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REVIEW

Improvement of oocyte quality through the SIRT signaling pathway

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Abstract

Background: Oocyte quality is one of the major deciding factors in female fertility competence.

Methods: PubMed database was searched for reviews by using the following keyword "oocyte quality" AND "Sirtuins". The methodological quality of each literature review was assessed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.

Main Findings: Oxidative stress has been recognized as the mechanism attenuating oocyte quality. Increasing evidence from animal experiments and clinical studies has confirmed the protective roles of the sirtuin family in improving oocyte quality via an antioxidant effect.

Conclusion: The protective roles in the oocyte quality of the sirtuin family have been increasingly recognized.

KEYWORDS
infertility, oocyte, ovarian aging, oxidative stress, sirtuins

1 | INTRODUCTION

Impaired oocyte quality has been recognized as a crucial factor affecting female fertility. The decline of oocyte quality is commonly caused by oxidative damage associated with maternal aging.[1,2] Due to the change in cultural and social conceptions, women have been offered the equivalent chance to pursue professional careers, leading to the worldwide tendency of delayed childbearing age and subsequent increases in maternal age. Consequently, a better understanding of improving age-related impairment of oocyte quality has been acquiring scientific interest considerably.

Although the biological mechanism of impaired oocyte quality has not been currently understood definitely, different components have been indicated to be related to this process.[3–5] Oxidative stress caused by reactive oxygen species (ROS) during ovarian aging has been pointed out to be the key factor in the decline of oocyte quality,[4,6] characterized by mitochondrial dysfunction as well as impairment of the microenvironment in ovary.[5]

Sirtuins, a family of nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylases and ADP-ribosyltransferases, have emerged as critical regulators in genome maintenance, aging, and chromosomal integrity of the oocyte.[7,8] Recently, growing evidence has confirmed that the crosstalk between ROS and the sirtuin family has a key role in regulating the cellular aging process. Sirtuins are also demonstrated to protect oocytes against oxidative stress.[9] These proteins may be potential markers for ovarian aging, and SIRT1, SIRT3, and SIRT6 are known as target molecules for delaying organ aging.[10] This review aims to summarize an overview of

the mechanism and importance of the Sirt signaling pathway in the improvement of oocyte quality.

2 | OOCYTE QUALITY IMPAIRMENT BY AGING

Aging manifests gradual depletion of follicles and reduced oocyte quality in ovaries characterized by the reduced ability to yield competent oocytes for fertilization and subsequent embryo development. Oxidative stress has been recognized as one of the causal mediators affecting oocyte quality throughout three distinct stages: excessive production of ROS, the mobilization of antioxidants, and oxidative damage to major targets. Excessive ROS affects the oocyte quality by shortening the telomere length, inducing DNA damage and mutagenesis. Mitochondria are the main generator of ROS and accumulating errors in mitochondria lead to apoptosis, which compromises follicle development in mammals.[11] Furthermore, ROS may induce the activation of nuclear factor-kappa and the inflammatory agents, interferon (IFN)-γ and lipopolysaccharides (LPS), which synergistically increase ROS production.[12]

The most well-established explanation of impaired oocyte quality in aging is the deterioration of mitochondria function caused by ROS. As commonly described in the literature, mitochondria are organelles that have determinant roles in oocyte function. They are the key source of energy production in the form of adenosine triphosphate (ATP) required for several processes including meiotic spindle assembly, chromosome segregation, fertilization, and subsequent embryogenesis in mammals.[13] The low number of mitochondria and/or impairment in mitochondrial function results in a shortage of energy required for meiosis during oocyte maturation, which potentially leads to chromosomal aberrations in mice and humans.[14] Mitochondria also join in several processes required for proper fertilization and embryo development including the Ca^{2+} homeostasis process, apoptosis regulation, and management of oxidative stress in both mice and humans.[4,15,16] During aerobic metabolism, mitochondria produce unavoidable by-products, namely ROS.[17] A moderate concentration of ROS is essential for several intracellular processes including ventilation, nerve transmission, and immune regulatory processes.[18] However, excessive accumulation of ROS caused by the decline of aging-associated cellular respiratory functions can damage cellular lipids, proteins, and DNA, implicating their normal function.[17] This oxidative stress affects the telomere function, leading to deletions or point mutations in the mitochondrial genome, a decline in ATP production, meiotic spindle abnormality, genomic instability, and resulting in mammalian oocyte incompetence. It has been reported that mitochondrial DNA (mtDNA) copy number and function in oocytes of aging mice and women are reduced, accompanied by higher incidences of abnormalities of spindle assembly and chromosome segregation.[14,19–21] These subsequently lead to chromosomal segregation disorders, maturation and fertilization failures, or oocyte/embryo fragmentation in both mice[22] and humans.[23] In human aging oocytes, there are a decrease in the mitochondrial fraction and an increase in the mitochondrial matrix density.[24] The decline of the mitochondrial respiratory function associated with the aging of granulosa cells (GCs) triggers the increased production of ROS in mice.[25] Furthermore, there are increases in oxidatively damaged lipids, proteins, and DNA in different ovarian compartments, including murine GCs and stromal tissue, along with alterations of antioxidant-enzyme expression.[25]

The suggested etiology of oxidative stress is age-related impaired follicular vascularization.[26,27] A significant negative correlation between age and ovarian perifollicular blood flow was observed in the follicular phase, caused by accumulated glycation end-products in follicular fluid during ovarian aging in humans and mice.[26,27] To adapt to this condition, the granulosa and theca cells increase the synthesis of vascular endothelial growth factor (VEGF), which nevertheless fails in completing the adequate response. This is supposed to be the result of low responsiveness of endothelial cells, hampering ovarian stroma vessels, or increasing the distance between the perifollicular blood vessels in the aging ovary.[26]

The other explanation for decreased oocyte quality in human ovarian aging is disruption of the communication between GCs and oocyte affecting the follicular development.[26] Oocyte secrets various paracrine growth factors such as growth differentiation factor-9, and bone morphogenetic protein-15, which are responsible for the GCs' proliferation, differentiation and play the critical role in the follicular development and maturation.[11,28] In humans, oocyte senescence is also reported to be linked to the shortening of telomere in cumulus cells (CCs), whose length has been recognized to be a marker of embryo quality.[29] CCs from advanced-age patients undergoing IVF present increased apoptosis and are related to remarkably lower fertilization and pregnancy rates.[11]

3 | ROLES OF SIRT SIGNALING PATHWAY IN OOCYTE QUALITY

3.1 | Cellular Sirt signaling pathway

Sirtuins (or silent information regulator 2 family—SIRT family) are proteins of the NAD^+-dependent deacetylases family. Sirtuins belong to class III histone deacetylases (HDAC), characterized by the catalytic activity of the enzymes depending on NAD+ and the NAD+/NADH ratio.[30] The main action of Sirtuins is protein acetylation, an important post-translational modification related to different metabolic pathways in mammals.[8] Sirtuins have been described as key regulators in many cellular processes including apoptosis,[31,32] cell reprogramming,[32,33] DNA repair,[34] redox homeostasis,[35] energy metabolism,[36,37] and tumorigenesis.[37] They also play a pivotal role in sensing intracellular oxidative stress via modulating the NAD+/NADH ratio[38] (Figure 1). It can be distinguished between seven members of the sirtuin family discovered in mammals (SIRT1-7).[39] Of

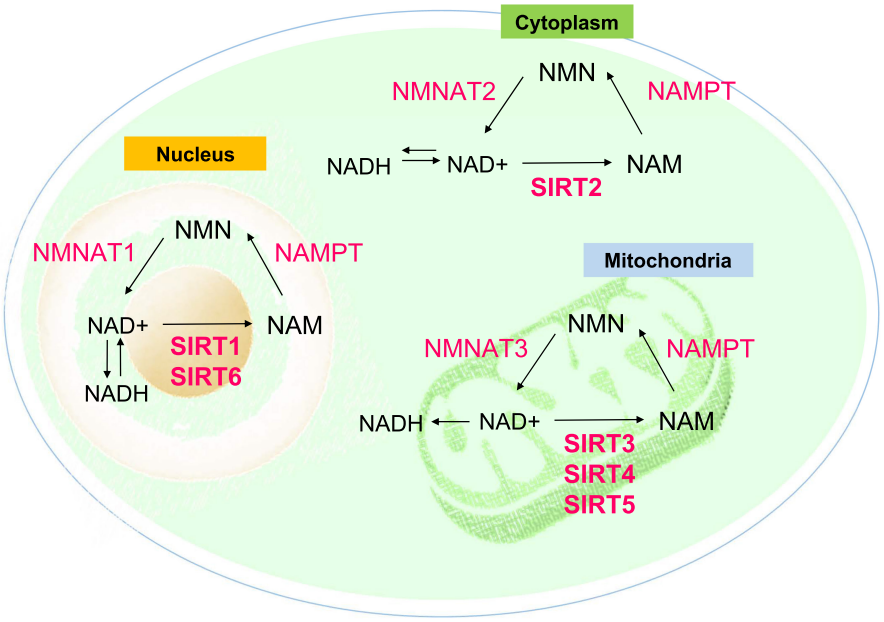

FIGURE 1 Roles of SIRT1-7 in sensing intracellular oxidative stress via modulating the NAD+/NADH ratio in different cell organelles. NAD+, oxidative nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMAT1,2,3, nicotinamide mononucleotide adenylyltransferase 1,2,3; NAMPT, nicotinamide phosphoribosyltransferase; NMN, nicotinamide mononucleotide.

these, SIRT1 and SIRT2 are found both in the nucleus and the cytoplasm. SIRT3 is mainly localized in both mitochondria and nucleus.[8] SIRT4 and SIRT5 are mitochondrial sirtuins, and SIRT6 and SIRT7 are nuclear ones (Figure 1).[8,37] In addition to protein acetylation, some sirtuins contribute to several cellular processes via other activities. For instance, the action of SIRT4 and SIRT6 is not deacetylation but ADP-ribosylation,[40] whereas SIRT5 can demalonylate and desuccinylate proteins.[41]

Among members of the sirtuin family, the role of SIRT1 in mammalian health is the most commonly discussed, especially for its anti-aging effects. Upon being activated by stressful events, SIRT1 binds different molecular targets and deacetylates these molecules to regulate energy homeostasis, gene silencing, metabolism, genomic stability, and cell survival.[37,39,42,43] For instance, SIRT1 activates AMP-activated protein kinase (AMPK), leading to the enhancement of mitochondrial functioning and transcriptional activity.[44,45] SIRT1 deacetylates the Werner helicase and NBS1, which repair DNA damage.[46] In *Sirt1*$^{-/-}$ mice, there is an increase in chromosomal aberrations and impaired DNA repair.[47] Moreover, SIRT1 alters gene damage during the mammalian aging process, contributing to genomic integrity and age-related changes in gene expression.[48] SIRT1 also plays a decisive role in cell fate by interacting with several target components modulating the threshold for apoptosis such as FOXO3a, p53, Ku70, E2F1, nuclear factor-κB (NF-κB) complex, and TGF-β signaling.[37,42] In addition, by regulating p53 activity, SIRT1 potentially works as a tumor promoter or suppressor depending on the specific context.[49] Another target of SIRT1 is the peroxisome proliferator-activated receptor gamma-coactivator-1α (PGC-1α), which plays a principal role in gluconeogenesis and lipid metabolism in a cell-line derived from a pheochromocytoma of the rat adrenal medulla and hepatocytes.[50,51]

3.2 | The role of Sirt signaling pathways in oocyte quality

In mammals, the sirtuin family has been demonstrated to ameliorate the oocyte quality by regulating the redox state.[38] Meanwhile, impairment in SIRT's function is declared to result in fertility deficits.[38,39] The potential roles of SIRT signaling pathways in oocyte quality are summarized in Figure 2.

The first widely discussed component of this family recognized as a key transcription factor strongly implicated in aging and lifespan is SIRT1. In mice, SIRT1 expresses at mRNA and protein levels in ovarian tissues and luteinized granulosa cells, taking the role of a guardian of meiosis.[52] SIRT1 was indicated to reduce the aging-induced defects including murine oocyte morphological changes, ROS accumulation, spindle morphology, and mitochondrial function.[53] Results from mice experiments indicate the role of SIRT1 in the adaptive response to oxidative stress as well as in protecting oocytes against loss of developmental competence with reproductive and postovulatory aging via the SIRT1-FOXO3A axis.[54,55] Inhibiting SITR1 increases ROS levels and disturbs the spindle organization of murine oocytes.[52] SIRT1 also involves in nutritional status and regulator of the cell cycle during folliculogenesis and luteinization processes.[38] Furthermore, SIRT1 is demonstrated to orchestrate the adaptive response to oxidative stress in murine oocytes by modulating antioxidant enzymatic response.[52] The inhibition of SIRT1 activity by a specific inhibitor, Ex527 results in the upregulation of the MnSod gene and prevention of ROS increase in diverse cell types.[56,57] In bovine, the treatment of Ex527, a specific inhibitor of SIRT1, prevented the massive activation of primordial follicles induced by cyclophosphamide. The treatment of Ex527 in 3 days could reduce the overexpression SIRT1 induced by cyclophosphamide.[58] These results suggest that SIRT1 can be a potential molecule to be targeted to prevent the burn out of dormant primordial follicles

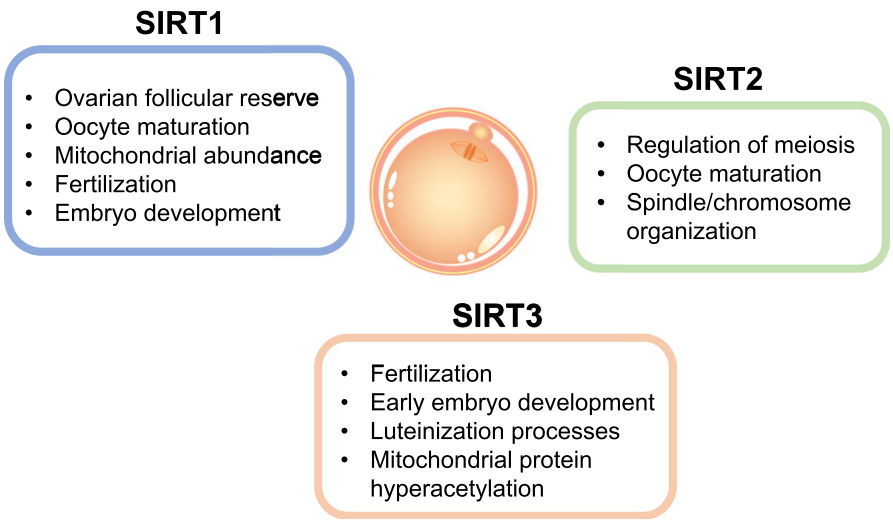

FIGURE 2 Roles of SIRT signaling pathways in regulating oocyte quality. The evidence of SIRT signaling pathway in regulating oocyte quality have been demonstrated in SIRT1, 2, and 3.

caused by cyclophosphamide. In aging murine oocyte, the disruption of the SIRT1-FOXO3A-MnSOD pathway along with the decrease of miR-132, a validated SIRT1 modulator were observed.[52] Whereas in vitro maturation assay result indicated that SIRT1 regulated the redox state and ensured normal spindle assembly during oocyte maturation.[52] In another study, the activation of SIRT1 by resveratrol reduces the penetrance of maternal age-associated defects in murine oocytes. The addition of resveratrol in to the maturation medium enhanced SIRT1 protein expression in oocyte increases the ATP content in matured oocytes, the overall mitochondria number and mitochondrial membrane potential, the ratio of normal fertilization, and the total cell number of blastocysts.[59] In mice, treatment with 5 mg/kg/day of rapamycin to obtain a caloric restriction phenotype throughout mTOR suppression presented enhanced follicle reserve and increased expression of SIRT1 and SIRT6.[60] In bovine, inhibition of SIRT1 resulted in a higher ratio of abnormal fertilization.[61] In comparison with young bovines, oocytes derived from the aging cows exhibited a higher level of abnormal fertilization and blastocysts with low total cell numbers.[61] In aged murine oocytes, the levels of NAD+ and nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2) were decreased and the Specific depletion of NMNAT2 in oocytes increased meiotic abnormalities and metabolic dysfunction. The overexpression or activation of SIRT1 could recover these defective phenotypes. It also revealed the importance of the NAD+/SIRT1 axis in mediating the effects of NMNAT2 on oocyte quality control.[62] Similar findings are reported in another study demonstrating that the loss of oocyte-SIRT1 affects ovarian follicular reservoir, oocyte maturation, oocyte mitochondrial abundance, oxidative stress, fertilization, embryo development, and fertility during aging in mice. Of note, eliminating this key sirtuin from growing oocytes has no effect in young females.[63]

In terms of SIRT2, it manifests importance in metabolisms by deacetylating cytoplasmic transcription factors and relocating them in the nuclear.[8] One specific role of SIRT2 is peripheral myelination by promoting both arborization and downstream expression of myelin-specific genes, emerging its role in neurological function.[64–66] It mediates the acetylation status of tubulin in a NAD-dependent manner.[67] In mouse oocytes, greater spindle and chromosome defects along with impaired microtubule-kinetochore interaction were found after the depletion of SIRT2's activity.[68] In addition, a lower SIRT2 protein level was observed in oocytes from aging mice, indicating that a decreased SIRT2 may be a contributing factor to oocyte age-dependent deficits.[68] In a mice experiment, SIRT2-dependent BubR1 deacetylation was shown to regulate meiotic apparatus in normal oocytes and to mediate the effects of maternal age on oocyte quality.[69] The depletion of SIRT2 disrupts maturational progression and spindle/chromosome organization, along with compromised kinetochore-microtubule attachments.[69] The enhancement activation of SIRT1 and SIRT2 induced by the antioxidant NAC could delay oocyte aging in mice.[70]

SIRT3 whose expression is highest in the metabolic tissues (liver, kidney, and heart) takes part in lipid and glucose metabolism in mammals.[8,71] It regulates the acetylation of several principal metabolic enzymes including acetyl-CoA synthetase, long-chain acyl-CoA dehydrogenase, and 3-hydroxy-3-methylglutaryl-CoA synthase 2.[8] The hyperacetylation of mitochondrial protein caused by the knockout of the SIRT3 gene in mice is associated with a high risk of metabolic syndrome development.[72] SIRT3 is supposed to be relevant to fertilization and early embryo development.[38] In vitro maturation experiment of oocytes from both mice and human, the supplementation of quercetin increases anti-oxidative activity via reduction of SIRT3 expression resulting in the higher rate of successful maturation.[73] In human, the knockdown of SIRT3 significantly elevates ROS generation in GCs.[74] In addition, SIRT3 depletion also leads to decreased mRNA expression of aromatase, 17β-hydroxysteroid dehydrogenase 1, steroidogenic acute regulatory protein, cholesterol side-chain cleavage enzyme, and 3β-hydroxysteroid dehydrogenase in GCs and subsequent decrease in progesterone secretion, indicating the positive role of SIRT3 in the folliculogenesis and luteinization processes.[74] On the other hand, activation of SIRT3 function might help to sustain human reproduction by maintaining GCs as well as oocytes function.[74] Furthermore, maternally derived SIRT3 appears to have a protective role in early embryo development against stress conditions during in vitro fertilization and culture in mice. It is critical to maintain mitochondrial homeostasis SIRT3 and to prevent the

activation of the ROS-p53 pathway, which is responsible for developmental defects.[38] In advanced-aged women, the level of SIRT3 mRNA in both GCs and CCs decrease significantly compared to the ones in young women.[75]

In aging mice's oocytes, a dramatic decrease in SIRT1, 2, and 3 mRNA levels accompanied by increased intracellular ROS were observed. In addition, the administration of nicotinamide to inhibit SIRT1, 2, and 3 was reported to accelerate postovulatory oocyte aging in mice.[76] The inhibited expression of SIRT3 induced by high palmitic acid downregulates the AMPK/SIRT3 pathway inducing ceramide accumulation, mitochondrial protein hyperacetylation, and dysfunction in porcine oocytes.[77]

Other member in SIRTs family including SIRT4, SIRT5, SIRT6, and SIRT7 have been also detected to ameliorate the oocyte quality. SIRT4, recognized as a deacetylase enzyme, play a key role in energy metabolism. It is also demonstrated to be a tumor suppressor in several malignant conditions including prostate cancer. It regulates pancreatic insulin secretion by interacting with glutamate dehydrogenase (GDH) or insulin-degrading enzyme.[78,79] Furthermore, SIRT3 works with SIRT4 to maintain mitochondrial NAD+ levels following stress, inhibiting apoptosis.[80] SIRT4 was shown to regulate energy metabolism and meiotic apparatus that have critical role in oocyte maturation. For detail, SIRT4 overexpression disrupts the mitochondrial redistribution and induces meiotic defects during oocyte maturation. Meanwhile, there are a remarkable increase of spindle/chromosome defects when SIRT4 is knocked down in oocytes of aged mice.[81] In another experiment, knockdown of SIRT4 could prevent aging-induced dysfunction of mitochondria in postovulatory phage.[82] The supplementation of Coenzyme Q10 was detected to reduce the mitochondria dysfunction in aged oocyte by weakening the SIRT4 overexpression.[82] SIRT5 manifests a fundamental role in maintaining energy homeostasis by desuccinylating several metabolic enzymes.[8] Notably, recent data declared that suppression of SIRT5's activity could reduce SARS-CoV-2 viral levels by interacting with related-replication non-structural protein, Nsp14.[83] Its gene expression in GCs significantly decreased in both granulosa and cumulus cells in diminished ovarian reserve and advanced maternal age patient compared normal ovarian reserve patients.[75] SIRT6 is identified to join in chromatin remodeling, DNA repair, gene transcription, oxidative stress, and energy metabolism.[84] *Sirt6*-deficient mice showed attenuation of NF-κB signaling via H3K9 deacetylation at chromatin, leading to cellular senescence.[85] It is also known to delay the progression of chronic nephropathy by its antioxidant and anti-inflammation effect in mammals.[84] Evidence from the porcine experiment showed that inhibition of SIRT6 in cumulus-free oocytes reduced the rate of first polar body extrusion.[86] Furthermore, this inhibition suppressed cumulus expansion and gap junctional communication.[86] SIRT7 modulates RNA polymerase 1 transcription that participates in both lipid metabolism and mitochondrial functioning.[87,88] Its specific knockdown leads to a disorganized spindle/chromosomes and the loss of the cortical actin cap, disrupting meiotic maturation, and subsequently generates an aneuploid oocytes. Notably, in obese mice, SIRT7 protein level in oocyte is decreased significantly, whereas the overexpression of SIRT7 improves maternal obesity-associated meiotic defects and oxidative stress in oocytes.[89]

4 | THERAPEUTICS INVOLVING THE SIRT SIGNALING PATHWAY TO IMPROVE OOCYTE QUALITY

The potential therapeutics involving the Sirt signaling pathways are summarized in Figure 3.

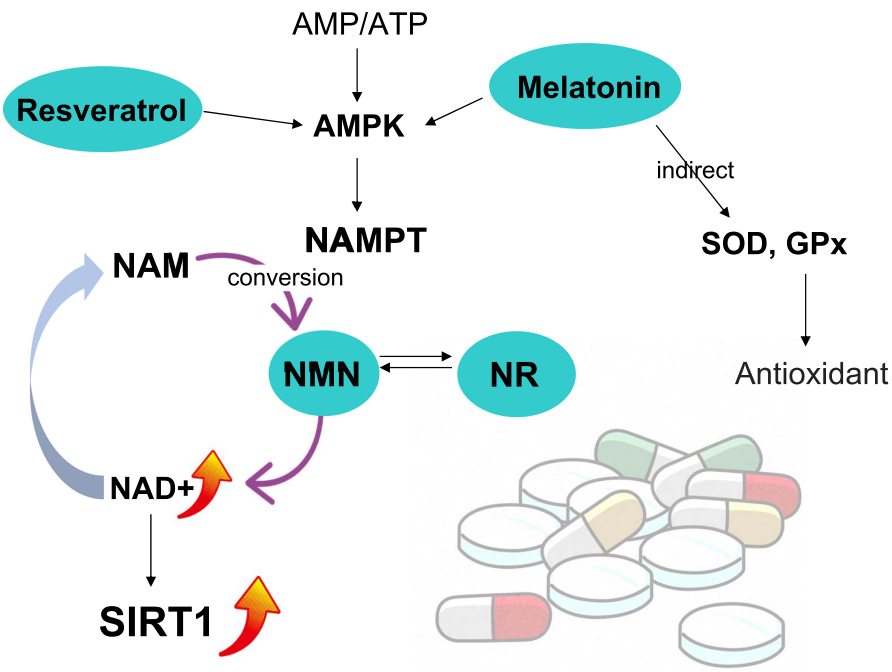

FIGURE 3 Potential therapeutics involving the SIRT signaling pathway. Currently, supplementation of four different therapeutics, melatonin, resveratrol, nicotinamide mononucleotide (NMN), and nicotinamide riboside (NR) has demonstrated to restore oocyte quality through SIRT signaling pathways. The action of these therapeutics was integrated mainly in activation of SIRT1 induced by elevated NAD+. AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; GPx, glutathione peroxidase; NAD+, oxidative nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; SOD, super oxide dismutase.

4.1 | Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine hormone produced mainly by the pineal gland modulating several important physiological reactions.[90,91] Functioning as an antioxidant, melatonin and its derivatives protects cells from oxidation, inflammation, and apoptosis.[92]

In reproductive health, increasing data indicate that melatonin combats oxidative stress, and maintains mitochondrial function, preventing age-related oxidative stress and reproductive system disorders.[91] It exists in all stages of the porcine oocyte, delays ovarian aging as well as improves oocyte maturation and embryo development.[93–95] Melatonin strengthens mitochondria antioxidant functions by scavenging toxic free radicals, protecting cellular membranes, and mitochondria function, delaying the decline of human oocyte quality.[96] Animal experiments of several species showed that melatonin facilitates oocyte maturation by modulating the generation of luteinizing hormone, cumulus cell expansion, oocyte maturation factors, DNA methylation, and histone acetylation.[12]

In mice, melatonin manifests the antioxidant effect by directly activating the sirtuins pathway, MT1/AMPK pathway, or by indirectly enhancing the total antioxidant capacity (TAC) of antioxidant enzymes and superoxide dismutase (SOD).[97] Its treatment can activate the ovarian SIRT1 and SIRT3 mRNA expression levels.[97] Melatonin can be also synthesized in the follicular granulosa cells and oocytes. Its insufficient concentration in follicular fluid relates highly to advanced maternal age-related meiotic defects in mice.[98] Meanwhile, high concentrations of melatonin in murine follicular fluid resist the oxidative stress accompanied by free oxygen radicals released during ovulation.[98] Melatonin administration in aging mice elevated significantly the number and density of transzonal projection (TZP) in cumulus-oocyte complexes and prevented TZP retraction in vitro, which are important to maintain communication between GCs and oocytes as well as facilitate oocyte maturation.[98] In aging mice, melatonin reverses the meiosis-deficient phenotype via SIRT1/SOD2, a major antioxidant enzyme in oocytes.[99] Another work revealed that melatonin reduced advanced maternal age-associated meiotic defects in aging mice through the SIRT2-dependent H4K16 deacetylation pathway.[100] In addition, melatonin protects mitochondrial function and reduces oxidative stress damage in mice oocytes, by decreasing the level of 8-hydroxydeoxyguanosine (8-OHDG) in mitochondria.[101] Furthermore, melatonin enhances the activities of SIRT3 and superoxide dismutase 2 (SOD2), inhibiting the autophagic death of murine hepatocytes, which then protect ovarian cells and reduce follicular atresia.[102]

Mice model experiment showed that long-term administration of melatonin can significantly reduce ovarian aging, indicated by the significantly increased number and quality of oocytes.[101] The addition of 1 mM melatonin decreased ROS levels, spindle abnormalities, and DNA breakage ratio in mice oocytes affected by 10-Hydroxycamptothecin.[92] Similarly, in vivo supplementation of melatonin suppresses mitochondrial dysfunction, reversing oocyte meiotic deteriorations in mice.[103] Another data identified melatonin treatment delayed postovulatory mouse oocyte aging via a SIRT1-MnSOD-dependent pathway, suggesting molecular mechanisms support the further application of melatonin in infertility treatment.[104]

In humans, oral administration of melatonin during in vitro maturation significantly attenuates oxidative stress and meiotic defects in oocytes in obese females through the SIRT3-SOD2-dependent mechanism.[105] Clinical trials reported a remarkable increase in the number of retrieved and mature oocytes after supplementation of melatonin during the IVF cycle.[106,107] In addition, melatonin treatment under the IVF-ET program was also declared to improve the fertilization and pregnancy rates of women with low fertilization rates (≤50%).[108] However, according to a recent randomized control trial, treatment with melatonin yielded no difference in the number of oocytes retrieved, number of MII, fertilization rate, embryo quality, clinical pregnancy rate, or live birth rate between the treatment and control groups.[109] In a systematic review and meta-analysis, melatonin treatment remarkably increased the number of oocytes collected, maturated oocytes, good quality embryos, as well as the clinical pregnancy rate.[110] According to a meta-analysis including randomized control trial, oral melatonin supplements during IVF increase the number of mature oocytes, albeit not significant.[111] On the other hand, one study showed that the proportion of mature oocytes (metaphase II stage oocytes/total retrieved oocytes) did not change after melatonin supplementation, and the biochemical pregnancy rate was not significantly higher in the group that received melatonin supplementation.[112]

4.2 | Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound known as an antioxidant, anti-inflammatory, and anti-aging agent.[39] Resveratrol has been demonstrated to improve the quality of aging oocytes owing to its antioxidant and anti-apoptotic effects in mammals. Increasing data have indicated its protective effects on oocytes from age-dependent deficits as a potent SIRT1 activator.[18,39] Resveratrol was identified to indirectly activate SIRT1 via modulating the activity of nicotinamide phosphoribosyltransferase and AMPK.[18,113]

In mice, resveratrol treatment for 12 months was declared to increase SIRT1 mRNA levels and to improve the number and quality of oocytes compared to those of age-matched aging mice, suggested by spindle morphology and chromosome alignment. Also, resveratrol ameliorated age-associated low embryo development in a dose-dependent manner.[114] In addition, we have recently explored the fertility outcome after different durations of resveratrol treatment in vivo by using aging mice model experiment. The results demonstrated that even a short-term (one week) treatment of resveratrol increased the level expression levels of Sirt1, Sirt3, Sirt4, Sirt5, and Sirt7 and improve the mitochondria's function but not copy number of mitochondrial DNA in aging mice leading to increases in the rates of implantation and live offspring as well as decreases in the

abortion rate without causing any abnormalities in fetuses and placentas. The higher serum resveratrol concentration resulted in a higher implantation rate as well as the live offspring rate.[115] These results suggested that resveratrol may be a potential anti-aging therapy for women with advanced age.

In aging bovine, resveratrol was reported to improve the oocyte quality by both increasing mitochondrial generation, and degradation in oocytes along with modulating genes in granulose cells whose expression levels are associated with the development of oocyte and embryo.[116] In another similar experiment, supplementation of maturation medium for oocytes derived from aging bovines with resveratrol improved the fertilization ratio.[61]

Similar findings were established in porcine oocytes revealing that the addition of resveratrol treatment increased SIRT1 activation and resulted in a subsequent improved mitochondria function during the in vitro aging.[117] In consistence, the supplementation of a glycosidic form of resveratrol in in vitro maturation (IVM) medium increased SIRT1 protein and decrease oxidative stress, resulting in a better blastocyst development in bovine.[118] Other data also confirmed the significant increase of sirtuin-1 gene's expression in bovine granulosa cells, cumulus cells, oocytes, and blastocysts along with the reduced ROS after resveratrol treatment.[119]

4.3 | Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR)

Functioning as NAD+ intermediates, NMN and NR have been shown to ameliorate effectively age-associated disorders.[120] Their treatment was identified to increase NAD+ levels and subsequently promote SIRT1 activation in neurovascular units.[121,122] In addition, the molecular analysis presented that neurovascular protective effects of NMN are mediated by the induction of genes involved in mitochondrial rejuvenation, suggesting that these NAD+ intermediates can be used in mitochondria-targeted interventions.[121] NMN was proved to replenish NAD+ levels and restore the expression of genes related to oxidative stress in multiple organs by activation of SIRT1 in both high-fat diet-induced and aging mice.[123]

Regarding oocyte quality, in vivo supplementation of NMN was reported to increase the ovulation of oocytes as well as to enhance their meiotic competency and fertilization ability in aging mice. In addition, transcriptome analysis showed that NMN could restore mitochondrial function and eliminate the accumulated ROS to suppress apoptosis in oocytes of aging mice.[124] In another experiment in aging mice, NMN could ameliorate the developmental potential of oocytes mediated by transgenic overexpression of the NAD+-dependent deacetylase SIRT2.[125] Supplementation with NMN in the embryo culture medium also improved blastocyst formation in embryos derived from oocytes from aging females.[125] NMN treatment was further presented to suppress the accumulation of mtDNA mutations caused by NADH/NAD+ redox state in mice.[126] A similar result was reported in porcine oocytes that NMN supplementation rescued the meiotic defects and mitochondrial function caused by ethylene glycol butyl ether exposure via restoring NAD+ level and eliminating the excessive ROS.[127] In terms of NR, it was found to reduce levels of ROS and spindle anomalies in aging mouse oocytes. Its supplementation also improved ovarian mitochondrial energy metabolism together and decreased mitochondrial clustering.[128]

5 | CONCLUSION

A strong piece of evidence of protective roles in the oocyte quality of the sirtuin family has been increasingly accumulated. Following the basic and animal studies, some potential therapeutics involving the Sirt signaling pathways are found to improve the oocyte quality in advanced-age women. Although these therapeutics are available as supplemental diets and convenient for patients to be able to purchase at their wish, their applications in infertility treatment are still controversial. To conclude the usage of supplemental diets as an "add-on therapy" in reproductive medicine, well-designed randomized control trials are required.

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CONFLICT OF INTEREST STATEMENT

Kazuhiro Kawamura and Kim Cat Tuyen Vo declare that they have no conflict of interest.

HUMAN RIGHTS STATEMENT AND INFORMED CONSENT

This article does not contain any study with human participants that have been performed by any of the authors.

ANIMAL STUDIES

This article does not contain any study with animal studies that have been performed by any of the authors.

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