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# Nicotinamide Mononucleotide (NMN) as a Solution of Decrease Nicotinamide Adenine Dinucleotide ($NAD^+$) in Aging

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## ABSTRACT

Advances in the control of infectious diseases have contributed to increasing life expectancy. As a result, the aging population has increased. Data shows that there were 771 million elderly in 2022, which is estimated to increase to 1.6 billion in 2050. This condition causes changes in disease patterns that lead to diseases related to age and aging. Recently, nicotinamide mononucleotide (NMN) has received much attention. Therefore, the authors made this review article using the literature review method to describe role of NMN as an anti-aging modality and prevention of disease associated with a decrease in nicotinamide adenine dinucleotide ($NAD^+$). Decreased $NAD^+$ levels occur through several mechanisms, including activation of PARP-1 by oxidative stress, consumption of $NAD^+$ by CD38 enzymes and sirtuins, injury induced by sterile alpha and toll/interleukin receptor motif-containing protein 1 (SARM1) in axon degeneration, and increased mitochondrial permeability transition (MPT). NMN can increase $NAD^+$ levels in the Salvage and Preiss-Handler pathways so that they will make a positive impact on aging, Parkinson's, Alzheimer's, obesity, cerebral ischemia, heart disease, and type 2 diabetes. The administration of NMN in low doses does not cause significant side effects.

***Keywords:*** aging, anti-aging, $NAD^+$, NMN

## INTRODUCTION

The success of controlling infectious diseases supports increased life expectancy. Data shows that there were 771 million elderly in 2022, which is estimated to increase to 1.6 billion in 2050.[1] In Indonesia, there were 22.630.882 elderly in 2016 and 31.320.066 people in 2022.[2] This condition causes changes in disease patterns that lead to diseases related to age and aging.[3] As a result, the demand for medical practices related to age management is increasing. Various modalities are given, including nutritional supplements, drugs, exercise programs, and hormone therapy.[4] Therefore, it is crucial to study the modalities of aging management.

Recently, NMN has received much attention. Researchers are targeting NMN as an anti-aging modality and prevention of several diseases. NMN are bioactive nucleotides formed from the reaction between nicotinamide and ribose nucleosides with phosphate groups.[5] Generally, NMN is found in plants and animals. NMN is also found in bacteria and yeast.[6] NMN work by returning $NAD^+$ levels. Returning $NAD^+$ levels can repair mitochondrial damage, which is responsible for aging.[7] NMN also has pharmacological effects on Alzheimer's disease, obesity, cerebral ischemia, heart disease, and type 2

diabetes.[8] The broad potential of NMN has driven several studies, including in cell culture, animal, and human clinical trials. Therefore, this review intends to present current knowledge about NMN as an anti-aging supplement and prevention of diseases triggered by decreased $NAD^+$ in aging.

## MATERIALS & METHODS

The author uses the literature review method with the keywords "NMN", "$NAD^+$", "anti-aging", and "aging" as well as the Boolean logic "AND" to obtain specific research journals. Searches were done on the database pages of ScienceDirect, Pubmed, and ResearchGate journals. The data was accompanied by inclusion and exclusion criteria. The inclusion criteria are an increase in $NAD^+$ by NMN in aging. Preferred research should not contradict newer studies and be arranged systematically according to the problem topic discussed.

## RESULT AND DISCUSSION

### Nicotinamide mononucleotide (NMN)

Nicotinamide mononucleotide (NMN) is a bioactive nucleotide divided into the α and β anomeric forms. β NMN is the active form of NMN. NMN is usually found in the nucleus, mitochondria, and cytoplasm. This compound is also found in placental tissue and body fluids, such as blood and urine.[9] NMN is one of the precursors of $NAD^+$ biosynthesis with the lowest side effects. The study results in animal models showed that systemic administration of NMN would increase $NAD^+$ biosynthesis in the pancreas, liver, adipose tissue, heart, skeletal muscle, kidney, testes, eyes, and aorta in both normal and pathological conditions. Intraperitoneal administration of NMN also increased $NAD^+$ levels in the hippocampus and hypothalamus within 15 minutes. This study shows that NMN can cross the blood-brain barrier (BBB) and contribute significantly to $NAD^+$ biosynthesis in the brain.[10]

### Nicotinamide adenine dinucleotide ($NAD^+$)

Nicotinamide adenine dinucleotide ($NAD^+$) was first discovered as a ferment coenzyme. After further research, it was found that $NAD^+$ also plays a role in redox homeostasis, metabolites in glycolysis, tricarboxylic acid cycle (TCA), oxidative phosphorylation (OXPHOS), and cell signalling.[11] $NAD^+$ also plays a role in various biological processes in the body, such as DNA repair, gene expression, enzyme control, neuronal inflammation, cell death, and aging.[9] Several enzymes are controlled by $NAD^+$, such as sirtuins, poly-ADP-ribose polymerase (PARPs), and CD38/157 ectoenzymes. $NAD^+$ biosynthesis is mediated by NAMPT and SIRT1, which together regulate metabolism and circadian rhythms. The biosynthesis of $NAD^+$ in the body decreases when getting older.[12]

### Mechanism of nicotinamide adenine dinucleotide ($NAD^+$) depletion

The decrease of $NAD^+$ occurs with age. This condition is generally found at 40–60 years. Decreased $NAD^+$ occurs in skeletal muscle, liver, pancreas, adipose tissue, and skin.[13] As a comparison, $NAD^+$ levels found in the skin tissue of newborns, adults, and the elderly, respectively were $8.54 \pm 1.55$, $2.74 \pm 0.41$, and $1.06 \pm 0.91$ ng/mg protein.[14] The decrease in $NAD^+$ results from increased consumption and decreased synthesis capacity. This condition can be found in obese patients with decreased $NAD^+$ levels due to PARP-1 activation and decreased synthesis by NAMPT.[15-16]

The increase in $NAD^+$ consumption is explained through several pathways: 1) Activation of PARP-1 by oxidative stress. This mechanism is the main cause of the decrease in $NAD^+$ levels by producing ADP-ribose polymerase in DNA repair.[17] 2) Consumption of $NAD^+$ by the CD38 enzyme. This condition generally occurs in cases of cerebral ischemia. The CD38 enzyme uses $NAD^+$ to produce cyclic ADP-ribose and nicotinamide.[18] 3) Consumption of $NAD^+$ by sirtuins enzymes in type 1

diabetes. Sirtuins use $NAD^+$ to perform deacetylation functions, deglutarylase activity, lipoamidase, demalonylase, and desuccinylase.[19] 4) Injury induced by sterile alpha and SARM1 mediates $NAD^+$ consumption in cases of axonal degeneration.[20] 5) An increase in MPT in myocardial infarction.[21] Meanwhile, the reduced capacity for $NAD^+$ synthesis occurs due to decreased NAMPT activity in metabolic organs exposed to high-fat diets (HFD) and aging.[13] Decreased activity of NANAT3 and NNT enzymes also affects the synthesis. Age is the main factor in decreasing the activity of this enzyme.[22]

**Involvement of $NAD^+$ in aging and disease**

The decrease of $NAD^+$ has implications for the disruption of DNA repair. It is followed by decreased SIRT1 activity, increased PARP-1 activity, and mitochondrial dysfunction which ends in aging. Aging is a downregulation of energy production by mitochondria in various organs. Besides aging, decreased $NAD^+$ also triggers some diseases.[23] The study results showed that aging and diseases caused by a decrease in $NAD^+$ could be prevented by administering NMN. These compounds will increase $NAD^+$ levels in tissues, energy metabolism, physical activity, preventing age- and weight-related diseases, increasing sensitivity to insulin and plasma lipids, and visual function. An increase in $NAD^+$ also increases mitochondrial oxidative metabolism in skeletal muscle and prevents changes in gene expression in the aging process. Decreased muscle mass and strength is a sign of aging. The loss of 85% $NAD^+$ in the body can degrade muscle mass and reduce muscle strength in old rats. However, after the administration of $NAD^+$, the muscle mass and function of the rats returned quickly.[10] Aging in women is also marked by decreased fertility. The results showed that the administration of low doses of NMN was able to improve oocyte quality in aging women.[9] This result shows the involvement of $NAD^+$ decline in the aging process.

Reduced $NAD^+$ levels are involved in the pathogenesis of several age-related diseases. The role of $NAD^+$ in increasing insulin sensitivity and plasma lipids explains why reduced $NAD^+$ can induce type 2 diabetes mellitus and NAFLD. Several studies have shown that restoring $NAD^+$ levels can improve glucose intolerance and fat profile in old rats induced with type 2 diabetes. [24-25] $NAD^+$ deficiency is also found in cases of obesity due to reduced activity of NAMPT, SIRT1, SIRT3, SIRT7, and oxidative stress trigger PARP-1 activation. Return of $NAD^+$ levels show a reduction in the level of obesity. [15,26] In cases of myocardial infarction, a decrease in $NAD^+$ is shown due to reduced NAMPT activity. If $NAD^+$ levels are not restored, this condition can lead to apoptosis, including increased caspase-3 and decreased anti-apoptotic Bcl-Xl.[27]

$NAD^+$ levels affect vision and the brain. Research shows that returning $NAD^+$ to normal levels can prevent 93% of glaucoma.[28] Additionally, $NAD^+$ deficiency in the brain will disrupt its metabolism, bioenergy, and homeostasis. If not immediately restored, it will continue to disrupt DNA repair, neuron and stem cell activity, glial cell activation, inflammation, signalling disturbances to adaptive stress responses, calcium homeostasis disorders, oxidative damage, and mitochondrial dysfunction.[29] Depletion of $NAD^+$ levels induced diseases caused by neuronal degeneration, including xeroderma pigmentosum group A (XPA), Cockayne syndrome (CS), and ataxia telangiectasia (AT).[30] The involvement of reduced $NAD^+$ has also been reported in Parkinson's, Alzheimer's, and hypertensive disease (HTD). Other studies have shown that giving $NAD^+$ can prevent Parkinson's and Alzheimer's. Administration of NMN restored ATP and reduced the accumulation of reactive oxygen species (ROS), lipid transfer protein (LTP), and Aβ oligomer involved in neuronal death.[9]

**Mechanism of $NAD^+$ restoration by NMN**

Synthesis, degradation, and recycling of $NAD^+$ occur in the cytoplasm, nucleus, Golgi apparatus, and peroxisomes. Based on literature studies, it was found that NMN effectively increases the concentration of $NAD^+$ in tissues to produce therapeutic effects.[31] Four pathways are used in $NAD^+$ synthesis: Kynurenine pathway using Tryptophan (Trp), Preiss-Handler pathway, Salvage pathway, and NRH Salvage pathway. Of these four pathways, NMN is involved in $NAD^+$ biosynthesis via the Salvage and Preiss-Handler pathways.[32]

**Kynurenine pathway**

The Kynurenine pathway uses Tryptophan (Trp) to synthesize $NAD^+$ by employing the SLC7A5 and SLC36A4 transporters across the plasma membrane. When Trp is added intracellularly, it will be converted into formyl kynurenine (FK) and catalyzed into kynurenine. Kynurenine serves as a branch point which will be converted to kynurenic acid through kynurenine aminotransferases (KATs) and be quinaldic acid or 3-hydroxykynurenine (3-HK) by kynurenine 3-monooxygenase (KMO). 3-HK via tryptophan 2,3-dioxygenase (KYNU) is converted into 3-hydroxyanthranilic acid (3-HAA) and oxidized to α-amino-β-carboxymuconate-ε-semialdehyde (ACMS) by 3-hydroxyanthranilic acid oxygenation (3HAO). ACMS is the next branching point because it is either spontaneously converted to quinolinic acid or enzymatically converted to picolinic acid. Then, quinolinic acid joins the Preiss-Handler pathway forming nicotinic acid mononucleotide (NAMN) by administration of quinolinate phosphoribosyltransferase (QPRT). Some metabolites of the Kynurenine pathway are neurotoxic, including 3-HAA and quinolinic acid.[32]

**Preiss-Handler pathway**

The Preiss-Handler pathway synthesizes $NAD^+$ by metabolizing NA precursors in three steps and combines with the Kynurenine pathway in the second step. NA-internalized is carried by the SLC5A8 and SLC22A13 transporters into the plasma membrane and converted to NAMN by nicotinic acid phosphoribosyltransferase (NaPRT). Quinolinic acid from the Kynurenine pathway is metabolized to NAMN via quinolinic acid phosphoribosyl transferase (QPRT), which is one of the essential steps for $NAD^+$ synthesis via the Kynurenine pathway. Furthermore, NAMN will be converted into nicotinic acid adenine dinucleotide (NAAD) by nicotinamide-nucleotide adenylyl transferase (NMNAT) 1-3. At the end of the cycle, NAAD is converted to $NAD^+$ by $NAD^+$ synthase (NADS) using ATP.[32]

**The Salvage pathway**

The Salvage pathway is the most effective pathway for increasing intracellular $NAD^+$ compared to the Kynurenine and Preiss-Handler. Inside the cell, NAM is metabolized to NMN with the help of NAMPT and then converted to $NAD^+$ by NMNAT1−3. NAMPT can be divided into intracellular NAMPT (iNAMPT) and extracellular NAMPT (eNAMPT). NMNAT1 is a core enzyme with focused expression in tissues, such as skeletal muscle, heart, kidney, liver, and pancreas. NMNAT2 is mainly found in the cytosol and Golgi bodies, whereas NMNAT3 is located in the mitochondria and cytoplasm. Extracellular $NAD^+$ and NMN are normally catabolized to NAM or NR by the membrane-bound NADases ADP-ribosyl cyclases (CD38/CD157) and CD73. The small NAM molecule can diffuse into the cell, while the larger NR molecule is transported into the cell using the equilibrative nucleoside transporter 1,2,4 (ENT 1,2,4). Several studies have stated that NR is internalized and phosphorylated into NMN by nicotinamide riboside kinase 1 or 2 (NRK1/NRK2), which will then be converted into $NAD^+$.[32]

**NRH Salvage pathway**

The NRH Salvage pathway is a recently found potential pathway. Sometimes these

pathways merge with conventional Salvage. This pathway is initiated by transporting extracellular NRH across the cell membrane to be phosphorylated by NRH kinase or adenosine kinase (AK). AK is an essential enzyme in this pathway because it converts NRH to nicotinamide mononucleotide (NMNH). After the conversion from NRH to NMNH, NMNH is converted to NADH via NMNAT1−3 and then oxidized to $NAD^+$.[32]

**Effects of NMN administration on aging and disease**

Administration of NMN has broad health benefits. Compared to the genetic approach, the administration of NMN as an $NAD^+$ precursor is easier to achieve. The role of administration NMN is to restore mitochondrial biogenesis, cell protection ability against ROS, repair DNA damage, stimulate neuron regeneration, prevent cell aging, and increase stem cells.[33] Administration of NMN also improves the span of health and age in preclinical models.[34] Other studies have shown that NMN can repair vascular dysfunction, oxidative stress, suppress weight gain, increase physical activity, insulin sensitivity, and restore plasma lipid profiles.[35] The table below summarizes some research results regarding the benefits of boosting $NAD^+$ by NMN.

**Table 1: Effects of administration NMN.**

| Method | Models | Treatment | Result | Authors |
|---|---|---|---|---|
| Preclinical | C57BL/6 young male rats | Intraperitoneal injection of 500 mg NMN for 14 days | Rats that were given NMN injections had low levels of oxidative stress, high mitochondrial bioenergy, recovery of cerebro-microvascular function related to cognitive enhancement, and increased performance in walking | [36] |
| Preclinical | Male C57BL/6 rats (6 weeks) | Injections of corticosterone (CORT) 20 mg/kg to induce depression and 300 mg/kg NMN supplementation orally | Rats that were given NMN supplementation experienced changes in liver transcriptome patterns, increased mitochondrial and lipid metabolism in the liver, and reduced depressive behaviour in mice | [37] |
| Preclinical | Female C57BL/6 rats (40 weeks) | Injection of 0.5 mg/ml NMN for 20 weeks | Rats that were given NMN injections experienced an increase in ovarian reserve, estrus cycle and endocrine function, and an increase in the number of primordial, primary, secondary, antral, and ovarian corpus luteum follicles | [38] |
| Preclinical | Diabetic mice db/db (8 weeks) | Injection of 500 mg/k NMN for 14 days | Mice that were given NMN injections experienced an increase in $NAD^+$ and SIRT1 levels and kidney protection from nephropathic diabetes for up to 20 weeks after supplementation was stopped | [39] |
| Preclinical | C57BL/6 mice were divided into three groups: young mice (3 months), old mice (24 months) | Intraperitoneal injection of 500 mg/day NMN on third group | Old rats given NMN supplementation experienced increased vascular function, miRNA expression profiles in | [40] |

| | | | | |
|---|---|---|---|---|
| | without NMN supplementation, and old mice (24 months) with intraperitoneal NMN supplementation 500 mg/day | | the aorta, and reduced oxidative stress | |
| Clinical | Obese postmenopausal women with prediabetes (n=25) | Oral supplementation of 250 mg/day NMN | Women who were given NMN supplementation experienced improvements in skeletal muscle insulin signalling, insulin sensitivity, and muscle remodelling compared with the placebo group | [41] |
| Clinical | Healthy men (n=10) | Oral supplementation of 100, 250, and 500 mg NMN | Men with NMN supplementation experienced increased serum bilirubin levels, plasma concentrations of N-methyl-2-pyridon-5-carboxamide, N-methyl-4-pyridon-5-carboxamided, and decreased creatinine serum, chloride, and blood glucose levels | [42] |
| Clinical | Young and middle-aged runners (n = 48) were divided into 3 groups | Each group received 300, 600 and 1200 mg/day NMN supplementation | Runners who are given NMN supplementation experience an increase in the first ventilation threshold (VT1) and power (VT2) thereby maximizing the use of $O_2$ by skeletal muscles | [43] |
| Clinical | Healthy middle-aged participants (n=36) | Oral supplementation of NMN at a dose of 125 mg twice daily | Participants who received NMN supplementation experienced increased synthesis and metabolism of $NAD^+$, improved vascular function, and reduced risk of arterial stiffness than the placebo group. | [44] |
| Clinical | Healthy participants (n=80) were divided into four groups | A placebo group and a group given NMN supplementation at doses of 300 mg, 600 mg, and 900 mg | Participants who received NMN supplementation experienced a significant increase in $NAD^+$ in blood, increased physical endurance, and improved general health condition. | [45] |

* This table represents studies that covering the effects of NMN supplementation on increasing $NAD^+$ levels and physiological functions of the body in animal and human models. Sample size (n) is indicated as the number of participants in the study.

## NMN Safety

NMN's safety is still being researched. A clinical study showed that giving NMN 300 mg/kg for one month is safe.[11] other studies showed that oral administration of NMN 300 mg/kg for one year was well tolerated and did not cause toxicity effects.[10] NMN administration can be tolerated at low doses but has a negative impact if given at high doses. Research conducted on healthy Japanese men showed that 500 mg of NMN was well tolerated without causing significant side effects.[42] Clinical trials conducted by Irie et al. found that single oral administration of NMN in doses of 100, 250, and 500 mg was well tolerated and did not cause changes in temperature, oxygen saturation, blood pressure, and heart rate. Changes in eye parameters, ocular fundus, and neurological system were also not found. Administration of NMN does not increase nicotinamide in the blood and thus

avoids the toxicity it triggers.[42] However, increased $NAD^+$ can also be procancerous or anticancer depending on conditions. Generally, giving excess NMN will lead to cancer. Conversely, giving NMN in low doses for breast and lung cancer is anticancer.[46] Preclinical studies showed that anticancer properties were also found in leukemia-induced mice. Meanwhile, clinical research shows that increasing $NAD^+$ can treat skin cancer.[11] When compared with fellow $NAD^+$ precursors like NR. Giving NR can increase rats' low-density lipoprotein (LDL), fatty liver, and insulin resistance. This condition is inversely proportional to the administration of NMN, which can reduce intrahepatic triglyceride levels, cholesterol, and improve plasma lipid profiles.[9] A clinical trial conducted by Yushino et al. on 25 prediabetic women who were given NMN 250 mg/day NMN for ten weeks showed increased insulin sensitivity without side effects. This study shows that the administration of NMN as an $NAD^+$ precursor has the lowest side effects compared to NR.[41]

## CONCLUSION

Administration of NMN can return $NAD^+$ levels through the Salvage and Preiss-Handler pathways. Compared to the genetic approach, administering NMN as an $NAD^+$ precursor is easier. Restoring $NAD^+$ levels support mitochondrial biogenesis, protects cells against ROS, repairs DNA damage, stimulates neuron regeneration, prevents cell aging, and increases stem cells. NMN also restore vascular dysfunction, suppress weight gain, oxidative stress, increase physical activity, insulin sensitivity, and restore plasma lipid profiles. This mechanism explains the positive impact that NMN can have on aging, Parkinson's, Alzheimer's, obesity, cerebral ischemia, heart disease, and type 2 diabetes. The administration of NMN can be tolerated at low doses but has a negative impact if given at high doses.

***Declaration by Authors***

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## REFERENCES

1. United Nation (UN), Department of Economic and Social Affairs PD. World population prospects 2022. Available from: www.un.org/development/ desa/pd/. Accessed Mar 28, 2022.
2. Kementerian Kesehatan Republik Indonesia. Lansia berdaya bangsa sejahtera. Available from: https://www.kemkes.go.id/article/view/22111500004/2022-lansia-berdaya-bangsa-sejahtera.html. Accessed Mar 28, 2022.
3. Rea IM, Gibson DS, McGilligan V, et al. Age and age-related diseases: Role of inflammation triggers and cytokines. *Front Immunol*. 2018; 9:1–28.
4. Diamanti-Kandarakis E, Dattilo M, Macut D, et al. Aging and anti-aging: A combo-endocrinology overview. *Eur J Endocrinol.* 2017; 176(6):R283–R308.
5. Bieganowski P, Brenner C, Hb R, et al. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to $NAD^+$ in fungi and humans. *Cell.* 2004; 117(4):495–502.
6. Marinescu GC, Popescu R, Dinischiotu A. Size exclusion chromatography method for purification of nicotinamide mononucleotide (NMN) from bacteria cells. *Sci Rep.* 2018; 8(1):1–11.
7. Yamamoto T, Byun J, Zhai P, et al. Nicotinamide mononucleotide, an intermediate of $NAD^+$ synthesis, protects the heart from ischemia and reperfusion. *PLoS One.* 2014; 9(6): e98972.
8. Poddar SK, Sifat AE, Haque S, et al. Nicotinamide mononucleotide: Exploration of diverse therapeutic applications of a potential molecule. *Biomolecules*. 2019; 9(1):34–49.
9. Nadeeshani H, Li J, Ying T, et al. Nicotinamide mononucleotide (NMN) as an anti-aging health product – Promises and safety concerns. *J Adv Res* [Internet]. 2022; 37:267–78. Available from: *https://doi.org/10.1016/j.jare.2021.08.003*

10. Mills KF, Yoshida S, Stein LR, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab.* 2017; 24(6):795–806.
11. Reiten O, Wilvang M, Mitchell S, et al. Preclinical and clinical evidence of $NAD^+$ precursors in health, disease, and ageing. *Mech Ageing Dev* [Internet]. 2021; 199:111–567. Available from: *https://doi.org/10.1016/j.mad.2021.111567*
12. Imai S, Guarente L. $NAD^+$ and sirtuins in aging and disease. *Trends Cell Biol.* 2014; 24(8):464–71.
13. Yoshino J, Mills K, Yoon M, et al. Nicotinamide mononucleotide, a key $NAD^+$ intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. *Cell Metab.* 2012; 14(4):528–36.
14. Massudi H, Grant R, Braidy N et all. Age-associated changes in oxidative stress and $NAD^+$ metabolism in human tissue. *PLoS One*. 2012; 7:e42357.
15. Rappou E, Jukarainen S, Rinnankoski-tuikka R, et al. Weight loss is associated with increased $NAD^+$/SIRT1 expression but reduced PARP activity in white adipose tissue. *J Clin Endocrinol Metab.* 2016; 101(12):63–73.
16. Ryu D, Zhang H, Ropelle ER, et al. $NAD^+$ repletion improves muscle function in muscular dystrophy and counters global PARylation. *Sci Transl Med.* 2017; 8(361):1–29.
17. Amours DD, Desnoyers S, Silva ID, et al. Poly (ADP-ribosyl) ation reactions in the regulation of nuclear functions. *Biochem J.* 1999; 268(2):249–68.
18. Long A, Park J, Klimova N, et al. CD38 knockout mice show significant protection against ischemic brain damage despite high level poly-ADP-ibrosylation. *Neurochem Res.* 2017; 42(1):283–93.
19. Sheline C. Involvement of SIRT1 in $Zn^{2+}$, streptozotocin, non-obese diabetic, and cytokine-mediated toxicities of beta-cells. *J Diabetes Metab.* 2012; 3(3):pii: 1000193.
20. Sasaki Y, Nakagawa T, Mao X, et al. NMNAT1 inhibits axon degeneration via blockade of SARM1-mediated $NAD^+$ depletion. *Elife*. 2016; e19749.
21. Schriewer J, Peek C, Bass J, et al. ROS-mediated PARP activity undermines mitochondrial function after permeability transition pore opening during myocardial ischemia-reperfusion. *J Am Heart Assoc.* 2013; 2(2): e000159.
22. Son M, Kwon Y, Son T, et al. Restoration of mitochondrial $NAD^+$ levels delays stem cell senescence and facilitates reprogramming of aged somatic cells. *Stem Cells.* 2016; 34(12):2840-51.
23. Scheibye-Knudsen M, Mitchell S, Fang E, et al. A high-fat diet and $NAD^+$ activate SIRT1 to rescue premature aging in Cockayne Syndrome. *Cell Metab.* 2014; 20(8):840–55.
24. Wang P, Yang X, Zhang Z, et al. Depletion of NAD pool contributes to impairment of endothelial progenitor cell mobilization in diabetes. *Metabolism*. 2016; 65(8):52–62.
25. Wang Z, Figueiredo-Pereira C, Oudot C, et al. Mitochondrion: A common organelle for distinct cell deaths?. *Int Rev Cell Mol Biol.* 2017; 331:245-87.
26. Canto C, Houtkooper R, Pirinen E, et al. The $NAD^+$ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab.* 2012; 15(6):838-47.
27. Zhang Y, Wang B, Fu X, et al. Exogenous $NAD^+$ administration significantly protects against myocardial ischemia/reperfusion injury in rat model. *Am J Transl Res*. 2016; 8(8):3342–50.
28. Williams P, Harder J, Foxworth N, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. *Science (80- ).* 2017; 355(6326):756-60.
29. Mattson M, Arumugam T. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. *Cell Metab*. 2018; 27(6):1176–99.
30. Fang E, Kassahun H, Croteau D, et al. $NAD^+$ replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. *Cell Metab*. 2016; 24(4):566–81.
31. Yoshino J, Baur J, Imai S. $NAD^+$ intermediates: the biology and therapeutic potential of NMN and NR. *Cell Metab*. 2018; 27(3):513–28.
32. Reiten O, Wilvang M, Mitchell S, et al. Preclinical and clinical evidence of $NAD^+$ precursors in health, disease, and ageing. *Mech Ageing Dev*. 2021; 199:111567.
33. Covarrubias A, Perrone R, Grozio A, et al. $NAD^+$ metabolism and its roles in cellular

processes during aging. *Nat Rev Mol Cell Biol*. 2021; 22(2):119–41.
34. Covarrubias A, Kale A, Perrone R, et al. Senescent cells promote tissue $NAD^+$ decline during aging via the activation of CD38(+) macrophages. *Nat Metab*. 2020; 2(11):1265–83.
35. de Picciotto N, Gano L, Johnson L, et al. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. *Aging Cell*. 2016; 15(3):522–30.
36. Tarantini S, Valcarcel-Ares MN, Toth P, et al. Nicotinamide mononucleotide (NMN) supplementation rescues cerebromicrovascular endothelial function and neurovascular coupling responses and improves cognitive function in aged mice. *Redox Biol* [Internet]. 2019; 24:101192. Available from: *https://doi.org/10.1016/j.redox.2019.101192*
37. Xie X, Yu C, Zhou J, et al. Nicotinamide mononucleotide ameliorates the depression-like behaviors and is associated with attenuating the disruption of mitochondrial bioenergetics in depressed mice. *J Affect Disord*. 2020; 263:166–74.
38. Huang P, Zhou Y, Tang W, et al. Long-term treatment of nicotinamide mononucleotide improved age-related diminished ovary reserve through enhancing the mitophagy level of granulosa cells in mice. *J Nutr Bochemistry*. 2022; 101:108911.
39. Yasuda I, Hasegawa K, Sakamaki Y, et al. Pre-emptive short-term nicotinamide mononucleotide treatment in a mouse model of diabetic nephropathy. *J Am Soc Nephrol*. 2021; 32(6):1355–70.
40. Kiss T, Giles C, Tarantini S, et al. Nicotinamide mononucleotide (NMN) supplementation promotes anti-aging mirna expression profile in the aorta of aged mice, predicting epigenetic rejuvenation and anti-atherogenic effects. *GeroScience*. 2019; 41(4):419–39.
41. Yoshino M, Yoshino J, Kayser B, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*. 2021; 372(6547):1224–9.
42. Irie J, Inagaki E, Fujita M, et al. Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy japanese men. *Endocr J*. 2020; 67(2):153–60.
43. Liao B, Zhao Y, Wang D, et al. Nicotinamide mononucleotide supplementation enhances aerobic capacity in amateur runners: A randomized, double-blind study. *J Int Soc Sports Nutr* [Internet]. 2021; 18(54):1–9. Available from: *https://doi.org/10.1186/s12970-021-00442-4*
44. Katayoshi T, Uehata S, Nakashima N, et al. Nicotinamide adenine dinucleotide metabolism and arterial stiffness after long-term nicotinamide mononucleotide supplementation: a randomized, double-blind, placebo-controlled trial. *Sci Rep* [Internet]. 2023; 13(1):1–9. Available from: *https://doi.org/10.1038/s41598-023-29787-3*
45. Yi L, Maier AB, Tao R, et al. The efficacy and safety of β-nicotinamide mononucleotide (NMN) supplementation in healthy middle-aged adults: a randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial. *GeroScience* [Internet]. 2023; 45(1):29–43. Available from: *https://doi.org/10.1007/s11357-022-00705-1*
46. Demarest T, Babbar M, Okur M, et al. $NAD^+$ metabolism in aging and cancer. *Annu Rev Cancer Biol*. 2019; 3:105–30.

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