



Review

N1-Methylnicotinamide: An Anti-Ovarian Aging Hormetin?

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ABSTRACT

Ovarian aging occurs due to the reduction of the quality and quantity of the oocytes, and is regulated by mitochondrial survival and apoptotic signals. Reactive Oxygen Species (ROS) are one of those signals considered detrimental to cellular homeostasis. Nowadays, ROS are regarded as a regulatory factor at low levels as it induces the stress resistance which in turn increases the longevity. It is believed that the main mechanism for the life-promoting role of the ROS mediated by the 5' Adenosine Monophosphate-activated Protein Kinase (AMPK). N1-Methylnicotinamide (MNAM) is well known for its anti-diabetic, anti-thrombotic, and anti-inflammatory activity. Aldehyde oxidase 1 (AOX1) is a detoxifying enzyme, which metabolizes the MNAM and produces two metabolites including N1-methyl-2-pyridone-5- carboxamide (2py) and N1-methyl-4-pyridone-3-carboxamide (4py). The activity of AOX1 enhances the production of ROS and improves the longevity. It has been reported that the MNAM could postpone the aging through the induction of low-level stress. It has been documented that the production of MNAM is significantly higher in the cumulus cells of the patients with Polycystic Ovary Syndrome (PCOS) and its administration on the rat model of PCOS has been shown to alleviate the hyperandrogenism and successfully activate the ovarian AMPK. Therefore, it can be hypothesized that the anti-ovarian aging effects of the MNAM are possibly based on the activation of AMPK through transient elevation of the ROS.

1. Ovarian Aging

It has been well documented that the fertility potential of the women gradually decreases with the increase in the chronological age (Broekmans et al., 2009). It is well known that fertility tends to decrease after the age of 30 while a loss of natural fertility happens around the age of 41 (Broekmans et al., 2004; Fédération et al., 1982; O'Connor et al., 1998; van Noord-Zaadstra et al., 1991v). Ovarian aging is clinically defined as the qualitative and quantitative reduction of the oocytes in the ovaries (May-Panloup et al., 2016; te Velde and Pearson, 2002t), which is associated with the low ovarian stimulation, pregnancy loss, and risk of miscarriage (May-Panloup et al., 2016). Furthermore, the reduction of the length of the menstrual cycle has been regarded as the first indication of the reproductive aging process (Treloar, 1967). The menopausal transition is defined as the reduced

number of follicles, which could lead to prolonged cycles and occurs at around the age of 46 (Soules et al., 2001b). It should be taken into account that the perimenopause is not the same as the menopausal transition and it is referred to as the year after the final menstrual period (Broekmans et al., 2009; den Tonkelaar et al., 1998d; Treloar, 1967). Menopause, defined as the final menstrual period, usually happens at around the age of 51 (Broekmans et al., 2009).

The female reproductive cycle consists of three main stages; follicular, luteal, and menstrual (Broekmans et al., 2009). In the follicular phase, the elevation of the follicle-stimulating hormone (FSH) is responsible for folliculogenesis and its reduction, because of estradiol negative feedback, is indispensable for the dominant follicle selection during this phase (Fauser and van Heusden, 1997; van Santbrink et al., 1995v; Welt et al., 2001). Furthermore, the luteinizing hormone (LH) induces the production of androgens in the antral follicles, and

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following their aromatization can provoke estradiol biosynthesis (Broekmans et al., 2009; Erickson et al., 1985). Correspondingly, in the late follicular phase and also luteal phase, LH is involved in the growth of dominant follicles, ovulation, and consecutive generation of the corpus luteum (Broekmans et al., 2009; Erickson et al., 1985). When it comes to menopausal transition, the elevation of FSH in the early follicular phase is accompanied by diminished follicle number (Soules et al., 2001a; Warburton, 2005). A growing body of evidence indicates that the levels of LH and FSH are significantly higher in post-menopausal women when compared with premenopausal ones (Gill et al., 2002; Hall et al., 2000). The level of follicular depletion is determined by the initial size of the follicles and the intensity of follicular atresia (Hussein, 2005; Tait and Green, 2010). Follicular atresia depends on the apoptosis of the oocytes and its surrounding cells, and mitochondria are among the important regulators of cell survival and apoptosis (Hussein, 2005; May-Panloup et al., 2016; Tait and Green, 2010).

2. Mitochondria and Ovarian Aging

Mitochondria are the active organelles responsible for providing the cellular energy, cell cycle, and apoptosis (McBride et al., 2006; Perkins and Frey, 2000). They are involved in a wide spectrum of metabolic processes such as calcium, amino acid, and lipid metabolism (Kuhlbrandt, 2015; Rizzuto et al., 2012). Mitochondria contain their own genome that encodes the genes for oxidative phosphorylation (OXPHOS) system, transfer of RNAs (tRNAs) and ribosomal RNAs (rRNAs), and the rest of required genes are encoded in the nucleus (Quiros et al., 2016). Therefore, mitonuclear communication is vital for cellular response to different kinds of signals depending on their sources (cytosolic, mitochondrial, or extracellular) (Quiros et al., 2016).

Since mitochondria are important factors in oocyte quality, they may be affected during ovarian aging (May-Panloup et al., 2016). In this respect, it has been reported that the functional, morphological, and metabolic aberrancies and their corresponding genes have been significantly altered in mitochondria of aged oocytes (Duran et al., 2011; Müller-Höcker et al., 1996; Wilding et al., 2001). Furthermore, mitochondrial DNA (mtDNA) replication could play a crucial role in embryonic development as inappropriate mtDNA content in the oocytes of women with ovarian ageing may lead to impaired mitochondrial biogenesis, and finally cause abnormal embryonic development (May-Panloup et al., 2016). McReynolds et al. (McReynolds et al., 2012) have also reported the effects of aging on ovarian granulosa cells, where aging women had significantly different proteome of these cells compared with younger ones (McReynolds et al., 2012). Moreover, the aggregation of damage in granulosa cells could affect the oocytes, leading to ovarian aging during a woman's lifetime (Tatone et al., 2008). Therefore, mitochondrial biogenesis in the granulosa cells may be changed by ovarian ageing and subsequently affects embryonic development (May-Panloup et al., 2016).

3. Mitohormesis

The term "hormesis" is referred to the states that have beneficial effects at low dose of stress and detrimental effects at high dose of stress (Paracelsus, von Bodenstein, 2020; Tapia, 2006). All the stressors exhibiting the "biphasic dose-response" are considered as a "hormetin" (Paracelsus, von Bodenstein, 2020; Tapia, 2006). The "mitohormesis", as a newly discovered concept is also referred to as health-promoting effects of the mitochondrial hormetins such as Reactive Oxygen Species (ROS), Caloric Restriction (CR), exercise, metabolites, and nutritional agents (Schulz et al., 2007; Tapia, 2006). ROS and metabolites are discussed in the following sections. Barcena et al., thoroughly reviewed the mitohormesis signaling (Barcena et al., 2018).

3.1. ROS

Harman proposed a hypothesis for the relationship between ROS and aging in the 1950s (Harman, 1956). According to this theory, the elevation of ROS are the main cause of aging and the reduction of ROS could improve the life span (Harman, 1956). Furthermore, he declared that somatic mtDNA mutations are notable inducers of the aging process (Harman, 1956). A great deal of data demonstrates that inappropriate DNA repair, the absence of supportive histones, the closeness of mtDNA to electron transport chain (ETC) and ROS could lead to an increase in mtDNA mutations (Druzhyina et al., 2008; Kasapoglu and Seli, 2020). Subsequently it stimulates the elevation of the ROS as this vicious cycle continues and it may cause more and more mtDNA mutations and ROS production (Druzhyina et al., 2008; Kasapoglu and Seli, 2020). Thereafter, the scientists started to use different types of compounds named "antioxidants" to control ROS production and thereby tried to delay the aging process (Schulz et al., 2007). But, some reports have indicated that the antioxidants could develop the cancer (Bardia et al., 2008; Lawenda et al., 2008; Myung et al., 2010) and decrease the lifespan (Lippman et al., 2009; Ward et al., 2007). Nowadays, ROS are considered as a regulatory factor at physiological concentrations and it may be a lifespan-promoting agent (Chandel, 2015; Holmström and Finkel, 2014; Shadel and Horvath, 2015). In other words, ROS-derived low-level stress induces the stress resistance so that, it increases the longevity (Chandel, 2015; Holmström and Finkel, 2014; Shadel and Horvath, 2015). This phenomenon is defined as "hormesis" as mentioned in the previous section (Ristow and Zarse, 2010). Since ROS are an end-product of the OXPHOS system in the mitochondria, this process is named as "mitohormesis" (Ristow and Zarse, 2010).

3.1.1. ROS and Ovarian Aging

It has been postulated that higher ROS production leads to a low fertilization rate of the oocyte (Tarin, 1996). Furthermore, ovarian samples obtained from the aged women have been shown to have significantly more damaged and mutated mitochondria (Barritt et al., 2000; Chan et al., 2005; Kasapoglu and Seli, 2020; Luoma et al., 2004). However, some other reports have indicated no significant morphological and genetic differences between the ovarian samples obtained from old and young women (Barritt et al., 1999; Brenner et al., 1998; Chan et al., 2006). It has been reported that older women who received normal mitochondria showed improvement in their fertility parameters (Ross et al., 2013). These conflicting results regarding the relationship between mitochondrial stress and reproductive aging led the scientists to switch to the "mitohormesis" concept versus the classic Harman's hypothesis as some of them consider the role of adaptive response to oxidative stress in ovarian aging (Kasapoglu and Seli, 2020; Pérez et al., 2009).

3.2. Metabolites

Mitonuclear communication is accomplished by many biological intermediate metabolites and ions regulating the cellular signaling pathways through effective crosstalk between the mitochondria and nucleus (Quiros et al., 2016). Adenosine Triphosphate (ATP) and Nicotinamide Adenine Dinucleotide (NAD^+) are two important metabolites playing vital roles in the mitonuclear crosstalk (Rizzuto et al., 2012).

3.2.1. ATP

Mitochondria are the central organelles responsible for conversion of dietary energy to cellular energy (Lin et al., 2000; Ristow and Zarse, 2010). These organelles produce the ATP about eightfold higher through OXPHOS in comparison with the glycolysis (Lin et al., 2000; Ristow and Zarse, 2010). Therefore, it is very important to maintain the ATP at physiological levels as deregulation of its levels could exacerbate the mitonuclear communication (Barcena et al., 2018; Ristow and

Zarse, 2010). It has been well documented that exercise, mitochondrial dysfunction, and some pharmaceuticals could activate the 5' Adenosine Monophosphate-activated Protein Kinase (AMPK) following the elevation of AMP/ATP ratio (Ristow and Zarse, 2010). AMPK, as an "energy sensor" regulates the metabolism and mitophagy and maintains the mitochondrial stability (Egan et al., 2011; Herzig and Shaw, 2018). It has been demonstrated that the mitochondrial ROS exerts its hormetic effects through many transcription factors such as AMPK, Forkhead box protein O (FOXO), P38, Target of Rapamycin (TOR), and Nuclear factor erythroid 2-related factor 2 (NRF2) and thereby induces the stress resistance and improves the lifespan (Schaar et al., 2015). AMPK is necessary for oocyte maturation and its communication with surrounding somatic cells (Bertoldo et al., 2015). Besides, it has been reported that ovarian AMPK significantly reduced in the PCOS mice compared to the healthy ones (Tao et al., 2017).

3.2.2. NAD⁺

NAD⁺ acts as a cofactor for the metabolites of the Krebs cycle where it leads to the production of energy in the OXPHOS system (Katsyuba and Auwerx, 2017). So, the balance of the NAD⁺/NADH ratio is crucial for metabolic function of the cells and is regulated by the mitochondria (Barcena et al., 2018). In addition to the roles of NAD⁺ as a cofactor, it is the main co-substrate for functional enzymes such as Sirtuins (SIRT1), poly ADP-ribose polymerases, and histone acetyltransferases (Fang et al., 2017; Imai and Guarente, 2016). A growing body of evidence indicates that SIRT-1 is involved in the improvement of lifespan (Banerjee et al., 2012; Rogina and Helfand, 2004). However, other reports have not verified such an effect (Boily et al., 2008; Burnett et al., 2011). These conflicting results regarding the role of SIRT-1 in the aging process encouraged the scholars to investigate other possible mediators for the anti-aging function of SIRT-1. In this respect, Schmeisser et al., (Schmeisser et al., 2013) reported that the methylation of nicotinamide (NAM) produced by the SIRT-1 from NAD⁺ and generation of N1-methylnicotinamide (MNAM) may be the main cause of anti-aging effects of the SIRT-1.

4. MNAM

Nicotinamide N-methyltransferase produces the MNAM through the consumption of NAM and S-Adenosylmethionine (SAM) (Aksoy et al., 1994; Pissios, 2017). MNAM is well known for its anti-diabetic, anti-thrombotic, and anti-inflammatory activity (Pissios, 2017). Its curative effects have been reported in a broad spectrum of disorders such as diabetes (Przyborowski et al., 2015; Watała et al., 2009), cardiovascular (Nejabati et al., 2018; Nejabati et al., 2019) and renal diseases (Tanaka et al., 2015), Parkinson's disease (Fukushima et al., 1995), and PCOS (Nejabati et al., 2020). Recently, in our previous study, we reviewed the roles of MNAM in the cardiovascular disease (Nejabati et al., 2018). MNAM acts as a guardian of the cardiovascular system through the regulation of Nitric Oxide (NO), and Prostaglandin I₂ (PGI₂) metabolism (Nejabati et al., 2018; Nejabati et al., 2019). Furthermore, it induces the formation of lipid droplets and uptake of Polyunsaturated Fatty Acids (PUFAs) and protects the cardiac cells against the lipotoxicity and detrimental oxidative stress (Nejabati et al., 2018).

A growing body of evidence indicates that the MNAM could be considered as an anti-inflammatory factor in the inflammatory diseases such as hepatitis and atherosclerosis (Jakubowski et al., 2016; Liu et al., 2017; Mateuszuk et al., 2016; Mateuszuk et al., 2009; Shadel and Horvath, 2015; Sternak et al., 2015). It has been reported that the MNAM reduces elevated plasma levels of liver transaminases and acute-phase proteins, liver histological damages, and secretion of inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF-α) and Interleukin 6 (IL-6) (Jakubowski et al., 2016). Furthermore, the secretion of MNAM has been shown to increase following impaired redox status, energy deficit, and systemic inflammation in the animal models of hepatitis (Sternak et al., 2015). This increased level of MNAM in the

inflammatory diseases has been considered as compensatory response of MNAM especially in protection of liver and heart in the disorders such as hepatitis and atherosclerosis (Jakubowski et al., 2016; Mateuszuk et al., 2016; Mateuszuk et al., 2009; Shadel and Horvath, 2015; Sternak et al., 2015). Furthermore, Fu et al. (Fu et al., 2019) have suggested that MNAM may have the potential for improvement in the treatment of Alzheimer's disease (AD). Their research indicated that MNAM reversed cognition deficits reducing neuroinflammation and apoptosis through the controlling NF-κB pathway (Fu et al., 2019). Another group investigated the possible roles of MNAM on oxidative markers in a rat model of diabetes mellitus. They found that MNAM is able to reduce protein carbonyls and DNA oxidation as they considered this anti-inflammatory agent as a modulator of the oxidation of proteins and DNA (Országhová et al., 2012).

4.1. MNAM and Aging

The clearance pathway of MNAM is based on its oxidation to two metabolites including N1-methyl-2-pyridone-5-carboxamide (2py) and N1-methyl-4-pyridone-3-carboxamide (4py) through the Aldehyde Oxidase 1 (AOX1) activity (Felsted and Chaykin, 1967). Generation of these compounds transiently increases the level of Hydrogen Peroxide (H₂O₂), which induces the antioxidant defense pathways such as FOXO and NRF2, and subsequently elevates the production of antioxidant enzymes like catalase and Glutathione S-Transferase (GST) (Schmeisser et al., 2013). All of these events finally induce the stress resistance which in turn leads to improvement of the lifespan (Schmeisser et al., 2013). Schmeisser et al., proposed this novel and interesting mechanism for the anti-aging properties of the MNAM (Schmeisser et al., 2013). It should be noted that, the low doses of MNAM have the life-promoting effect and its high doses have detrimental effect (Schmeisser et al., 2013). Therefore, MNAM improves the longevity in a hormetic fashion and it could be considered as a novel hormetin in the aging process.

Similar to the effects of the MNAM, a growing body of evidence indicates that the pharmacological intervention of stress-related pathways has been regarded as an effective strategy for treating certain neurologic diseases (Brunetti et al., 2020; Calabrese et al., 2020; Calabrese et al., 2018b; Miquel et al., 2018). The vitagene network is activated by the brain cells to generate the adaptive response and combat oxidative stress, as a hallmark of neurologic diseases. Furthermore, this network induces corresponding genes such as NRF-2, which in turn promote anti-oxidative enzymes (Calabrese et al., 2010; Calabrese et al., 2018a; Miquel et al., 2018). In this regard, it has been demonstrated that low doses of plant polyphenols also activate the vitagene network, thereby increasing the cellular antioxidant capacity and modulating neuroinflammation (Di Rosa et al., 2020; Leri et al., 2020). Moreover, they could have neuroprotective effects, thereby bringing about an increase in the lifespan of animals and humans (Leri et al., 2020). In addition to plant polyphenols, anserine, as a methylated compound, ameliorates nephropathy through the induction of the adaptive cellular stress response (Peters et al., 2018). Furthermore, Pilipenko et al. (Pilipenko et al., 2019) have conducted a study to examine the possible effects of the gammapyrone in the alleviation of neuroinflammation and oxidative stress in a rat model of AD (Pilipenko et al., 2019). They found that neuroprotective effects of the gammapyrone occur through the inhibition of neuroinflammation and the induction of the cellular protection against oxidative stress and mitochondrial dysfunction (Pilipenko et al., 2019).

4.2. MNAM in the Ovary

It has been reported that the NNMT has higher expression in the cumulus cells of the women with PCOS compared to the healthy controls (Kenigsberg et al., 2009). This evidence indicates that the production of MNAM increases in the cumulus cells (as the cells

surrounding the oocytes) under the pathological conditions such as PCOS although the reason for this result is not known yet. In our recent study, for the first time, we demonstrated the beneficial effects of MNAM on the PCOS (Nejabati et al., 2020). We reported that the MNAM modulates higher serum levels of Luteinizing Hormone (LH), testosterone, and also Cytochrome P450 family 17 subfamily A member 1 (CYP17A1) (as a rate-limiting enzyme for ovarian androgen production) gene expression in the ovary of the PCOS rats (Nejabati et al., 2020). Furthermore, the MNAM successfully activated the ovarian AMPK in these rats (Nejabati et al., 2020).

5. Possible Anti-Aging Effects of the MNAM in the Ovary

5.1. AOX1

AOX1 as a detoxifying enzyme metabolizes the MNAM and produces two metabolites including 2py and 4py (Felsted and Chaykin, 1967). These two compounds are excreted in the urine but there is no knowledge about their roles. The activity of AOX1 leads to production of the H₂O₂, which also enhances the production of ROS (Schmeisser et al., 2013). High ROS levels induce low-level stress, which is possibly due to the mitohormetic function of the MNAM through induction of the ROS (Schmeisser et al., 2013). Interestingly, the expression of AOX1 gene has been shown to significantly reduce in the granulosa and cumulus cells of the patients with PCOS (Koks et al., 2010; Wu et al., 2019). Given higher expression of the NNMT and lower expression of AOX1, it can be concluded that the production of MNAM is highly induced in the ovarian cells of the women with PCOS; however, subsequent metabolization of the MNAM is impaired and the low-level stress required for stress resistance would not be achieved. Some reports have indicated the role of ROS in the activation of AMPK (Ruiz et al., 2016). So, the metabolization of MNAM by AOX1 and finally elevation of the ROS are likely to induce the phosphorylation of AMPK and it could be proposed that the mitohormetic effects of the MNAM are partially mediated by the AMPK activation depending on the transient augmentation of the ROS in the ovary (Fig. 1).

5.2. AMPK

It has been well documented that the reduction of AMP/ATP ratio following caloric restriction, exercise, and consumption of some nutritional agents leads to the activation of AMPK (Herzig and Shaw, 2018). Higher AMPK levels change the target cells from anabolic to catabolic state and induce higher OXPHOS and ROS levels, and the mitohormetic signal of the ROS could also activate the AMPK (Barcena et al., 2018; Ristow and Zarse, 2010). Then, cellular adaptive response provokes the stress resistance and improves the life span (Barcena et al., 2018; Ristow and Zarse, 2010). As mentioned in the previous section, there are two studies providing important clues regarding the possible roles of the MNAM in the ovary. One report indicated a higher production of the MNAM in the ovary of the women with PCOS (Kenigsberg et al., 2009), and our report showed the potential of MNAM in the activation of AMPK as cellular energy sensor in the rat model of PCOS (Nejabati et al., 2020). Although, the precise mechanism of its effect on the ovary has not been elucidated, the activation of AMPK by the MNAM may be related to the hormetic potential of the MNAM in the ovary (Fig. 1). Although, it is not yet clear that the proposed mechanism is applicable on the effects of MNAM on the ovary. But it could pave the way for investigating the roles of MNAM in the ovarian aging especially regarding the AMPK activation.

5.3. Testosterone and Estradiol

It has been reported that ovarian aging and PCOS have similar indications (Acuna et al., 2009; Bukovsky et al., 2000; Park and Choi, 2012; Rezvanfar et al., 2014). Hyperandrogenism is one of the

important characteristics of the PCOS pathophysiology damaging the follicular maturation and developing the anovulation, abnormal cycles, and cytogenesis (Goodarzi et al., 2011; Motta, 2010; Rezvanfar et al., 2014). On the other hand, it is obvious that the menopause is accompanied with the reduction of estradiol levels and could lead to various diseases such as diabetes, obesity, and cardiovascular problems (Genazzani et al., 2007; Parikh et al., 2012; Welt and Carmina, 2013). The main underlying mechanism is based on the protective effects of the estradiol against follicular apoptosis, and the modulation of oxidative stress (Lund et al., 1999; Seino et al., 2002). In the ovarian aging and PCOS, hyperandrogenism and low estradiol levels are partially responsible for follicular atresia, abnormal oxidative stress, and apoptosis (Lund et al., 1999; Rezvanfar et al., 2014; Seino et al., 2002). Therefore, all the therapeutic strategies targeting the hyperandrogenism and promoting the estradiol levels could delay the ovarian aging process. In this regard, we recently showed that the MNAM reduces the testosterone and estradiol levels (Nejabati et al., 2020). Interestingly, in this review study, we mentioned that the MNAM induces low-level stress and thereby enhances the lifespan. Our report showed the reductive effects of MNAM on the estradiol level (Nejabati et al., 2020) thus, it can be hypothesized that the anti-aging effects of the MNAM are possibly related to the estradiol levels. MNAM decreases the estradiol levels and possibly provokes a transient increase in the ROS, and this low-level stress activates the mitohormetic signaling mediators such as AMPK (Fig. 1).

6. Conclusion

Mitohormetic effect of the ROS are a relatively new idea suggesting that the mitochondrial ROS may be a life-promoting molecule if it generates the low-level stress as its higher doses could have a detrimental effect on the cellular homeostasis. Recent studies have shown that the mitohormetic effect of the ROS may be partially mediated by the AMPK as cellular energy sensor. So, therapeutic agents inducing the formation of low cellular ROS have attracted a great deal of attention recently. MNAM is well known as an anti-diabetic, anti-thrombotic, and anti-inflammatory factor; however, there is not sufficient evidence regarding its anti-aging roles. In this regard, Schmeisser et al., reported a valuable evidence showing that the MNAM induces low-level stress in the cellular system and its hormetic effects lead to the generation of the stress response and thereby promotes the longevity. It has been reported that the endocrine abnormalities such as hyperandrogenism induces the ovarian aging process as seen in the PCOS thus, the PCOS can be considered as an aging-associated disease. It has been documented that the production of MNAM is significantly higher in the cumulus cells of the patients with PCOS and its administration on the PCOS rats has been shown to alleviate the hyperandrogenism and successfully activate the ovarian AMPK. Therefore, it was hypothesized that the anti-ovarian aging effects of the MNAM possibly result from the activation of AMPK through transient elevation of the ROS. Although, it is recommended to thoroughly investigate the roles of the MNAM in the ovarian aging and related disorders like PCOS in the context of mitohormetins such as ROS. Of note, in the current hypothetical review, we considered MNAM as a hypothetical hormetin and there is not enough solid data to support the idea of this paper. The idea of our hypothetical review is only based on the findings of our original work (Nejabati et al., 2020), which addressed the therapeutic effects of MNAM on PCOS rats and also anti-aging roles of MNAM, which proposed by Schmeisser et al. (Schmeisser et al., 2013). It should be taken into account that the anti-ovarian ageing effects of the MNAM, which have been proposed in the current study, were based on animal studies and to date, there is no evidence in terms of human studies. However, given the higher production of MNAM and lower expression of AOX1 in the cumulus cells of women with PCOS, and the life-promoting mechanism for MNAM, provided by Schmeisser et al. (Schmeisser et al., 2013), it can be concluded that the induction of the adaptive stress response is

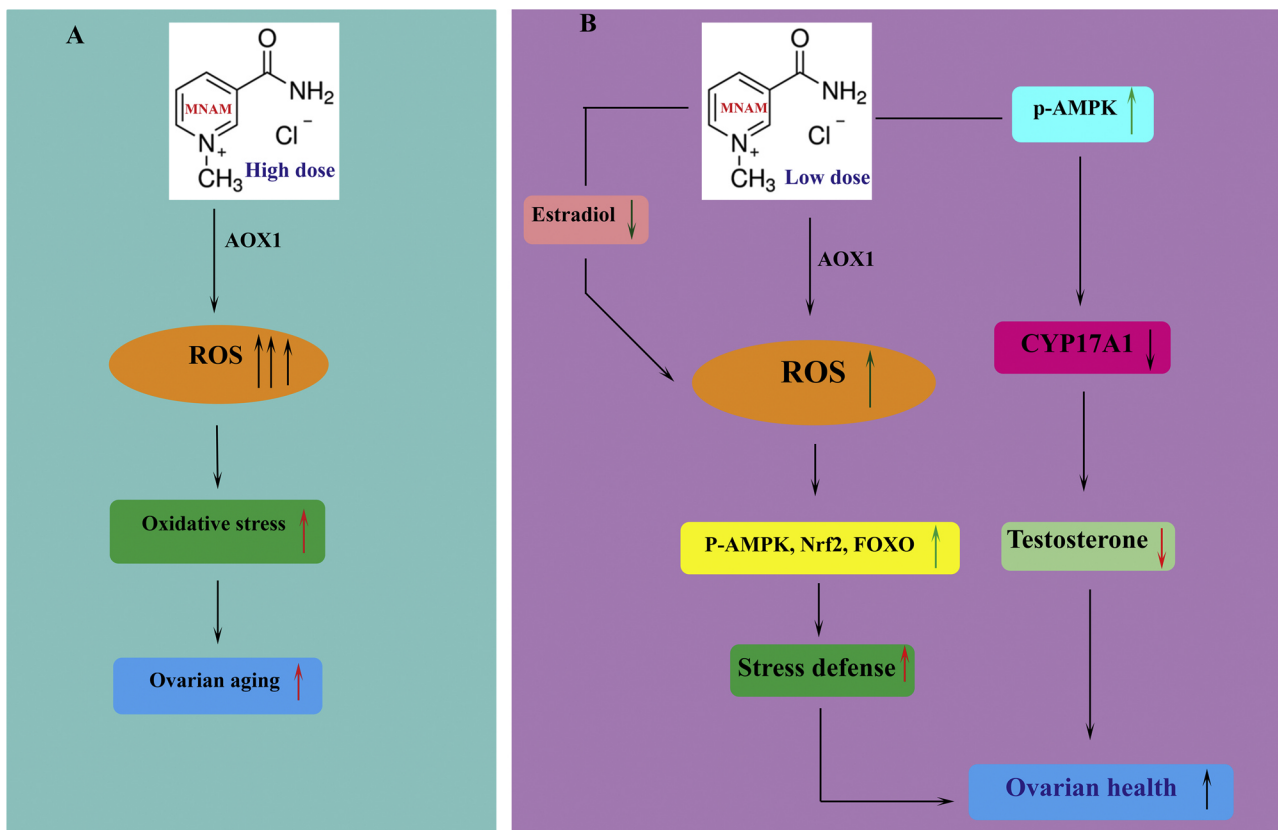


Fig. 1. Possible mechanism of the MNAM in ovarian aging. **A)** The high dose of MNAM leads to the production of extreme ROS, causes oxidative stress and accelerates ovarian aging. **B)** The low dose of MNAM leads to the generation of ROS after oxidation by AOX1. ROS-derived low level stress could activate AMPK and subsequently the elevation of stress defense may have anti-ovarian aging effects. MNAM may also activate AMPK directly and could reduce testosterone and estradiol levels, which are responsible for induction of ROS production. **MNAM**, N1-methylnicotinamide; **AOX1**, aldehyde oxidase; **AMPK**, 5' adenosine monophosphate-activated protein kinase; **ROS**, reactive oxygen species.

impaired in the pathological conditions like PCOS and ovarian ageing. The adaptive mechanism of Schmeisser et al. (Schmeisser et al., 2013) is proposed for the ovary in the current review and there is a need for more in depth investigation in animal studies and if possible, the obtained knowledge be translated to humans. Therefore, the life-promoting effects of MNAM and the corresponding mechanism may not have been attributed to its possible anti-ovarian ageing effects and it should not be confused with the investigation of 'lifespan increase' and 'anti-ovarian ageing' phenomena.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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References

- Acuna, E., Fornes, R., Fernandois, D., Garrido, M.P., Greiner, M., Lara, H.E., Paredes, A.H., 2009. Increases in norepinephrine release and ovarian cyst formation during ageing in the rat. *Reproductive biology and endocrinology* : RB&E 7, 64.
- Aksoy, S., Szumlanski, C.L., Weinshilboum, R.M., 1994. Human liver nicotinamide N-methyltransferase. cDNA cloning, expression, and biochemical characterization. *Journal of Biological Chemistry* 269, 14835–14840.
- Banerjee, K.K., Ayyub, C., Ali, S.Z., Mandot, V., Prasad, N.G., Kolthur-Seetharam, U., 2012. dSir2 in the adult fat body, but not in muscles, regulates life span in a diet-dependent manner. *Cell reports* 2, 1485–1491.
- Barcena, C., Mayoral, P., Quiros, P.M., 2018. Mitohormesis, an Antiaging Paradigm.

- International review of cell and molecular biology 340, 35–77.
- Bardia, A., Tleyjeh, I.M., Cerhan, J.R., Sood, A.K., Limburg, P.J., Erwin, P.J., Montori, V.M., 2008. Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clinic Proceedings* 23–34.
- Barritt, J.A., Brenner, C.A., Cohen, J., Matt, D.W., 1999. Mitochondrial DNA rearrangements in human oocytes and embryos. *Molecular human reproduction* 5, 927–933.
- Barritt, J.A., Cohen, J., Brenner, C.A., 2000. Mitochondrial DNA point mutation in human oocytes is associated with maternal age. *Reproductive BioMedicine Online* 1, 96–100.
- Bertoldo, M., Faure, M., Dupont, J., Froment, P., 2015. AMPK: a master energy regulator for gonadal function. *Frontiers in neuroscience* 9, 235.
- Boily, G., Seifert, E.L., Bevilacqua, L., He, X.H., Sabourin, G., Estey, C., Moffat, C., Crawford, S., Saliba, S., Jardine, K., 2008. SirT1 regulates energy metabolism and response to caloric restriction in mice. *PloS one* 3.
- Brenner, C.A., Wolny, Y.M., Barritt, J.A., Matt, D.W., Munne, S., Cohen, J., 1998. Mitochondrial DNA deletion in human oocytes and embryos. *Molecular human reproduction* 4, 887–892.
- Broekmans, F.J., Faddy, M.J., Scheffer, G., te Velde, E.R., 2004. Antral follicle counts are related to age at natural fertility loss and age at menopause. *Menopause* 11, 607–614.
- Broekmans, F.J., Soules, M.R., Fauser, B.C., 2009. Ovarian aging: mechanisms and clinical consequences. *Endocrine reviews* 30, 465–493.
- Brunetti, G., Di Rosa, G., Scuto, M., Leri, M., Stefani, M., Schmitz-Linneweber, C., Calabrese, V., Saul, N., 2020. Healthspan Maintenance and Prevention of Parkinson's-like Phenotypes with Hydroxytyrosol and Oleuropein Aglycone in *C. elegans*. *Int J Mol Sci* 21.
- Bukovsky, A., Ayala, M.E., Dominguez, R., Keenan, J.A., Wimalasena, J., McKenzie, P.P., Caudle, M.R., 2000. Postnatal androgenization induces premature aging of rat ovaries. *Steroids* 65, 190–205.
- Burnett, C., Valentini, S., Cabreiro, F., Goss, M., Somogyvári, M., Piper, M.D., Hoddinott, M., Sutphin, G.L., Leko, V., McElwee, J.J., 2011. Absence of effects of Sir2 over-expression on lifespan in *C. elegans* and *Drosophila*. *nature* 477, 482–485.
- Calabrese, E.J., Calabrese, V., Tsatsakis, A., Giordano, J.J., 2020. Hormesis and Ginkgo biloba (GB): Numerous biological effects of GB are mediated via hormesis. *Ageing Res Rev* 101019.
- Calabrese, V., Cornelius, C., Dinkova-Kostova, A.T., Calabrese, E.J., Mattson, M.P., 2010. Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxidants & redox signaling* 13, 1763–1811.

- Calabrese, V., Santoro, A., Monti, D., Crupi, R., Di Paola, R., Latteri, S., Cuzzocrea, S., Zappia, M., Giordano, J., Calabrese, E.J., Franceschi, C., 2018a. Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. *Free radical biology & medicine* 115, 80–91.
- Calabrese, V., Santoro, A., Trovato Salinaro, A., Modafferi, S., Scuto, M., Albouchi, F., Monti, D., Giordano, J., Zappia, M., Franceschi, C., Calabrese, E.J., 2018b. Hormetic approaches to the treatment of Parkinson's disease: Perspectives and possibilities. *J Neurosci Res* 96, 1641–1662.
- Chan, C., Liu, V., Lau, E., Yeung, W., Ng, E., Ho, P., 2005. Mitochondrial DNA content and 4977 bp deletion in unfertilized oocytes. *Molecular human reproduction* 11, 843–846.
- Chan, C.C., Liu, V.W., Lau, E.Y., Yeung, W.S., Ng, E.H., Ho, P.-C., 2006. Mitochondrial DNA deletion in granulosa and cumulus oophorus cells. *Fertility and sterility* 85, 780–782.
- Chandel, N.S., 2015. Evolution of mitochondria as signaling organelles. *Cell metabolism* 22, 204–206.
- den Tonkelaar, I., Te Velde, E., Looman, C., 1998d. Menstrual cycle length preceding menopause in relation to age at menopause. *Maturitas* 29, 115–123.
- Di Rosa, G., Brunetti, G., Scuto, M., Trovato Salinaro, A., Calabrese, E.J., Crea, R., Schmitz-Linneweber, C., Calabrese, V., Saul, N., 2020. Healthspan Enhancement by Olive Polyphenols in *C. elegans* Wild Type and Parkinson's Models. *Int J Mol Sci* 21.
- Druzhyna, N.M., Wilson, G.L., LeDoux, S.P., 2008. Mitochondrial DNA repair in aging and disease. *Mechanisms of ageing and development* 129, 383–390.
- Duran, H.E., Simsek-Duran, F., Oehninger, S.C., Jones Jr., H.W., Castora, F.J., 2011. The association of reproductive senescence with mitochondrial quantity, function, and DNA integrity in human oocytes at different stages of maturation. *Fertility and sterility* 96, 384–388.
- Egan, D.F., Shackelford, D.B., Mihaylova, M.M., Gelino, S., Kohnz, R.A., Mair, W., Vasquez, D.S., Joshi, A., Gwinn, D.M., Taylor, R., 2011. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. *Science* 331, 456–461.
- Erickson, G.F., Magoffin, D.A., Dyer, C.A., Hofeditz, C., 1985. The ovarian androgen producing cells: a review of structure/function relationships. *Endocrine reviews* 6, 371–399.
- Fang, E.F., Lautrup, S., Hou, Y., Demarest, T.G., Croteau, D.L., Mattson, M.P., Bohr, V.A., 2017. NAD⁺ in aging: molecular mechanisms and translational implications. *Trends in molecular medicine* 23, 899–916.
- Fausser, B., van Heusden, A.M., 1997. Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocrine reviews*.
- Fédération, C., Schwartz, D., Mayaux, M., 1982. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. *New England Journal of Medicine* 306, 404–406.
- Felsted, R.L., Chaykin, S., 1967. N1-methylnicotinamide oxidation in a number of mammals. *Journal of Biological Chemistry* 242, 1274–1279.
- Fu, L., Liu, C., Chen, L., Lv, Y., Meng, G., Hu, M., Long, Y., Hong, H., Tang, S., 2019. Protective effects of 1-Methylnicotinamide on Aβ 1–42-induced cognitive deficits, neuroinflammation and apoptosis in mice. *Journal of Neuroimmune Pharmacology* 14, 401–412.
- Fukushima, T., Tawara, T., Lsohe, A., Hojo, N., Shiwa, K., Yamane, Y., 1995. Radical formation site of cerebral complex I and Parkinson's disease. *Journal of neuroscience research* 42, 385–390.
- Genazzani, A.R., Pluchino, N., Luisi, S., Luisi, M., 2007. Estrogen, cognition and female ageing. *Human reproduction update* 13, 175–187.
- Gill, S., Sharpless, J.L., Rado, K., Hall, J.E., 2002. Evidence that GnRH decreases with gonadal steroid feedback but increases with age in postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism* 87, 2290–2296.
- Goodarzi, M.O., Dumesic, D.A., Chazenbalk, G., Azziz, R., 2011. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nature reviews. Endocrinology* 7, 219–231.
- Hall, J.E., Lavoie, H.B., Marsh, E.E., Martin, K.A., 2000. Decrease in gonadotropin-releasing hormone (GnRH) pulse frequency with aging in postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism* 85, 1794–1800.
- Harman, D., 1956. Aging: a theory based on free radical and radiation chemistry. *Journal of gerontology* 11, 298–300.
- Herzig, S., Shaw, R.J., 2018. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nature reviews Molecular cell biology* 19, 121.
- Holmström, K.M., Finkel, T., 2014. Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nature reviews Molecular cell biology* 15, 411–421.
- Hussein, M.R., 2005. Apoptosis in the ovary: molecular mechanisms. *Human reproduction update* 11, 162–178.
- Imai, S.-I., Guarente, L., 2016. It takes two to tango: NAD⁺ and sirtuins in aging/longevity control. *npj Aging and Mechanisms of Disease* 2, 1–6.
- Jakubowski, A., Sternak, M., Jablonski, K., Ciszek-Lenda, M., Marcinkiewicz, J., Chlopicki, S., 2016. 1-Methylnicotinamide protects against liver injury induced by concanavalin A via a prostacyclin-dependent mechanism: A possible involvement of IL-4 and TNF-α. *International immunopharmacology* 31, 98–104.
- Kasapoglu, I., Seli, E., 2020. Mitochondrial Dysfunction and Ovarian Aging. *Endocrinology*.
- Katsyuba, E., Auwerx, J., 2017. Modulating NAD⁺ metabolism, from bench to bedside. *The EMBO journal* 36, 2670–2683.
- Kenigsberg, S., Bentov, Y., Chalifa-Caspi, V., Potashnik, G., Ofir, R., Birk, O.S., 2009. Gene expression microarray profiles of cumulus cells in lean and overweight-obese polycystic ovary syndrome patients. *Molecular human reproduction* 15, 89–103.
- Koks, S., Velthuis, A., Sarapik, A., Altmäe, S., Reinmaa, E., Schalkwyk, L., Fernandes, C., Lad, H., Soomets, U., Jaakma, Ü., 2010. The differential transcriptome and ontology profiles of floating and cumulus granulosa cells in stimulated human antral follicles. *Molecular human reproduction* 16, 229–240.
- Kuhlbrandt, W., 2015. Structure and function of mitochondrial membrane protein complexes. *BMC biology* 13, 89.
- Lavenda, B.D., Kelly, K.M., Ladas, E.J., Sagar, S.M., Vickers, A., Blumberg, J.B., 2008. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *Journal of the national cancer institute* 100, 773–783.
- Leri, M., Scuto, M., Ontario, M.L., Calabrese, V., Calabrese, E.J., Bucciantini, M., Stefani, M., 2020. Healthy effects of plant polyphenols: molecular mechanisms. *International journal of molecular sciences* 21, 1250.
- Lin, S.-J., Defossez, P.-A., Guarente, L., 2000. Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science* 289, 2126–2128.
- Lippman, S.M., Klein, E.A., Goodman, P.J., Lucia, M.S., Thompson, I.M., Ford, L.G., Parnes, H.L., Minasian, L.M., Gaziano, J.M., Hartline, J.A., 2009. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama* 301, 39–51.
- Liu, M., Chu, J., Gu, Y., Shi, H., Zhang, R., Wang, L., Chen, J., Shen, L., Yu, P., Chen, X., Ju, W., Wang, Z., 2017. Serum N1-Methylnicotinamide is Associated With Coronary Artery Disease in Chinese Patients. *Journal of the American Heart Association* 6.
- Lund, S.A., Murdoch, J., Van Kirk, E.A., Murdoch, W.J., 1999. Mitogenic and antioxidant mechanisms of estradiol action in preovulatory ovine follicles: relevance to luteal function. *Biology of reproduction* 61, 388–392.
- Luoma, P., Melberg, A., Rinne, J.O., Kaukonen, J.A., Nupponen, N.N., Chalmers, R.M., Oldfors, A., Rautakorpi, I., Peltonen, L., Majamaa, K., 2004. Parkinsonism, premature menopause, and mitochondrial DNA polymerase γ mutations: clinical and molecular genetic study. *The Lancet* 364, 875–882.
- Mateuszuk, L., Jasztal, A., Maslak, E., Gasior-Glogowska, M., Baranska, M., Sitek, B., Kostogry, R., Zakrzewska, A., Kij, A., Walczak, M., Chlopicki, S., 2016. Antiatherosclerotic Effects of 1-Methylnicotinamide in Apolipoprotein E/Low-Density Lipoprotein Receptor-Deficient Mice: A Comparison with Nicotinic Acid. *The Journal of pharmacology and experimental therapeutics* 356, 514–524.
- Mateuszuk, L., Khomich, T.I., Slominska, E., Gajda, M., Wojcik, L., Lomnicka, M., Gwozdz, P., Chlopicki, S., 2009. Activation of nicotinamide N-methyltransferase and increased formation of 1-methylnicotinamide (MNA) in atherosclerosis. *Pharmacological reports : PR* 61, 76–85.
- May-Panloup, P., Boucret, L., Chao de la Barca, J.-M., Desquiere-Dumas, V., Ferré-L'Hotellier, V., Morinière, C., Descamps, P., Procaccio, V., Reynier, P., 2016. Ovarian ageing: the role of mitochondria in oocytes and follicles. *Human reproduction update* 22, 725–743.
- McBride, H.M., Neuspiel, M., Wasiak, S., 2006. Mitochondria: more than just a powerhouse. *Current biology : CB* 16, R551–560.
- McReynolds, S., Dzieciatkowska, M., McCallie, B.R., Mitchell, S.D., Stevens, J., Hansen, K., Schoolcraft, W.B., Katz-Jaffe, M.G., 2012. Impact of maternal aging on the molecular signature of human cumulus cells. *Fertility and sterility* 98, 1574–1580 e1575.
- Miquel, S., Champ, C., Day, J., Aarts, E., Bahr, B.A., Bakker, M., Bánáti, D., Calabrese, V., Cederholm, T., Cryan, J., 2018. Poor cognitive ageing: Vulnerabilities, mechanisms and the impact of nutritional interventions. *Ageing research reviews* 42, 40–55.
- Motta, A.B., 2010. Dehydroepiandrosterone to induce murine models for the study of polycystic ovary syndrome. *The Journal of steroid biochemistry and molecular biology* 119, 105–111.
- Müller-Höcker, J., Schäfer, S., Weis, S., Muñscher, C., Strowitzki, T., 1996. Morphological-cytochemical and molecular genetic analyses of mitochondria in isolated human oocytes in the reproductive age. *MHR: Basic science of reproductive medicine* 2, 951–958.
- Myung, S.-K., Kim, Y., Ju, W., Choi, H., Bae, W.K., 2010. Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. *Annals of Oncology* 21, 166–179.
- Nejabati, H.R., Mihanfar, A., Pezeshkian, M., Fattahi, A., Latifi, Z., Safaie, N., Valiloo, M., Jodati, A.R., Nouri, M., 2018. N1-methylnicotinamide (MNAM) as a guardian of cardiovascular system. *J Cell Physiol* 233, 6386–6394.
- Nejabati, H.R., Samadi, N., Roshangar, L., Nouri, M., 2019. N1-methylnicotinamide as a possible modulator of cardiovascular risk markers in polycystic ovary syndrome. *Life sciences*, 116843.
- Nejabati, H.R., Samadi, N., Shahnazi, V., Mihanfar, A., Fattahi, A., Latifi, Z., Bahrami-asl, Z., Roshangar, L., Nouri, M., 2020. Nicotinamide and its metabolite N1-Methylnicotinamide alleviate endocrine and metabolic abnormalities in adipose and ovarian tissues in rat model of Polycystic Ovary Syndrome. *Chemico-Biological Interactions*, 109093.
- O'Connor, K.A., Holman, D.J., Wood, J.W., 1998. Declining fecundity and ovarian ageing in natural fertility populations. *Maturitas* 30, 127–136.
- Országhová, Z., Uličná, O., Liptáková, A., Žitňanová, I., Muchová, J., Watala, C., Ďuračková, Z., 2012. Effects of N1-methylnicotinamide on oxidative and glycoxidative stress markers in rats with streptozotocin-induced diabetes mellitus. *Redox Report* 17, 1–7.
- Paracelsus, von Bodenstein, A., Aureoli Paracelsi Labyrinth und Irrgang der vermeinten Artzet: Item Sieben Defensiones oder Schirmreden [ua]. *Durch Adam von Bodenstein A.n Tag geben. Perna*.
- Parikh, N.I., Cnattingius, S., Mittleman, M.A., Ludvigsson, J.F., Ingelsson, E., 2012. Subfertility and risk of later life maternal cardiovascular disease. *Human reproduction (Oxford, England)* 27, 568–575.
- Park, J.H., Choi, T.S., 2012. Polycystic ovary syndrome (PCOS)-like phenotypes in the d-galactose-induced aging mouse model. *Biochem Biophys Res Commun* 427, 701–704.
- Pérez, V.I., Van Remmen, H., Bokov, A., Epstein, C.J., Vijg, J., Richardson, A., 2009. The overexpression of major antioxidant enzymes does not extend the lifespan of mice. *Ageing cell* 8, 73–75.

- Perkins, G.A., Frey, T.G., 2000. Recent structural insight into mitochondria gained by microscopy. *Micron* (Oxford, England : 1993) 31, 97–111.
- Peters, V., Calabrese, V., Forsberg, E., Volk, N., Fleming, T., Baelde, H., Weigand, T., Thiel, C., Trovato, A., Scuto, M., 2018. Protective actions of anserine under diabetic conditions. *International journal of molecular sciences* 19, 2751.
- Pilipenko, V., Narbute, K., Amara, I., Trovato, A., Scuto, M., Pupure, J., Jansone, B., Poikans, J., Bisenieks, E., Klusa, V., 2019. GABA-containing compound gammayprone protects against brain impairments in Alzheimer's disease model male rats and prevents mitochondrial dysfunction in cell culture. *Journal of neuroscience research* 97, 708–726.
- Pissios, P., 2017. Nicotinamide N-methyltransferase: more than a vitamin B3 clearance enzyme. *Trends in Endocrinology & Metabolism* 28, 340–353.
- Przyborowski, K., Wojewoda, M., Sitek, B., Zakrzewska, A., Kij, A., Wandzel, K., Zoladz, J.A., Chlopicki, S., 2015. Effects of 1-methylnicotinamide (MNA) on exercise capacity and endothelial response in diabetic mice. *PLoS one* 10, e0130908.
- Quiros, P.M., Mottis, A., Auwerx, J., 2016. Mitonuclear communication in homeostasis and stress. *Nature reviews. Molecular cell biology* 17, 213–226.
- Rezvanfar, M.A., Shojaei Saadi, H.A., Gooshe, M., Abdolghaffari, A.H., Baeeri, M., Abdollahi, M., 2014. Ovarian aging-like phenotype in the hyperandrogenism-induced murine model of polycystic ovary. *Oxidative medicine and cellular longevity* 2014, 948951.
- Ristow, M., Zarse, K., 2010. How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). *Experimental gerontology* 45, 410–418.
- Rizzuto, R., De Stefani, D., Raffaello, A., Mammucari, C., 2012. Mitochondria as sensors and regulators of calcium signalling. *Nature reviews. Molecular cell biology* 13, 566–578.
- Rogina, B., Helfand, S.L., 2004. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. *Proceedings of the National Academy of Sciences* 101, 15998–16003.
- Ross, J.M., Stewart, J.B., Hagström, E., Brené, S., Mourier, A., Coppotelli, G., Freyer, C., Lagouge, M., Hoffer, B.J., Olson, L., 2013. Germline mitochondrial DNA mutations aggravate ageing and can impair brain development. *Nature* 501, 412–415.
- Ruiz, R., Maria Perez-Villegas, E., Carrión, M., 2016. AMPK function in aging process. *Current drug targets* 17, 932–941.
- Schaar, C.E., Dues, D.J., Spielbauer, K.K., Machiela, E., Cooper, J.F., Senchuk, M., Hekimi, S., Van Raamsdonk, J.M., 2015. Mitochondrial and cytoplasmic ROS have opposing effects on lifespan. *PLoS genetics* 11.
- Schmeisser, K., Mansfeld, J., Kuhlow, D., Weimer, S., Priebe, S., Heiland, I., Birringer, M., Groth, M., Segref, A., Kanfi, Y., 2013. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nature chemical biology* 9, 693.
- Schulz, T.J., Zarse, K., Voigt, A., Urban, N., Birringer, M., Ristow, M., 2007. Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. *Cell metabolism* 6, 280–293.
- Seino, T., Saito, H., Kaneko, T., Takahashi, T., Kawachiya, S., Kurachi, H., 2002. Eight-hydroxy-2'-deoxyguanosine in granulosa cells is correlated with the quality of oocytes and embryos in an in vitro fertilization-embryo transfer program. *Fertil Steril* 77, 1184–1190.
- Shadel, G.S., Horvath, T.L., 2015. Mitochondrial ROS signaling in organismal homeostasis. *Cell* 163, 560–569.
- Soules, M.R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., Woods, N., 2001a. Executive summary: stages of reproductive aging workshop (STRAW). *Climacteric* 4, 267–272.
- Soules, M.R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., Woods, N., 2001b. Stages of reproductive aging workshop (STRAW). *Journal of women's health & gender-based medicine* 10, 843–848.
- Sternak, M., Jakubowski, A., Czarnowska, E., Slominska, E.M., Smolenski, R.T., Szafarz, M., Walczak, M., Sitek, B., Wojcik, T., Jaształ, A., Kaminski, K., Chlopicki, S., 2015. Differential involvement of IL-6 in the early and late phase of 1-methylnicotinamide (MNA) release in Concanavalin A-induced hepatitis. *International immunopharmacology* 28, 105–114.
- Tait, S.W., Green, D.R., 2010. Mitochondria and cell death: outer membrane permeabilization and beyond. *Nature reviews Molecular cell biology* 11, 621–632.
- Tanaka, Y., Kume, S., Araki, H., Nakazawa, J., Chin-Kanasaki, M., Araki, S.-i., Nakagawa, F., Koya, D., Haneda, M., Maegawa, H., 2015. 1-Methylnicotinamide ameliorates lipotoxicity-induced oxidative stress and cell death in kidney proximal tubular cells. *Free Radical Biology and Medicine* 89, 831–841.
- Tao, X., Chen, L., Cai, L., Ge, S., Deng, X., 2017. Regulatory effects of the AMPK- α -SIRT1 molecular pathway on insulin resistance in PCOS mice: an in vitro and in vivo study. *Biochemical and biophysical research communications* 494, 615–620.
- Tapia, P.C., 2006. Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: "Mitohormesis" for health and vitality. *Medical hypotheses* 66, 832–843.
- Tarin, J.J., 1996. Potential effects of age-associated oxidative stress on mammalian oocytes/embryos. *MHR: Basic science of reproductive medicine* 2, 717–724.
- Tatone, C., Amicarelli, F., Carbone, M.C., Monteleone, P., Caserta, D., Marci, R., Artini, P.G., Piomboni, P., Focarelli, R., 2008. Cellular and molecular aspects of ovarian follicle ageing. *Human reproduction update* 14, 131–142.
- te Velde, E.R., Pearson, P.L., 2002t. The variability of female reproductive ageing. *Human reproduction update* 8, 141–154.
- Treloar, A.E., 1967. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 12, 77–126.
- van Noord-Zaadstra, B.M., Looman, C.W., Alsbach, H., Habbema, J.D., te Velde, E.R., Karbaat, J., 1991v. Delaying childbearing: effect of age on fecundity and outcome of pregnancy. *British Medical Journal* 302, 1361–1365.
- van Santbrink, E.J., Hop, W.C., van Dessel, T.J., de Jong, F.H., Fauser, B.C., 1995v. Decremental follicle-stimulating hormone and dominant follicle development during the normal menstrual cycle. *Fertility and sterility* 64, 37–43.
- Warburton, D., 2005. Biological aging and the etiology of aneuploidy. *Cytogenetic and genome research* 111, 266–272.
- Ward, N.C., Wu, J.H., Clarke, M.W., Puddey, I.B., Burke, V., Croft, K.D., Hodgson, J.M., 2007. The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Journal of hypertension* 25, 227–234.
- Watała, C., Kaźmierczak, P., Dobaczewski, M., Przygodzki, T., Bartuś, M., Łomnicka, M., Słomińska, E.M., Duračková, Z., Chlopicki, S., 2009. Anti-diabetic effects of 1-methylnicotinamide (MNA) in streptozocin-induced diabetes in rats. *Pharmacological Reports* 61, 86–98.
- Welt, C.K., Carmina, E., 2013. Clinical review: Lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. *The Journal of clinical endocrinology and metabolism* 98, 4629–4638.
- Welt, C.K., Smith, Z.A., Pauler, D.K., Hall, J.E., 2001. Differential regulation of inhibin A and inhibin B by luteinizing hormone, follicle-stimulating hormone, and stage of follicle development. *The Journal of Clinical Endocrinology & Metabolism* 86, 2531–2537.
- Wilding, M., Dale, B., Marino, M., di Matteo, L., Alviggi, C., Pisaturo, M.L., Lombardi, L., De Placido, G., 2001. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. *Human Reproduction* 16, 909–917.
- Wu, R.-x., Dong, Y.-y., Yang, P.-w., Wang, L., Deng, Y.-h., Zhang, H.-w., Huang, X.-y., 2019. CD36-and obesity-associated granulosa cells dysfunction. *Reproduction, Fertility and Development* 31, 993–1001.