

## REVIEW ARTICLE

# Melatonin as Potential Targets for Delaying Ovarian Aging

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**Abstract:** In previous studies, oxidative stress damage has been solely considered to be the mechanism of ovarian aging, and several antioxidants have been used to delay ovarian aging. But recently, more reports have found that endoplasmic reticulum stress, autophagy, sirtuins, mitochondrial dysfunction, telomeres, gene mutation, premature ovarian failure, and polycystic ovary syndrome are all closely related to ovarian aging, and these factors all interact with oxidative stress. These novel insights on ovarian aging are summarized in this review. Furthermore, as a pleiotropic molecule, melatonin is an important antioxidant and used as drugs for several diseases treatment. Melatonin regulates not only oxidative stress, but also the various molecules, and normal and pathological processes interact with ovarian functions and aging. Hence, the mechanism of ovarian aging and the extensive role of melatonin in the ovarian aging process are described herein. This systematic review supply new insights into ovarian aging and the use of melatonin to delay its onset, further supply a novel drug of melatonin for ovarian aging treatment.

**Keywords:** Melatonin, oxidative stress, endoplasmic reticulum stress, autophagy, ovarian ageing.

## 1. INTRODUCTION

The female reproductive cycle is mainly determined by the ovarian lifespan, and decreased fertility and even infertility is caused by the shortening of the female reproductive cycle, attributed to the ovarian lifespan, particularly ovarian aging.

Women suffer a significant reduction in fecundity and an increase in the probability of infertility in their late thirties, accompanied by decreased ovarian functions [1]. The functions of the human ovary alternate dynamically with the menopausal period [2]. An increase in fibrous tissues and a decrease in the number of primordial follicles are two obvious characteristics observed histologically in the aged ovary [2], especially after 38 years of age [3]. There is also a gradual decline in oocyte quantity and quality [4], accompanied by increased aneuploidy and unfavorable oocyte maturation [5, 6]. A reduction in oocyte quality and diminishing follicles and oocytes are main traits of ovarian aging [7, 8].

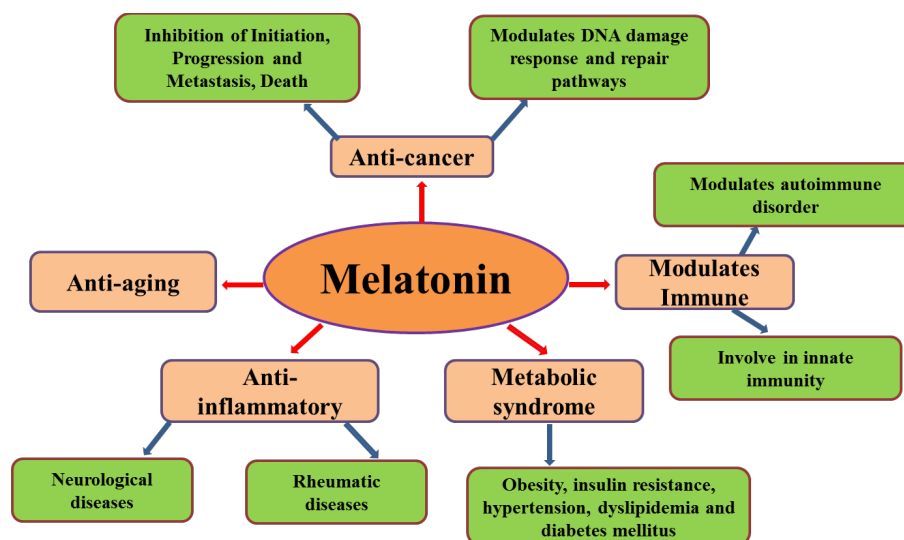
Clinically, ovarian aging is characterized by a diminished ovarian reserve (DOR), accompanied with a decrease in anti-Müllerian hormone, an increase in follicle-stimulating hormone (FSH) and a decrease in the antral follicular count (AFC) [9].

The complications of ovarian aging have several causes. Previous studies have suggested that menopause [3], chemotherapy [10], endocrinological disorder, genetic mutation, and micro-environmental factors [11] are associated with and inducers of ovarian aging. The pathology and the mechanism of ovarian aging are complicated and not fully known. Understanding the mechanism of ovarian aging will provide new insights and drugs to delay ovarian aging and improve female fertility.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland and released in a circadian manner; its secretion is exclusively at night and is regulated by light and dark environment [12, 13]. Exogenous melatonin administration has no obvious short- or long-term adverse effects and is well tolerated [13]. Melatonin involves several physiological and pathological processes (Fig. 1). As an anti-cancer agent for the prevention and treatment of cancer [14], melatonin regulates DNA damage response and repair pathways. It interacts with DNA damage agents to increase their efficacy in cancer therapy

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**Fig. (1).** The roles of melatonin. Melatonin involve in the anti-cancer, anti-aging, modulates immune, anti-inflammatory, metabolic syndrome.

[15] and alleviates cancer at the initiation, progression, and metastasis phases [16, 17]. Melatonin is involved in immune regulation and may aggravate some autoimmune conditions, but it mitigates other conditions such as multiple sclerosis [18]. It is part of the innate immunity, involving the regulation of monocytes-macrophages, dendritic cells, neutrophils, eosinophils, basophils, mast cells, and natural killer cells [19]. Melatonin is used as an anti-inflammatory factor [20] for dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, brain ischemia/reperfusion, and traumatic central nervous system injuries [21]. Melatonin also plays an important role in rheumatic diseases [22]. Used as an antioxidant, melatonin is an efficient targeting molecule in metabolic syndromes, such as obesity, insulin resistance, hypertension, dyslipidemia, and diabetes mellitus [23]. Hence, as a pleiotropic molecule, melatonin is essential for several physiological and pathological processes and is a very effective target molecular for preventing and curing diseases.

Previous studies revealed that as an antioxidant, melatonin plays an important role in anti-aging [24], primarily oxidative stress damage [24]. Other research found that oxidative stress (OS) damage is not only a mechanism of melatonin anti-aging; ER stress, autophagy, the sirtuin family, advanced glycation end-products (AGEs), mitochondrial dysfunction, gene mutation, telomeres, premature ovary failure (POF), and polycystic ovary syndrome (PCOS) are all closely associated with ovarian aging.

## 2. OXIDATIVE STRESS AND OVARIAN AGING

Reactive oxygen species (ROS) are chemically reactive molecules that play vital roles in the regulation of various cell functions and biological processes [25]. Physiological levels of ROS are essential for ovarian function, but excessive ROS may overpower the body's natural antioxidant defense system, accompanied by increased oxidative stress (OS) damage [26]. OS is present in all organs and cells and has been recently reported to play an important role in the normal functioning of the female reproductive system and in

the pathogenesis of reproductive diseases such as polycystic ovary syndrome and unexplained infertility [27]. The roles of OS in female reproduction were summarized by Agarwal *et al.* [28]. Higher OS in the follicular microenvironment accelerates ovarian aging [29]. Long-term OS induced by ozone inhalation reduces ovarian reserves, decreases ovarian function, and induces ovarian aging-related disorders [30]. The aged ovary has a transformed oxidative stress defense profile compared to the control (26-day-old) group, elevated vitamin E levels at 0, 2, and 24 hours were found in aging mice after PGF2alpha. At 2 and 24 hours after PGF2alpha, aging ovaries had lower glutathione reductase levels [31], which is a marker of OS. The decrease in antioxidant gene expression was accompanied by increased oxidative damage in the aging mouse ovary [32].

ROS in the follicular fluid can be used as biochemical markers to measure ovarian aging and follicular metabolic age [33]. ROS affects oocyte growth during follicle growth *in vivo* and is closely related to ovarian aging [34]. Oxidative stress is a prominent mediator associated with oocyte aging. The quantity and quality of oocytes greatly decrease due to apoptosis induced by OS, and the oocyte functions are determined by the balance between ROS and antioxidants. Additionally, the significance of ROS and OS is emphasized in other organs aging, such as brain aging [35], heart aging [36, 37], vascular aging [38], placental aging-related pathologies [39], liver aging [40]. Therefore, the ROS and OS play important role in aging.

## 3. AUTOPHAGY AND OVARIAN AGING

Autophagy is an intracellular bulk degradation system in which a portion of the cytoplasm is enveloped in double-membrane-bound structures referred to as autophagosomes, which undergo maturation and fusion with lysosomes for degradation [41, 42]. As an evolutionarily conservative mechanism, autophagy promotes cellular survival at a baseline level. Cell death is triggered by inhibited or overactive autophagy also referred to as a "double-edged sword" [43].

The role of autophagy in ovarian follicle development and atresia was reviewed in our previous studies [44]. Germ cell death during the establishment of the ovarian reserve occurs principally by autophagy or apoptosis [45]. Before oocytes are enclosed into a primordial follicle, deficiency in nutrients/growth factors activates protective autophagy, but germ cell death is triggered if starvation is prolonged [46]. Autophagy is inhibited by autophagy suppressor VDAC2 during the developing ovary through a complex of VDAC2-BECN1-BCL2L1 in mammals [47], and dysfunction of autophagy level induces dysfunctional ovarian development.

Resveratrol-induced autophagy and mitochondrial synthesis in oocytes of early antral follicles in aged cows further suggests the role of autophagy [48]. Ovarian follicle atresia is triggered by autophagy, which also regulates primordial follicle atresia [49]. Autophagy promotes the formation of the primordial follicle pool [50] in the perinatal period in mice. Germ cell losses are caused by knocking out autophagy genes *Becn1* and *Atg7*; *Becn1*<sup>+/-</sup> ovaries had 56% fewer germ cells, while no germ cells were detected in *Atg7*<sup>-/-</sup> ovaries [50, 51].

Germ cell-specific *Atg7* knockout causes primary ovarian insufficiency (POI) in female mice [52]. The primordial follicle is activated and primary ovarian insufficiency is triggered by knocking out autophagy gene *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) through poor regulation of the PI3K pathway [53]. The diminished ovarian reserve is the main reason for ovarian aging, and ovarian follicle atresia is the major cause of follicular expenditure at all stages of the ovarian lifespan [54]. Increased follicle atresia and granulosa cell apoptosis occurred in aging mice [55].

Autophagy inducer rapamycin treatment has a beneficial effect on the reserve of the ovarian follicle pool and female reproductive lifespan in animals. We optimistically consider that rapamycin or its derivatives could be used as an effective drug for preventing POF and delaying the onset of menopause in obese and even healthy women in the future [56]. Autophagy plays a vital role in ovarian follicle development, and abnormal autophagy causes excessive ovarian follicle atresia and POF, accompanied by ovarian aging.

#### 4. ER STRESS AND OVARIAN AGING

The endoplasmic reticulum (ER) is an important organelle for synthesis, protein folding, and transport. Homeostasis of the ER can be disturbed by the depletion of Ca<sup>2+</sup>, hypoxia, and the dysfunction of N-terminal glycosylation, causing ER stress [57, 58] accompanied by unfolded and misfolded proteins accumulating in the ER. Furthermore, the ER load was mitigated through unfolded protein response (UPR) referred to as one branch of the ER stress response [59].

Ovarian follicle atresia is a characteristic of ovarian aging, accompanied by granulosa cell apoptosis [54, 55], and research has suggested that aging ovaries have poor granulosa cells [60]. ER microenvironment homeostasis plays a crucial role in folliculogenesis, cumulus cell survival, cumulus-oocyte complex, and oocyte quality. The regulation of ER homeostasis/stress is likely to be a key mechanism for

folliculogenesis and oocyte maturation [61]. Previous studies have suggested that the ER stress-mediated apoptotic pathway is involved in ovarian follicle atresia [62, 63] and ovarian granulosa cell apoptosis [64]. The role of ER stress and UPR in ovarian follicle development and atresia was reviewed by our team and others [59, 65]. The impairment of endoplasmic reticulum proteostasis is triggered in aging, and ER unfolded protein response (UPR<sup>ER</sup>) operates as a central player to maintain ER homeostasis or the induction of cell death in chronically damaged cells [66]. ER stress is a driver of brain aging, and the UPR controls global proteostasis at the whole organism level [66]; the role of ER stress and UPR in aging was studied by Taylor *et al.* [67]. The aging process is characterized by the progressive accumulation of damaged biomolecules in the endoplasmic reticulum, a result of increased oxidative stress accompanying cellular senescence [68]. Aging induces ER stress [69]. ER stress and UPR are involved in aging, demonstrating that UPR is an important determinant of lifespan [70]. A “healthy” proteome is essential for cell survival, but protein misfolding or dysfunction of proteostasis is caused by aging [71]. Proteostasis is controlled by a network of molecular chaperones and clearance pathways that are involved in the recognition, refolding, and/or clearance of aberrant proteins [71]. As protein-quality control mechanisms, misfolded and unfolded proteins are controlled through ER-associated degradation (ERAD) under the supervision of UPR [59]. Proteostasis is closely related to aging [72, 73], and is controlled by UPR<sup>ER</sup> [74]. This evidence further suggests that ER stress and UPR are involved in ovarian aging.

#### 5. SIRTUIN FAMILY AND OVARIAN AGING

Sirtuins (silent information regulators, SIRT1-SIRT7) are unique histone deacetylases (HDACs) whose activity depends on NAD<sup>+</sup> levels and thus on the cellular metabolic status [75]. SIRT1s regulate several biological processes such as cell survival, senescence, proliferation, apoptosis, DNA repair, cell metabolism, and caloric restriction [76]. Seven SIRT family members have been identified in mammals. SIRT1 and SIRT2 are localized in the nucleus and cytoplasm, SIRT3, SIRT4, and SIRT5 are mitochondrial, and SIRT6 and SIRT7 are nuclear [77]. The seven SIRT1s are considered potential targets for the treatment of human pathologies, including neurodegenerative diseases, cardiovascular diseases, and cancer [76] because of the important roles of sirtuin in brain aging [75], vascular aging [77], and cancer [78]. The expression of SIRT1, SIRT3, and SIRT6 in the ovary is closely related to the ovarian reserve, suggesting its vital roles in ovarian aging and might be a target molecule for the anti-aging of ovaries [79]. Sirtuins may be markers of ovarian aging. A high-fat (HF) diet induces obesity and may promote ovarian follicle development and the rate of ovarian follicle loss *via* activating mTOR and suppressing SIRT1 signaling, thus leading to POF. Therefore, suppressing mTOR and activating SIRT1 signaling prolongs the ovarian lifespan [80]. Ovarian functions at various regulatory levels are controlled by sirtuins (SIRT1s) [81]. The increased expression of SIRT1 during the primordial to primary follicle transition [82] plays important roles in ovarian development and decreased or inhibited expression of SIRT1 might induce POF and ovarian aging. SIRT1 expression in ovarian tissue

decreases in rats with PCOS, and upregulating SIRT1 expression using exenatide suggests that exenatide may be a vital therapeutic target for PCOS [83]. Inhibiting the expression of SIRT1 adversely affects porcine oocyte meiosis [84]. Impairment of SIRT1 signaling is closely related to oocyte aging [85]. Caloric restriction (CR) inhibits ovarian follicle development and follicle loss through the activation of SIRT1 signaling in mice [86]. Resveratrol ameliorates the quality of pig oocytes derived from early antral follicles *via* the activation of SIRT1 [87]. Increased expression of SIRT1 contributes to ovarian follicle atresia and granulosa cell apoptosis [88]. SIRT1 activator (SRT1720) improves the ovarian follicle reserve and extends the ovarian lifespan in diet-induced obesity in female mice through the activation of SIRT1 and the suppression of mTOR signaling [89]. Mitochondrial SIRT3 and its target glutamate dehydrogenase vary in ovarian follicular cells accompanied by reduced ovarian reserve or advanced maternal age [90]. Mitochondrial SIRT5 also emerges in ovarian follicular cells and is altered by reduced ovarian reserve and advanced maternal age [90]. SIRT1 and transcription factor NF- $\kappa$ B (p50/p65) are involved in the regulation of porcine ovarian cell function [91]. Rapamycin extends the ovarian lifespan and further preserves the follicle pool reserve in female rats through the activation of mTOR and sirtuin expression [92]. CR (caloric restriction) prolongs mammals' lifespans and inhibits ovary development, further preserving the reserve of germ cells, and the potential mechanism is closely associated with the expression of SIRT1 and SIRT6 proteins in rats [93]. SIRT6 plays vital roles in modulating telomere structure, DNA repair, metabolism, and NF- $\kappa$ B pathway in mammalian aging [94]. The sirtuins, especially SIRT1, SIRT3, and SIRT6, are closely related to ovarian follicle development and may regulate ovarian aging.

## 6. ADVANCED GLYCATION END-PRODUCTS AND OVARIAN AGING

Advanced glycation end-products (AGEs) are the end-products of a chemical procedure called the Maillard reaction in which the carbonyl group of carbohydrates reacts non-enzymatically with primary amino groups of proteins [95, 96]. At present, studies have revealed that AGEs are involved in several diseases such as type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MetS), cardiovascular disease (CVD), aging, inflammation, and neurodegenerative disorders [97-102]. The role of AGEs in female reproduction has been investigated, especially the mechanisms of AGEs in reproductive physiology and the hypothalamic-pituitary-ovarian axis. AGEs receptors (AGEs-RAGEs) might contribute to the etiology of PCOS and infertility, and AGE inhibitors might be potential therapeutic targets of PCOS and infertility [103]. The roles of AGEs-RAGEs in ovarian functions were reviewed by Merhi *et al.* [103] and Tatone *et al.* [104]. Furthermore, the roles AGEs play in the ovarian aging was emphasized and summarized by Pertynska-Marczewska *et al.* [29], Szafarowska *et al.* [105], Li *et al.* [8], and Tatone *et al.* [106, 107].

## 7. MITOCHONDRIAL DYSFUNCTION

Mitochondria play important roles in energy metabolism, cell proliferation, and cell apoptosis. Mitochondria are the

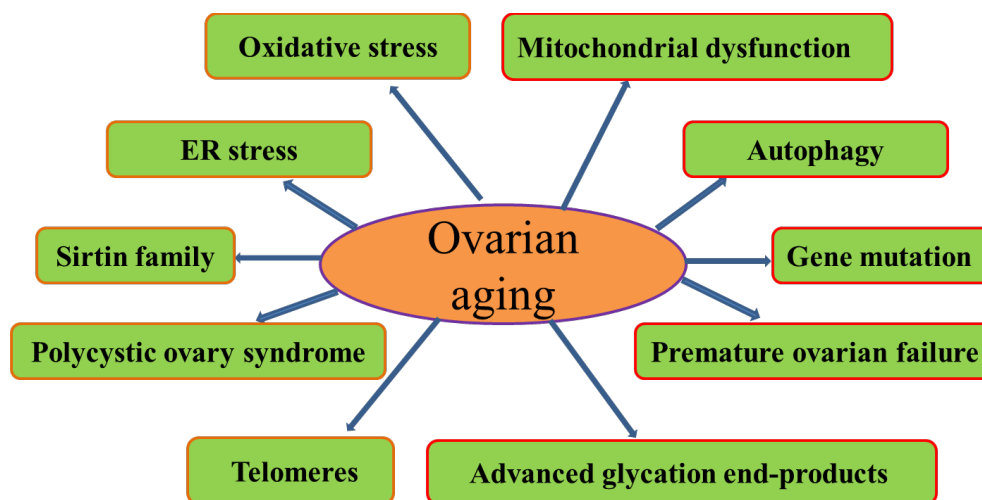
most prominent organelles in the oocyte, and oocyte mitochondria inherited by offspring attributed to sperm mitochondria are degraded immediately after fertilization [108]. In fact, only a small percentage of these oocyte mitochondria are metabolically active [109]. Oocyte mitochondria are typically small and round, with few cristae that wrap the periphery of the organelle [110]. Additionally, the mitochondrial genome also plays a vital role in ovarian follicle development [111]. Mitochondrial dysfunction triggers ovarian dysfunction, infertility, and ovarian aging [112]. Mitochondrial function and energy production degrade with age, adversely affecting ovarian reserves and chromosome segregation [113]. Mitochondria and mitochondrial DNA (mtDNA) content decrease in aged oocytes [114]. Mitochondria in elderly mice and hamsters undergo significant morphological changes, including mitochondrial vacuolization, cristae alterations, and changes in cytoplasmic lamellae [114]. Hence, the mitochondrial activity can be used as a biomarker to assess oocyte quality [115].

An individual's mtDNA comes entirely from his or her mother; this is attributed to the mitochondria derived from the egg only [116]. Mature oocytes have at least 100,000 copies of mtDNA, with 1-2 copies per organelle. Although this is a high genome copy number, mtDNA sequence variants are detected to segregate rapidly between generations, and this has emerged as a developmental bottleneck for the transmission of mtDNA [117]. Ovary and oocyte dysfunction is caused by mtDNA mutation, and human ovarian aging is triggered by mtDNA deletion [2]. The mutation in coenzyme Q9 (COQ9) affects ovarian function, especially oocyte quality, ovarian follicle numbers, and hormones [118]. Mitochondrial SIRT5 is detected in ovarian follicular cells and varies by ovarian reserve and advanced maternal age [119].

Mitochondrial cytochrome C oxidase 1 gene mutations in patients increase the incidence of POI [120], which has a prevalence ranging from 1% to 5% of the female population [120]. In humans, POLG mutations can lead to premature aging phenomena such as isolated POI [121]. Deletion 4 977 bp of granular cell mitochondria DNA in patients diminishes ovarian reserves [122]. Repeated ovarian stimulation induces oxidative damage and mtDNA mutations in aging mouse ovaries [123]. Fragile X premutation (FXPM) states, including FXPOI, may cause mitochondrial dysfunction [124, 125]; ovarian abnormalities are caused in a mouse model of Fragile X primary ovarian insufficiency [126]. A mutation in the inner mitochondrial membrane peptidase 2-like gene (Immp2L) affects mitochondrial function and impairs fertility in mice [127]. However, previous results do not support mitochondrial dysfunction as the main mechanism of reproductive aging [128]. Therefore, the relationship between mitochondrial dysfunction and ovarian aging is still controversial and needs to be studied in the future.

## 8. GENE MUTATION

Previous research revealed 44 genetic variants that are associated with the age of onset of natural menopause [129]. This can be divided into 3 major groups based on gene function: genes implicated in genome stability (DNA repair), immune function, and mitochondrial biogenesis [129]. Popu-



**Fig. (2).** The reasons causing ovarian aging. More reasons are closely associated with ovarian aging.

lation-based genome-wide association studies have identified 44 genomic loci associated with age of menopause, and 29 of 44 loci harbor DNA damage-response genes [130]. BRCA mutations causing DNA repair deficiency are closely related to ovarian aging [131], and the impairment of BRCA1-related DNA double-strand break repair contributes to ovarian aging in mice and humans [132]. Lack of a novel centromere protein SYCP2L accelerates reproductive aging in females [133]. Low FMR1 gene alleles decrease ovarian reserves in young women [134]. GDF9 mutations in young women also diminish ovarian reserves [135]. Glutamate cysteine ligase modifier subunit (Gclm) elevates ovarian oxidative stress and accelerates age-related ovarian failure in mice [136]. *Nrf2*<sup>-/-</sup> mice have hardly any primordial follicles compared to *Nrf2*<sup>+/+</sup> mice, consistent with accelerated ovarian aging [137]. FOXL2 plays an essential role in granulosa cell homeostasis, and its failure triggers ovarian aging and tumorigenesis [138]. More genes associated with ovarian aging will be identified.

## 9. TELOMERES

Telomeres are markers of cellular aging as their length declines with cell division [139]. Telomere length is closely associated with reproductive aging [140-142]. Shorter telomeres correlate with a reduced mitotic capacity in primordial germ cells during fetal development, limiting the size of the follicular pool [143]. Telomere length and telomerase activity are impaired in peripheral blood leukocytes and granulosa cells in patients with biochemical POI [144]. Long-term side effects of low telomerase activity and increased ROS exposure are potential reasons for telomere shortening in oocytes in female mice of reproductive age [145]. Estrogen deficiency shortens telomeres in mouse granulosa cells and accelerates ovarian aging *in vivo* [146]. Telomerase control of telomere homeostasis further mediates estrogen-induced ovarian aging [147]. The vital role of telomeres in female reproductive aging has been summarized by several studies [143, 148-150].

## 10. POF AND OVARIAN AGING

POF, also called POI, is a common cause of female infertility characterized by amenorrhea, hypogonadism, and

elevated gonadotropin levels in women under the age of 40 [151]. Premature ovarian aging (POA) is a frequent precursor stage to POF [152], with reduced ovarian reserves and a low number of high-quality eggs. POF may indeed represent an acceleration of the aging process [153]. POF is an aspect of menopause without an obvious cause and may be regarded as a unique model for the study of the genetic mechanisms of ovarian aging [11]. Therefore, POF is the end of ovarian aging.

## 11. PCOS AND OVARIAN AGING

PCOS is a common endocrine disorder affecting 9-18% of women of reproductive age. It causes hyperandrogenism and infertility due to dysfunctional follicular maturation and anovulation [154]. Its etiology is still poorly understood [155]. Anti-Mullerian hormone (AMH) can be used as a satisfactory marker of ovarian reserve status in age-related decline [156]. The expected decline in AMH in PCOS patients closely related to reproductive aging appears weakened despite ovarian senescence [157]. A serum AMH result >36 pmol/L or above the 75 th percentile for age is an optimal criteria for the diagnosis of PCOS [156]. Serum AMH might predict ovulation function with aging in anovulatory women with PCOS [158]. Ovarian aging and PCOS share some prominently similar symptoms, effectors, and commonalities in the majority of characteristics [159]. Changes in the PCOS phenotype accompany advancing age [160], while the phenotype of PCOS improves with aging [161]. Indeed, the d-galactose-induced aging mouse model shows PCOS-like phenotypes [162]. Increased anti-Mullerian hormone (AMH) in women with PCOS suggests a delay in ovarian aging, and the reproductive lifespan of PCOS women is prolonged an average of 2 years beyond that of normo-ovulatory women [163]. Previous research reported that improved fertility was detected in some PCOS aging women [164]. The follicle cohort is reduced in PCOS women with aging ovaries, accompanied by decreased inhibin B and AMH levels. Follicle maturation, regulation, and ovulatory cycles were improved by enhanced FSH levels through lower inhibin B levels. Therefore, ovarian aging is closely associated with PCOS.

## 12. FOLLICULAR HYPOXIA AND INTRAOVARIAN KISSPEPTIN

Follicular hypoxia is the main mechanism leading to ovarian follicular senescence. There is a link between cumulus cell aging and oocyte quality decay [165]. Menopause is guided by an age-related decline in ovarian stem cell function rather than the depletion of a non-renewable follicular reserve [166]. Intraovarian kisspeptin (KISS1) is controlled by sympathetic nerves through a beta-adrenergic receptor. Increasing in ovarian sympathetic activity in aged rats is closely associated with an increased expression of KISS1; hence, KISS1 participates in ovarian follicular development during reproductive aging [167].

## 13. ANTI-AGING OF OS

Although ovarian aging is caused by several factors, OS is considered the main reason. For the past several years, antioxidants have been used to prevent the ovary from aging. Antioxidants have protective roles for oocytes in regard to nuclear maturation, functional mitochondria, spindle morphology, and DNA integrity [34]. Several antioxidants are used to prevent ovarian aging from OS damage, including Kuntai capsules [168], Vitex agnus-castus (Vitex) [169], Portulaca oleracea (purslane) [170], coenzyme Q10 [171, 172], Yifuning [173], C-phycoerythrin (PC) [174] N-acetyl-L-cysteine (NAC) [175], resveratrol [176] and others. Down-regulation of antioxidant gene expression was accompanied by increased oxidative damage in the aging mouse ovary [32]. Indeed, reduced ovarian reproductive function is caused by long-term moderate oxidative stress accompanied by decreased follicle quality and progesterone production [30]. Telomere shortening, DNA mutations, protein damage, apoptosis, and accelerated ovarian aging are triggered by an accumulation of free radicals with age [176]. In addition to OS damage, DNA mutations, protein damage, telomere shortening, and mitochondrial dysfunction induce ovarian aging.

## 14. CROSSTALK OF OS, SIRT1, MITOCHONDRIAL DYSFUNCTION, AND mtDNA MUTATION IN OVARY AGING

Upregulation of FOXL2 accumulates cells in the G1 phase and protects cells from oxidative damage, promotes oxidized DNA repair, and increases the amounts of antioxidant agent glutathione, and SIRT1 deacetylase inhibits FOXL2 activity related to cell cycle and DNA repair [138]. Oxidative damage and mitochondrial DNA mutations are caused by repeated ovarian stimulation of mouse ovaries [123]. Decreased expression of mitochondrial antioxidants Prdx3 and Txn2 and cytosolic antioxidants Glrx1 and Gstm2 may be involved in age-related ovarian oxidative damage to lipids, proteins, DNA, and other cellular components vital for maintaining ovarian function and fertility [32]. Several studies have suggested that mtDNA mutation leads to mitochondrial dysfunction, increased oxidative stress, and apoptosis in the aging ovary [177-179]. OS is related to SIRT1, mitochondrial dysfunction, and mtDNA mutations in ovarian function and aging. The accurate role of OS in SIRT1, mitochondrial dysfunction, and mtDNA mutation needs to be explored.

## 15. INTERCONNECTION OF OS, ER STRESS, AUTOPHAGY, AND MITOCHONDRIA IN THE AGING OVARY

Aging and age-related diseases might be the phenotypic consequences of oxidative damage targeting cellular proteins and proteome damage patterns progressing with age [180]. As a protein damage repair mechanism, endoplasmic reticulum unfolded protein response (UPR<sup>ER</sup>) and autophagy are vital for the degradation of misfolded and unfolded proteins in the ER load through ER-associated degradation (ERAD) and lysosome-mediated autophagy [59, 181-183], consistent with the ER load. Mitochondrial proteostasis is maintained by UPR<sup>mt</sup> and mitophagy [184]. Therefore, UPR<sup>ER</sup>, UPR<sup>mt</sup>, and autophagy are the main repair mechanisms for OS-induced proteome damage during aging. Protein homeostasis in the ER during aging is very important and redox homeostasis is controlled by protein homeostasis, but proteotoxic stress is triggered by the collapse of redox homeostasis [185]. The redox state in the cytosol and the ER changes in an opposing manner in response to proteotoxic challenges in young animals. The redox state in the cytosol becomes more oxidizing with age, whereas the ER is oxidizing and shifts toward reducing conditions during aging [186]. This is attributed to reduction in the cytosol, nucleus, and mitochondria; the endoplasmic reticulum represents a more oxidizing environment [187]. Hence, changes in proteostasis are the biomarkers of the start of aging [188].

Although ovarian OS, ER stress, autophagy, and mitochondria have been explored in several studies, it is unknown how they work together in ovarian aging.

## 16. CROSSTALK OF TELOMERES, OS, ER STRESS, AND AUTOPHAGY IN OVARIAN AGING

Telomeres are sensitive to oxidative stress, which can promote telomere shortening during aging, but this is reversed by antioxidants [189]. Decreasing telomere length contributes to cell senescence [190]. Telomere length and replicative senescence are regulated by oxidative stress [191]. ER stress activates telomerase [192], overexpression of telomerase reverse transcriptase (TERT) diminishes ER stress-induced cell death [193], and cellular senescence was regulated by endoplasmic reticulum UPR [194]. The potential roles of oxidative stress, ER stress, and autophagy are connected with each other in several cell types, suggesting that telomeres, oxidative stress, ER stress, and autophagy might be closely interlinked. This is a novel topic that needs further research.

## 17. MELATONIN TARGETS FOR MULTIPLE SIGNALING PATHWAYS IN AGEING

Melatonin is considered as an antioxidant, mitochondrial protector, autophagy modulator, and can be used as therapeutic targets for ageing and ageing-related diseases [195]. As an antioxidant, melatonin was used to treatment for several diseases through inhibiting oxidative stress damage. Mitochondrial bioenergetics decay triggers mitochondrial dysfunction in aging, and melatonin exerts its protective role against mitochondrial dysfunction associated with aging and age-associated disorders [196, 197], indeed, melatonin was used as a mitochondria-targeted antioxidant [198], melatonin



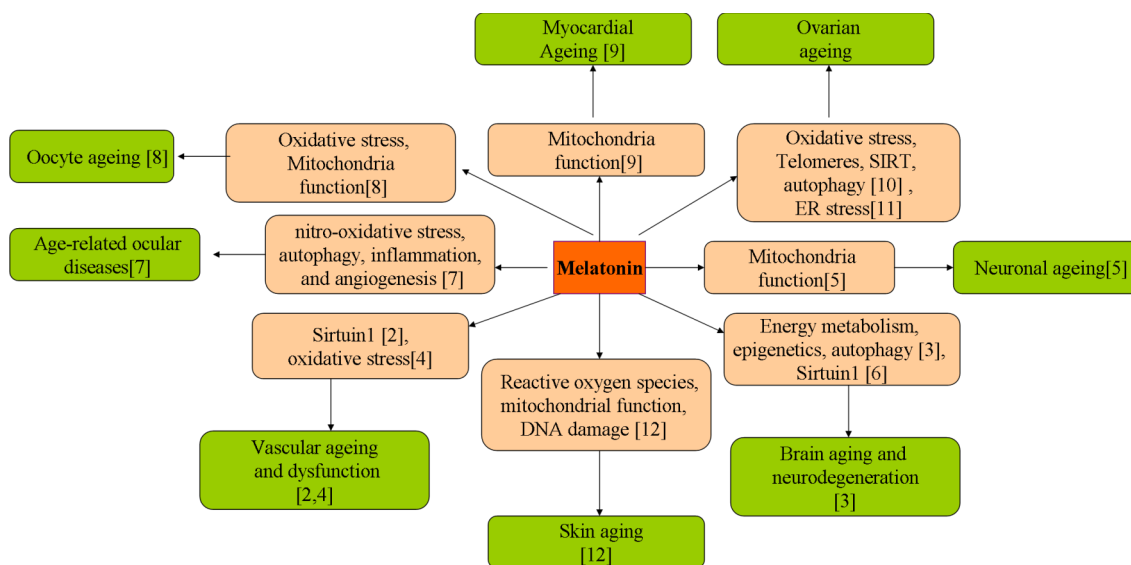
as mitochondrial protector targets to neurodegenerative diseases [199], and the mitochondrial function was enhanced by melatonin treatment [200]. The importance of melatonin in the mitochondrial function was summarized by several works, and the melatonin was a new drug for mitochondrial dysfunction induced diseases and ageing. The strong interconnection between sirtuin expression and aging processes was emphasized in recent study [201], the mammalian sirtuins play vital roles in regulating the ageing and longevity [202], and the sirtuins, especially, SIRT1 and SIRT3 are closely regulated by melatonin [203], especially, sirtuin 1 is upregulated by melatonin in aged tissues [204]. The regulation of melatonin on sirtuins was emphasized by several studies, and melatonin was a potential drug to anti-aging by regulating sirtuins. Administrated with melatonin could treat or prevent age-related macular degeneration through stimulation of telomerase activity [205], melatonin may delay the aging of gastric mucosa *via* activation on telomerase activity [206], and melatonin could be used as a drug to anti-ageing through activation telomerase. Undernutrition induced ER stress and ovarian follicle apoptosis is consistent with an accelerated ovarian aging phenotype, and accompanied with the decreased melatonin level [207], these changes emphasizes the interconnection of melatonin and ER stress in ageing. Meanwhile, the crosstalking of OS, ER stress, autophagy, mitochondria, sirtuins and telomerase emphasize that melatonin targets ageing through multiple signaling pathway, and this might be dependent on cell types and different conditions. In addition, the overexpression of advanced glycation end products (RAGE) was attenuated by the melatonin [208], the receptor for advanced glycation end products (RAGE) was reduced by melatonin [209], and melatonin was used as a therapeutic strategy for RAGE in aging. The significance of melatonin in the POF and PCOS was summarized by Tamura *et al.* [210], and melatonin was a potential drug for POF and PCOS therapy.

Hence, melatonin targets for aging through multiple signaling pathways, and the mechanism and signaling of melatonin was summarized in the process of anti-aging (Fig. 3),

as well as melatonin are used as therapeutic drugs for aging and aging related diseases.

### 18. MELATONIN USED AS A POTENTIAL THERAPEUTIC STRATEGY TO DELAY OVARIAN AGING

The importance of the antioxidant melatonin in ovarian functions has been summarized by several studies [223, 224]. Melatonin levels vary throughout human life and are known to decrease with age but the effects of declining melatonin levels are poorly understood. In women, decreasing melatonin levels during aging coincides with menopause [225]. The role of melatonin in anti-aging has been extensively explored in recent years. It has been shown that lifespan could be extended by the melatonin [24]. Melatonin ameliorates age-induced fertility declines and mitigates ovarian mitochondrial oxidative stress in mice [226]. The administration of melatonin to middle-aged female rats improved cytometric and endocrine functions and extended ovarian reproductive function [227]. The number of primordial follicles was not affected by long-term melatonin supplementation without delaying reproductive senescence in rats [228]. Tamura *et al.* revealed that the numbers of primordial, primary, and antral follicles increased in the ovaries of aging mice [229], and melatonin was used as a new drug for improving the oocyte quality [230]. RNA-sequencing results suggest that the mRNA expression of SIRT1 and LC3 and telomere length were enhanced due to melatonin treatment. Melatonin delayed ovarian aging through multiple mechanisms, including antioxidant action, telomere maintenance, stimulation of SIRT expression and ribosome function, and reduction in autophagy [229]. Therefore, the function of melatonin in ovarian anti-aging not only focused on oxidative stress, but also on maintaining telomeres, ribosome function, increasing SIRT expression, and reducing autophagy. The sirtuins, particularly SIRT1 and mitochondrial SIRT3, are closely related to melatonin [203]. Sirtuins maintain the genomic stability that is associated with aging [231]. Furthermore, autophagy and mitophagy are regulated by melatonin [232]. Early maternal exposure to undernutrition induces ovary ER stress and apoptosis in offspring. This is accompa-



**Fig. (3).** The mechanism and signaling pathway of melatonin anti-aging. Melatonin involve in anti-ageing through multiple pathway including oxidative stress, autophagy, mitochondria, Sirtuin and telomeres.

nied by ovarian phenotype characteristics of premature ovarian aging with reduced ovarian reserves and decreased melatonin synthesizing enzyme HIOMT and 2 undetectable melatonin receptors [207]. These results suggest the potential role of melatonin in ER stress, apoptosis, and ovarian aging. Melatonin enhances memory function in D-galactose-induced aging mice possibly *via* a reduction in elevated ROS and receptors for advanced glycation end-products (RAGE) [2323]. Melatonin reverses mitochondrial dysfunction and related disorders [234]. Melatonin could become an important medication for improving ovarian function and oocyte quality and offer new opportunities for the management of several ovarian diseases, such as POF and PCOS [229]. Melatonin interacts with endoplasmic reticulum stress and is closely related to autophagy and apoptosis [235].

In addition to OS, the regulation of melatonin on ER stress, autophagy, mitochondrial function, genomic stability, AGEs-RAGEs, POF, and PCOS might offer new insights into delaying ovarian aging. These issues need to be explored in the future.

## CONCLUSION

Novel insights into ovarian aging and usage of melatonin to delay ovarian aging are discussed in this review. In the past several years, the mechanism of ovarian aging has mainly focused on OS. The roles of ER stress, autophagy, and sirtuins in ovarian aging have recently been studied, and the relationship between ovarian aging and POF and PCOS was revealed. The mechanism of ovarian aging is complicated. Ovarian anti-aging drugs should not only focus on the repression of OS, but also on the regulation of ER stress, autophagy, sirtuins, AGEs-RAGEs, mitochondrial function, genomic stability, telomeres, POF, and PCOS. As a pleiotropic molecule, OS damage was ameliorated by melatonin as well as these various factors and processes; these are all closely related to melatonin in the aging ovary. Melatonin is the optimal molecular drug for ovarian anti-aging. The regulation of melatonin on the factors and processes discussed earlier in ovarian aging should be explored in the future, the significance of melatonin in ovarian ageing supply a novel drug for delaying ovarian aging and improving ovarian function.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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