (2017), 1835195, https://doi.org/10.1155/2017/1835195.
[12] N. Ma, J. Zhang, R.J. Reiter, X. Ma, Melatonin mediates mucosal immune cells, microbial metabolism, and rhythm crosstalk: a therapeutic target to reduce intestinal inflammation, Med. Res. Rev. 40 (2) (2020) 606–632, https://doi.org/10.1002/med.21628.
[13] F. Moradkhani, M. Moloudizargari, M. Fallah, N. Asghari, H. Heidari Khoei, M. H. Asghari, Immunoregulatory role of melatonin in cancer, J. Cell. Physiol. 235 (2) (2020) 745–757, https://doi.org/10.1002/jcp.29036.
[14] B.S. Alghamdi, The neuroprotective role of melatonin in neurological disorders, J. Neurosci. Res. 96 (7) (2018) 1136–1149, https://doi.org/10.1002/jnr.24220.
[15] G. Ji, W. Zhou, X. Li, J. Du, X. Li, H. Hao, Melatonin inhibits proliferation and viability and promotes apoptosis in colorectal cancer cells via upregulation of the microRNA-34a/449a cluster, Mol. Med. Rep. 23 (3) (2021) 187, https://doi.org/10.3892/mmr.2021.11826.
[16] D. Acuña-Castroviejo, G. Escames, C. Venegas, M.E. Díaz-Casado, E. Lima-Cabello, L.C. López, S. Rosales-Corral, D.X. Tan, R.J. Reiter, Extrapineal melatonin: sources, regulation, and potential functions, Cell. Mol. Life Sci.: CMLS 71 (16) (2014) 2997–3025, https://doi.org/10.1007/s00018-014-1579-2.
[17] J.A. Boutin, G. Ferry, Is there sufficient evidence that the melatonin binding site MT3 Is quinone reductase 2? J. Pharmacol. Exp. Ther. 368 (1) (2019) 59–65, https://doi.org/10.1124/jpet.118.253260.
[18] O. Nosjean, M. Ferro, F. Coge, P. Beauverger, J.M. Henlin, F. Lefoulon, J. L. Fauchere, P. Delagrange, E. Canet, J.A. Boutin, Identification of the melatonin-binding site MT3 as the quinone reductase 2, J. Biol. Chem. 275 (40) (2000) 31311–31317, https://doi.org/10.1074/jbc.M005141200.
[19] J. Meléndez, V. Maldonado, A. Ortega, Effect of melatonin on beta-tubulin and MAP2 expression in NIE-115 cells, Neurochem. Res. 21 (6) (1996) 653–658, https://doi.org/10.1007/BF02527721.
[20] B. Lacoste, D. Angeloni, S. Dominguez-Lopez, S. Calderoni, A. Mauro, F. Fraschini, L. Descarries, G. Gobbi, Anatomical and cellular localization of melatonin MT1 and MT2 receptors in the adult rat brain, J. Pineal Res. 58 (4) (2015) 397–417, https://doi.org/10.1111/jpi.12224.
[21] K.Y. Ng, M.K. Leong, H. Liang, G. Paxinos, Melatonin receptors: distribution in mammalian brain and their respective putative functions, Brain Struct. Funct. 222 (7) (2017) 2921–2939, https://doi.org/10.1007/s00429-017-1439-6.
[22] R. Gerbier, D. Ndiaye-Lobry, P.B. Martinez de Morentin, E. Cecon, L.K. Heisler, P. Delagrange, F. Gbahou, R. Jockers, Pharmacological evidence for transactivation within melatonin MT2 and serotonin 5-HT2C receptor heteromers in mouse brain, FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 35 (1) (2021) 21161, https://doi.org/10.1096/fj.202000305R.
[23] P. Klosen, S. Lapmanee, C. Schuster, B. Guardiola, D. Hicks, P. Pevet, M.P. Felder-Schmittbuhl, MT1 and MT2 melatonin receptors are expressed in nonoverlapping neuronal populations, J. Pineal Res. 67 (1) (2019) 12575, https://doi.org/10.1111/jpi.12575.
[24] W.M. Al-Ghoul, M.D. Herman, M.L. Dubocovich, Melatonin receptor subtype expression in human cerebellum, Neuroreport 9 (18) (1998) 4063–4068, https://doi.org/10.1097/00001756-199812210-00011.
[25] R. Hardeland, R.J. Reiter, B. Poeggeler, D.X. Tan, The significance of the metabolism of the neurohormone melatonin: antioxidative protection and formation of bioactive substances, Neurosci. Biobehav. Rev. 17 (3) (1993) 347–357, https://doi.org/10.1016/s0149-7634(05)80016-8.
[26] B. Poeggeler, R.J. Reiter, D.X. Tan, L.D. Chen, L.C. Manchester, Melatonin, hydroxyl radical-mediated oxidative damage, and aging: a hypothesis, J. Pineal Res. 14 (4) (1993) 151–168, https://doi.org/10.1111/j.1600-079x.1993.tb00498.x.
[27] D.X. Tan, L.C. Manchester, M.P. Terron, L.J. Flores, R.J. Reiter, One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J. Pineal Res. 42 (1) (2007) 28–42, https://doi.org/10.1111/j.1600-079X.2006.00407.x.
[28] R.J. Reiter, S.D. Paredes, L.C. Manchester, D.X. Tan, Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin, Crit. Rev. Biochem. Mol. Biol. 44 (4) (2009) 175–200, https://doi.org/10.1080/10409230903044914.
[29] S.A. Ganie, T.A. Dar, A.H. Bhat, K.B. Dar, S. Anees, M.A. Zargar, A. Masood, Melatonin: a potential anti-oxidant therapeutic agent for mitochondrial dysfunctions and related disorders, Rejuvenation Res. 19 (1) (2016) 21–40, https://doi.org/10.1089/rej.2015.1704.
[30] E. Miller, A. Morel, L. Saso, J. Saluk, Melatonin redox activity. Its potential clinical applications in neurodegenerative disorders, Curr. Top. Med. Chem. 15 (2) (2015) 163–169.
[31] R.J. Reiter, D.X. Tan, L.C. Manchester, S. Lopez-Burillo, R.M. Sainz, J.C. Mayo, Melatonin: detoxification of oxygen and nitrogen-based toxic reactants, Adv. Exp. Med. Biol. 527 (2003) 539–548, https://doi.org/10.1007/978-1-4615-0135-0_62.
[32] H. Tamura, M. Jozaki, M. Tanabe, Y. Shirafuta, Y. Mihara, M. Shinagawa, I. Tamura, R. Maekawa, S. Sato, T. Taketani, A. Takasaki, R.J. Reiter, N. Sugino, Importance of melatonin in assisted reproductive technology and ovarian aging, Int. J. Mol. Sci. 21 (3) (2020) 1135, https://doi.org/10.3390/ijms21031135.
[33] D.X. Tan, R. Hardeland, L.C. Manchester, B. Poeggeler, S. Lopez-Burillo, J. C. Mayo, R.M. Sainz, R.J. Reiter, Mechanistic and comparative studies of melatonin and classic antioxidants in terms of their interactions with the ABTS cation radical, J. Pineal Res. 34 (4) (2003) 249–259, https://doi.org/10.1034/j.1600-079x.2003.00037.x.
[34] L. Tesoriere, G. Avellone, L. Ceraulo, D. D'Arpa, M. Allegra, M.A. Livrea, Oxidation of melatonin by oxoferryl hemoglobin: a mechanistic study, Free Radic. Res. 35 (6) (2001) 633–642, https://doi.org/10.1080/10715760100301161.
[35] H. Zhang, G.L. Squadrito, R. Uppu, W.A. Pryor, Reaction of peroxynitrite with melatonin: a mechanistic study, Chem. Res. Z7Toxicol. 12 (6) (1999) 526–534, https://doi.org/10.1021/tx980243t.
[36] D.X. Tan, L.C. Manchester, M.P. Terron, L.J. Flores, R.J. Reiter, One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen

and nitrogen species? J. Pineal Res. 42 (1) (2007) 28–42, https://doi.org/10.1111/j.1600-079X.2006.00407.x.
[37] A. Galano, R.J. Reiter, Melatonin and its metabolites vs oxidative stress: From individual actions to collective protection, J. Pineal Res. 65 (1) (2018) 12514, https://doi.org/10.1111/jpi.12514.
[38] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (1) (2007) 44–84, https://doi.org/10.1016/j.biocel.2006.07.001.
[39] K. Apel, H. Hirt, Reactive oxygen species: metabolism, oxidative stress, and signal transduction, Annu. Rev. Plant Biol. 55 (2004) 373–399, https://doi.org/10.1146/annurev.arplant.55.031903.141701.
[40] T. Finkel, N.J. Holbrook, Oxidants, oxidative stress and the biology of ageing, Nature 408 (6809) (2000) 239–247, https://doi.org/10.1038/35041687.
[41] R.S. Balaban, S. Nemoto, T. Finkel, Mitochondria, oxidants, and aging, Cell 120 (4) (2005) 483–495, https://doi.org/10.1016/j.cell.2005.02.001.
[42] M.L. Circu, T.Y. Aw, Reactive oxygen species, cellular redox systems, and apoptosis, Free Radic. Biol. Med. 48 (6) (2010) 749–762, https://doi.org/10.1016/j.freeradbiomed.2009.12.022.
[43] P. Blondin, K. Coenen, M.A. Sirard, The impact of reactive oxygen species on bovine sperm fertilizing ability and oocyte maturation, J. Androl. 18 (4) (1997) 454–460.
[44] M. Attaran, E. Pasqualotto, T. Falcone, J.M. Goldberg, K.F. Miller, A. Agarwal, R. K. Sharma, The effect of follicular fluid reactive oxygen species on the outcome of in vitro fertilization, Int. J. Fertil. Women'S. Med. 45 (5) (2000) 314–320.
[45] O. Oyawoye, A. Abdel Gadir, A. Garner, N. Constantinovici, C. Perrett, P. Hardiman, Antioxidants and reactive oxygen species in follicular fluid of women undergoing IVF: relationship to outcome, Hum. Reprod. (Oxf., Engl.) 18 (11) (2003) 2270–2274, https://doi.org/10.1093/humrep/deg450.
[46] H. Iwata, M. Ohota, S. Hashimoto, Y. Nagai, Free oxygen radicals are generated at the time of aspiration of oocytes from ovaries that have been stored for a long time, Zygote (Camb., Engl.) 11 (1) (2003) 1–5, https://doi.org/10.1017/s0967199403001011.
[47] Y. Kitagawa, K. Suzuki, A. Yoneda, T. Watanabe, Effects of oxygen concentration and antioxidants on the in vitro developmental ability, production of reactive oxygen species (ROS), and DNA fragmentation in porcine embryos, Theriogenology 62 (7) (2004) 1186–1197, https://doi.org/10.1016/j.theriogenology.2004.01.011.
[48] G.C. Dalvit, P.D. Cetica, L.N. Pintos, M.T. Beconi, Reactive oxygen species in bovine embryo in vitro production, Biocell: Off. J. Soc. Latinoam. De. Microsc. Electron. Et. al 29 (2) (2005) 209–212.
[49] K. Papis, O. Poleszczuk, E. Wenta-Muchalska, J.A. Modlinski, Melatonin effect on bovine embryo development in vitro in relation to oxygen concentration, J. Pineal Res. 43 (4) (2007) 321–326, https://doi.org/10.1111/j.1600-079X.2007.00479.x.
[50] A.P. Goud, P.T. Goud, M.P. Diamond, B. Gonik, H.M. Abu-Soud, Reactive oxygen species and oocyte aging: role of superoxide, hydrogen peroxide, and hypochlorous acid, Free Radic. Biol. Med. 44 (7) (2008) 1295–1304, https://doi.org/10.1016/j.freeradbiomed.2007.11.014.
[51] O.J. Koo, G. Jang, D.K. Kwon, J.T. Kang, O.S. Kwon, H.J. Park, S.K. Kang, B. C. Lee, Electrical activation induces reactive oxygen species in porcine embryos, Theriogenology 70 (7) (2008) 1111–1118, https://doi.org/10.1016/j.theriogenology.2008.06.031.
[52] J.A. Stanley, K.K. Sivakumar, T.K. Nithy, J.A. Arosh, P.B. Hoyer, R.C. Burghardt, S.K. Banu, Postnatal exposure to chromium through mother's milk accelerates follicular atresia in F1 offspring through increased oxidative stress and depletion of antioxidant enzymes, Free Radic. Biol. Med. 61 (2013) 179–196, https://doi.org/10.1016/j.freeradbiomed.2013.02.006.
[53] M. Tiwari, S.K. Chaube, Moderate increase of reactive oxygen species triggers meiotic resumption in rat follicular oocytes, J. Obstet. Gynaecol. Res. 42 (5) (2016) 536–546, https://doi.org/10.1111/jog.12938.
[54] D. Xu, L. Wu, X. Jiang, L. Yang, J. Cheng, H. Chen, R. Hua, G. Geng, L. Yang, Q. Li, SIRT2 inhibition results in meiotic arrest, mitochondrial dysfunction, and disturbance of redox homeostasis during bovine oocyte maturation, Int. J. Mol. Sci. 20 (6) (2019) 1365, https://doi.org/10.3390/ijms20061365.
[55] Y. Li, Y. Miao, J. Chen, B. Xiong, SIRT6 maintains redox homeostasis to promote porcine oocyte maturation, Front. Cell Dev. Biol. 9 (2021), 625540, https://doi.org/10.3389/fcell.2021.625540.
[56] R.H. Hsieh, H.K. Au, T.S. Yeh, S.J. Chang, Y.F. Cheng, C.R. Tzeng, Decreased expression of mitochondrial genes in human unfertilized oocytes and arrested embryos, Fertil. Steril. 81 (Suppl 1) (2004) 912–918, https://doi.org/10.1016/j.fertnstert.2003.11.013.
[57] J.A. Barritt, C.A. Brenner, J. Cohen, D.W. Matt, Mitochondrial DNA rearrangements in human oocytes and embryos, Mol. Hum. Reprod. 5 (10) (1999) 927–933, https://doi.org/10.1093/molehr/5.10.927.
[58] Y. Cao, R. Li, W. Li, H. Liu, Y. Cai, Melatonin attenuates peroxynitrite-induced meiosis dysfunction in porcine oocytes, Reprod. Sci. (Thousand Oaks, Calif.) 28 (5) (2021) 1281–1289, https://doi.org/10.1007/s43032-020-00331-2.
[59] L. Yang, Y. Chen, Y. Liu, Y. Xing, C. Miao, Y. Zhao, X. Chang, Q. Zhang, The role of oxidative stress and natural antioxidants in ovarian aging, Front. Pharmacol. 11 (2020), 617843, https://doi.org/10.3389/fphar.2020.617843.
[60] U. Al-Zubaidi, D. Adhikari, O. Cinar, Q.H. Zhang, W.S. Yuen, M.P. Murphy, L. Rombauts, R.L. Robker, J. Carroll, Mitochondria-targeted therapeutics, MitoQ and BGP-15, reverse aging-associated meiotic spindle defects in mouse and human oocytes, Hum. Reprod. (Oxford, England) 36 (3) (2021) 771–784, https://doi.org/10.1093/humrep/deaa300.
[61] M. Sohel, B. Akyuz, Y. Konca, K. Arslan, S. Sariozkan, M.U. Cinar, Oxidative stress modulates the expression of apoptosis-associated microRNAs in bovine granulosa cells in vitro, Cell Tissue Res. 376 (2) (2019) 295–308, https://doi.org/10.1007/s00441-019-02990-3.
[62] Y.N. Cajas, K. Cañón-Beltrán, M. Ladrón de Guevara, M.G. Millán de la Blanca, P. Ramos-Ibeas, A. Gutiérrez-Adán, D. Rizos, E.M. González, Antioxidant nobiletin enhances oocyte maturation and subsequent embryo development and quality, Int. J. Mol. Sci. 21 (15) (2020) 5340, https://doi.org/10.3390/ijms21155340.
[63] Y.H. Edrey, A.B. Salmon, Revisiting an age-old question regarding oxidative stress, Free Radic. Biol. Med. 71 (2014) 368–378, https://doi.org/10.1016/j.freeradbiomed.2014.03.038.
[64] J. Lim, U. Luderer, Oxidative damage increases and antioxidant gene expression decreases with aging in the mouse ovary, Biol. Reprod. 84 (4) (2011) 775–782, https://doi.org/10.1095/biolreprod.110.088583.
[65] S.K. Chaube, T.G. Shrivastav, M. Tiwari, S. Prasad, A. Tripathi, A.K. Pandey, Neem (Azadirachta indica L.) leaf extract deteriorates oocyte quality by inducing ROS-mediated apoptosis in mammals, SpringerPlus 3 (2014) 464, https://doi.org/10.1186/2193-1801-3-464.
[66] K. Hoffmann, Melatonin inhibits photoperiodically induced testes development in a dwarf hamster, Die Nat. 59 (5) (1972) 218–219, https://doi.org/10.1007/BF00595517.
[67] A. Brzezinski, M.M. Seibel, H.J. Lynch, M.H. Deng, R.J. Wurtman, Melatonin in human preovulatory follicular fluid, J. Clin. Endocrinol. Metab. 64 (4) (1987) 865–867, https://doi.org/10.1210/jcem-64-4-865.
[68] Y. Nakamura, H. Tamura, H. Takayama, H. Kato, Increased endogenous level of melatonin in preovulatory human follicles does not directly influence progesterone production, Fertil. Steril. 80 (4) (2003) 1012–1016, https://doi.org/10.1016/s0015-0282(03)01008-2.
[69] H. Tamura, A. Takasaki, T. Taketani, M. Tanabe, F. Kizuka, L. Lee, I. Tamura, R. Maekawa, H. Aasada, Y. Yamagata, N. Sugino, The role of melatonin as an antioxidant in the follicle, J. Ovarian Res. 5 (2012) 5, https://doi.org/10.1186/1757-2215-5-5.
[70] R.J. WURTMAN, J. AXELROD, L.T. POTTER, The uptake of H3-melatonin in endocrine and nervous tissues and the effects of constant light exposure, J. Pharmacol. Exp. Ther. 143 (1964) 314–318.
[71] L. Rönnberg, A. Kauppila, J. Leppäluoto, H. Martikainen, O. Vakkuri, Circadian and seasonal variation in human preovulatory follicular fluid melatonin concentration, J. Clin. Endocrinol. Metab. 71 (2) (1990) 492–496, https://doi.org/10.1210/jcem-71-2-493.
[72] R.S. Barberino, V.G. Menezes, A. Ribeiro, R.C. Palheta, X. Jiang Jr., J. Smitz, M. Matos, Melatonin protects against cisplatin-induced ovarian damage in mice via the MT1 receptor and antioxidant activity, Biol. Reprod. 96 (6) (2017) 1244–1255, https://doi.org/10.1093/biolre/iox053.
[73] L. Zhang, Z. Zhang, J. Wang, D. Lv, T. Zhu, F. Wang, X. Tian, Y. Yao, P. Ji, G. Liu, Melatonin regulates the activities of ovary and delays the fertility decline in female animals via MT1/AMPK pathway, J. Pineal Res. 66 (3) (2019) 12550, https://doi.org/10.1111/jpi.12550.
[74] H. Tamura, A. Takasaki, I. Miwa, K. Taniguchi, R. Maekawa, H. Asada, T. Taketani, A. Matsuoka, Y. Yamagata, K. Shimamura, H. Morioka, H. Ishikawa, R.J. Reiter, N. Sugino, Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate, J. Pineal Res. 44 (3) (2008) 280–287, https://doi.org/10.1111/j.1600-079X.2007.00524.x.
[75] K.L. Hu, X. Ye, S. Wang, D. Zhang, Melatonin application in assisted reproductive technology: a systematic review and meta-analysis of randomized trials, Front. Endocrinol. 11 (2020) 160, https://doi.org/10.3389/fendo.2020.00160.
[76] A.S. Batıoğlu, U. Sahin, B. Gürlek, N. Oztürk, E. Unsal, The efficacy of melatonin administration on oocyte quality, Gynecol. Endocrinol.: Off. J. Int. Soc. Gynecol. Endocrinol. 28 (2) (2012) 91–93, https://doi.org/10.3109/09513590.2011.589925.
[77] O.G. Eryilmaz, A. Devran, E. Sarikaya, F.N. Aksakal, L. Mollamahmutoğlu, N. Cicek, Melatonin improves the oocyte and the embryo in IVF patients with sleep disturbances, but does not improve the sleeping problems, J. Assist. Reprod. Genet. 28 (9) (2011) 815–820, https://doi.org/10.1007/s10815-011-9604-y.
[78] B.N. Jahromi, S. Sadeghi, S. Alipour, M.E. Parsanezhad, S.M. Alamdarloo, Effect of melatonin on the outcome of assisted reproductive technique cycles in women with diminished ovarian reserve: a double-blinded randomized clinical trial, Iran. J. Med. Sci. 42 (1) (2017) 73–78.
[79] T. Nishihara, S. Hashimoto, K. Ito, Y. Nakaoka, K. Matsumoto, Y. Hosoi, Y. Morimoto, Oral melatonin supplementation improves oocyte and embryo quality in women undergoing in vitro fertilization-embryo transfer, Gynecol. Endocrinol.: Off. J. Int. Soc. Gynecol. Endocrinol. 30 (5) (2014) 359–362, https://doi.org/10.3109/09513590.2013.879856.
[80] J. Espino, M. Macedo, G. Lozano, Á. Ortiz, C. Rodríguez, A.B. Rodríguez, I. Bejarano, Impact of melatonin supplementation in women with unexplained infertility undergoing fertility treatment, in: Antioxidants, 8, Basel,, Switzerland, 2019, p. 338, https://doi.org/10.3390/antiox8090338.
[81] Q. Yang, L. Zhu, L. Jin, Human follicle in vitro culture including activation, growth, and maturation: a review of research progress, Front. Endocrinol. 11 (2020) 548, https://doi.org/10.3389/fendo.2020.00548.
[82] J.J. Eppig, Oocyte control of ovarian follicular development and function in mammals, Reproduction (Cambridge, England) 122 (6) (2001) 829–838, https://doi.org/10.1530/rep.0.1220829.

[83] Q.Y. Sun, Y.L. Miao, H. Schatten, Towards a new understanding on the regulation of mammalian oocyte meiosis resumption, Cell Cycle (Georgetown, Tex.) 8 (17) (2009) 2741–2747, https://doi.org/10.4161/cc.8.17.9471.
[84] P. Solc, R.M. Schultz, J. Motlik, Prophase I arrest and progression to metaphase I in mouse oocytes: comparison of resumption of meiosis and recovery from G2-arrest in somatic cells, Mol. Hum. Reprod. 16 (9) (2010) 654–664, https://doi.org/10.1093/molehr/gaq034.
[85] M. He, T. Zhang, Y. Yang, C. Wang, Mechanisms of oocyte maturation and related epigenetic regulation, Front. Cell Dev. Biol. 9 (2021), 654028, https://doi.org/10.3389/fcell.2021.654028.
[86] B. Pan, J. Li, The art of oocyte meiotic arrest regulation, Reprod. Biol. Endocrinol.: RBE 17 (1) (2019) 8, https://doi.org/10.1186/s12958-018-0445-8.
[87] J. Wang, Z. Zhuo, X. Ma, Y. Liu, J. Xu, C. He, Y. Fu, F. Wang, P. Ji, L. Zhang, G. Liu, Melatonin alleviates the suppressive effect of hypoxanthine on oocyte nuclear maturation and restores meiosis via the melatonin receptor 1 (MT1)-mediated pathway, Front. Cell Dev. Biol. 9 (2021), 648148, https://doi.org/10.3389/fcell.2021.648148.
[88] X. Tian, F. Wang, L. Zhang, C. He, P. Ji, J. Wang, Z. Zhang, D. Lv, W. Abulizi, X. Wang, Z. Lian, G. Liu, Beneficial effects of melatonin on the in vitro maturation of sheep oocytes and its relation to melatonin receptors, Int. J. Mol. Sci. 18 (4) (2017) 834, https://doi.org/10.3390/ijms18040834.
[89] Y. Fang, S. Deng, J. Zhang, H. Liu, Y. Li, X. Zhang, Y. Liu, Melatonin-mediated development of ovine cumulus cells, perhaps by regulation of DNA methylation, Molecules (Basel, Switzerland) 23 (2) (2018) 494, https://doi.org/10.3390/molecules23020494.
[90] Y. Fang, J. Zhang, Y. Li, X. Guo, J. Li, R. Zhong, X. Zhang, Melatonin-induced demethylation of antioxidant genes increases antioxidant capacity through RORα in cumulus cells of prepubertal lambs, Free Radic. Biol. Med. 131 (2019) 173–183, https://doi.org/10.1016/j.freeradbiomed.2018.11.027.
[91] T.C. Marques, E.C. da Silva Santos, T.O. Diesel, L.O. Leme, C.F. Martins, M. Dode, B.G. Alves, F. Costa, E.B. de Oliveira, M.L. Gambarini, Melatonin reduces apoptotic cells, SOD2 and HSPB1 and improves the in vitro production and quality of bovine blastocysts, Reprod. Domest. Anim. = Zuchthyg. 53 (1) (2018) 226–236, https://doi.org/10.1111/rda.13097.
[92] Y.W. Pang, X.L. Jiang, Y.C. Wang, Y.Y. Wang, H.S. Hao, S.J. Zhao, W.H. Du, X. M. Zhao, L. Wang, H.B. Zhu, Melatonin protects against paraquat-induced damage during in vitro maturation of bovine oocytes, J. Pineal Res. 66 (1) (2019) 12532, https://doi.org/10.1111/jpi.12532.
[93] Y. Wang, S. Zeng, Melatonin promotes ubiquitination of phosphorylated pro-apoptotic protein Bcl-2-interacting mediator of cell death-extra long (BimEL) in porcine granulosa cells, Int. J. Mol. Sci. 19 (11) (2018) 3431, https://doi.org/10.3390/ijms19113431.
[94] X. Tian, F. Wang, L. Zhang, P. Ji, J. Wang, D. Lv, G. Li, M. Chai, Z. Lian, G. Liu, Melatonin promotes the in vitro development of microinjected pronuclear mouse embryos via its anti-oxidative and anti-apoptotic effects, Int. J. Mol. Sci. 18 (5) (2017) 988, https://doi.org/10.3390/ijms18050988.
[95] J. Nie, P. Xiao, X. Wang, X. Yang, H. Xu, K. Lu, S. Lu, X. Liang, Melatonin prevents deterioration in quality by preserving epigenetic modifications of porcine oocytes after prolonged culture, Aging 10 (12) (2018) 3897–3909, https://doi.org/10.18632/aging.101680.
[96] Q. An, W. Peng, Y. Cheng, Z. Lu, C. Zhou, Y. Zhang, J. Su, Melatonin supplementation during in vitro maturation of oocyte enhances subsequent development of bovine cloned embryos, J. Cell. Physiol. 234 (10) (2019) 17370–17381, https://doi.org/10.1002/jcp.28357.
[97] S. Lee, J.X. Jin, A. Taweechaipaisankul, G.A. Kim, C. Ahn, B.C. Lee, Melatonin influences the sonic hedgehog signaling pathway in porcine cumulus oocyte complexes, 10.1111/jpi.12424, J. Pineal Res. 63 (3) (2017), https://doi.org/10.1111/jpi.12424.
[98] L. Liu, N. Labani, E. Cecon, R. Jockers, Melatonin target proteins: too many or not enough? Front. Endocrinol. 10 (2019) 791, https://doi.org/10.3389/fendo.2019.00791.
[99] C. Gennari Verruma, M. Credendio Eiras, A. Fernandes, R.A. Vila, C. Libardi Miranda Furtado, E. Silveira Ramos, R. Barbosa Lôbo, Folic acid supplementation during oocytes maturation influences in vitro production and gene expression of bovine embryos, Advance online publication, Zygote (Cambridge, England) (2021) 1–8, https://doi.org/10.1017/S0967199421000022.
[100] Z. Zhang, Y. Mu, D. Ding, W. Zou, X. Li, B. Chen, P.C. Leung, H.M. Chang, Q. Zhu, K. Wang, R. Xue, Y. Xu, H. Zou, P. Zhou, Z. Wei, Y. Cao, Melatonin improves the effect of cryopreservation on human oocytes by suppressing oxidative stress and maintaining the permeability of the oolemma, J. Pineal Res. 70 (2) (2021) 12707, https://doi.org/10.1111/jpi.12707.
[101] R. Amanvermez, M. Tosun, An update on ovarian aging and ovarian reserve tests, Int. J. Fertil. Steril. 9 (4) (2016) 411–415, https://doi.org/10.22074/ijfs.2015.4591.
[102] L. Yang, Y. Chen, Y. Liu, Y. Xing, C. Miao, Y. Zhao, X. Chang, Q. Zhang, The role of oxidative stress and natural antioxidants in ovarian aging, Front. Pharmacol. 11 (2020), 617843, https://doi.org/10.3389/fphar.2020.617843.
[103] S.K. Chaube, T.G. Shrivastav, M. Tiwari, S. Prasad, A. Tripathi, A.K. Pandey, Neem (Azadirachta indica L.) leaf extract deteriorates oocyte quality by inducing ROS-mediated apoptosis in mammals, SpringerPlus 3 (2014) 464, https://doi.org/10.1186/2193-1801-3-464.
[104] S. Regan, P.G. Knight, J.L. Yovich, Y. Leung, F. Arfuso, A. Dharmarajan, Granulosa cell apoptosis in the ovarian follicle-a changing view, Front. Endocrinol. 9 (2018) 61, https://doi.org/10.3389/fendo.2018.00061.
[105] Y. Huang, C. Hu, H. Ye, R. Luo, X. Fu, X. Li, J. Huang, W. Chen, Y. Zheng, Inflamm-aging: a new mechanism affecting premature ovarian insufficiency, J. Immunol. Res. 2019 (2019), 8069898, https://doi.org/10.1155/2019/8069898.
[106] I. Kasapoğlu, E. Seli, Mitochondrial dysfunction and ovarian aging, Endocrinology 161 (2) (2020) bqaa001, https://doi.org/10.1210/endocr/bqaa001.
[107] S. Wang, Y. Zheng, J. Li, Y. Yu, W. Zhang, M. Song, Z. Liu, Z. Min, H. Hu, Y. Jing, X. He, L. Sun, L. Ma, C.R. Esteban, P. Chan, J. Qiao, Q. Zhou, J.C. Izpisua Belmonte, J. Qu, F. Tang, G.H. Liu, Single-cell transcriptomic atlas of primate ovarian aging, e19, Cell 180 (3) (2020) 585–600, https://doi.org/10.1016/j.cell.2020.01.009.
[108] J. Lim, U. Luderer, Oxidative damage increases and antioxidant gene expression decreases with aging in the mouse ovary, Biol. Reprod. 84 (4) (2011) 775–782, https://doi.org/10.1095/biolreprod.110.088583.
[109] K.N. Prasad, M. Wu, S.C. Bondy, Telomere shortening during aging: attenuation by antioxidants and anti-inflammatory agents, Mech. Ageing Dev. 164 (2017) 61–66, https://doi.org/10.1016/j.mad.2017.04.004.
[110] M.L. Huang, S. Chiang, D.S. Kalinowski, D.H. Bae, S. Sahni, D.R. Richardson, The role of the antioxidant response in mitochondrial dysfunction in degenerative diseases: cross-talk between antioxidant defense, autophagy, and apoptosis, Oxid. Med. Cell. Longev. 2019 (2019), 6392763, https://doi.org/10.1155/2019/6392763.
[111] H. Sasaki, T. Hamatani, S. Kamijo, M. Iwai, M. Kobanawa, S. Ogawa, K. Miyado, M. Tanaka, Impact of oxidative stress on age-associated decline in oocyte developmental competence, Front. Endocrinol. 10 (2019) 811, https://doi.org/10.3389/fendo.2019.00811.
[112] J. Pineda-Pampliega, A. Herrera-Dueñas, E. Mulder, J.I. Aguirre, U. Höfle, S. Verhulst, Antioxidant supplementation slows telomere shortening in free-living white stork chicks, Proc. Biol. Sci. 287 (1918) (2020), 20191917, https://doi.org/10.1098/rspb.2019.1917.
[113] H. Tamura, M. Kawamoto, S. Sato, I. Tamura, R. Maekawa, T. Taketani, H. Aasada, E. Takaki, A. Nakai, R.J. Reiter, N. Sugino, Long-term melatonin treatment delays ovarian aging, J. Pineal Res. 62 (2) (2017), https://doi.org/10.1111/jpi.12381.
[114] E. Batnasan, S. Xie, Q. Zhang, Y. Li, Observation of parthanatos involvement in diminished ovarian reserve patients and Melatonin's protective function through inhibiting ADP-ribose (PAR) expression and preventing AIF translocation into the nucleus, Reprod. Sci. (Thousand Oaks, Calif.) 27 (1) (2020) 75–86, https://doi.org/10.1007/s43032-019-00005-8.
[115] E.Y. Hao, H. Chen, D.H. Wang, C.X. Huang, Y.G. Tong, Y.F. Chen, R.Y. Zhou, R. L. Huang, Melatonin regulates the ovarian function and enhances follicle growth in aging laying hens via activating the mammalian target of rapamycin pathway, Poult. Sci. 99 (4) (2020) 2185–2195, https://doi.org/10.1016/j.psj.2019.11.040.
[116] C. Yang, Q. Liu, Y. Chen, X. Wang, Z. Ran, F. Fang, J. Xiong, G. Liu, X. Li, L. Yang, C. He, Melatonin delays ovarian aging in mice by slowing down the exhaustion of ovarian reserve, Commun. Biol. 4 (1) (2021) 534, https://doi.org/10.1038/s42003-021-02042-z.
[117] C. Gao, H.B. Han, X.Z. Tian, D.X. Tan, L. Wang, G.B. Zhou, S.E. Zhu, G.S. Liu, Melatonin promotes embryonic development and reduces reactive oxygen species in vitrified mouse 2-cell embryos, J. Pineal Res. 52 (3) (2012) 305–311, https://doi.org/10.1111/j.1600-079X.2011.00944.x.
[118] Y. Xu, K.H. Zhang, M.H. Sun, M. Lan, X. Wan, Y. Zhang, S.C. Sun, Protective effects of melatonin against zearalenone toxicity on porcine embryos in vitro, Front. Pharmacol. 10 (2019) 327, https://doi.org/10.3389/fphar.2019.00327.
[119] R.L. Lane, B.D. Whitaker, Melatonin and tannic acid supplementation in vitro improve fertilization and embryonic development in pigs, Anim. Reprod. 15 (2) (2018) 118–123, https://doi.org/10.21451/1984-3143-AR2016-937.
[120] J. Qu, M. Sun, X. Wang, X. Song, H. He, Y. Huan, Melatonin enhances the development of porcine cloned embryos by improving DNA methylation reprogramming, Cell. reprogramming 22 (3) (2020) 156–166, https://doi.org/10.1089/cell.2019.0103.
[121] Y.J. Niu, W. Zhou, Z.W. Nie, K.T. Shin, X.S. Cui, Melatonin enhances mitochondrial biogenesis and protects against rotenone-induced mitochondrial deficiency in early porcine embryos, J. Pineal Res. 68 (2) (2020) 12627, https://doi.org/10.1111/jpi.12627.
[122] F. Xie, J. Zhang, M. Zhai, Y. Liu, H. Hu, Z. Yu, J. Zhang, S. Lin, D. Liang, Y. Cao, Melatonin ameliorates ovarian dysfunction by regulating autophagy in PCOS via the PI3K-Akt pathway, Reproduction (Cambridge,England) 162 (1) (2021) 73–82, https://doi.org/10.1530/REP-20-0643.
[123] S. Yi, B. Zheng, Y. Zhu, Y. Cai, H. Sun, J. Zhou, Melatonin ameliorates excessive PINK1/Parkin-mediated mitophagy by enhancing SIRT1 expression in granulosa cells of PCOS, Am. J. Physiol. Endocrinol. Metab. 319 (1) (2020) E91–E101, https://doi.org/10.1152/ajpendo.00006.2020.