FOR DISTRIBUTION TO
HEALTHCARE PROFESSIONALS ONLY

TRU NIAGEN®

ADDING HEALTH TO YEARS™ WITH NIAGEN® (NICOTINAMIDE RIBOSIDE)

Table of Contents

Introduction

Today, most people can expect to live into their sixties and beyond. Yet, while they may be living longer, they are not living healthier as they age. This dynamic has created a paradigm shift in the focus of conversations around healthy aging—from adding years to adding health to years.

Cellular Dysfunction Is Aging

The World Health Organization (WHO) has an established framework for defining and developing care protocols in support of healthy aging.[1] WHO states, "At the biological level, aging results from the impact of the accumulation of a wide variety of molecular and cellular damage over time." This perspective is consistent with the earlier Hallmarks of Aging framework (Table 1) which similarly suggests that cellular health is a central component in nine common characteristics of aging across organisms.

Hallmarks of Aging	
Primary Hallmarks (Causes of Damage)	Genomic Instability
	Telomere Attrition
	Epigenetic Alterations
	Loss of Proteostasis
Anatgonistic Hallmarks (Resposes to Damage)	Deregulated Nutrient Sensing
	Mitochondrial Dysfunction
	Cellular Senescence
Integrative Hallmarks (Culprits of the Phenotype)	Stem Cell Exhaustion
	Altered Intercellular Communication

Table 1
Table adapted from Lopez-Otin, C., et al., The hallmarks of aging. Cell, 2013. 153(6): p. 1194-217.

Both concepts agree an increased allostatic load from exposure to various physiological and metabolic stressors and subsequent epigenetic changes lead to cellular dysfunction. Consequently, a gradual decline in physical and mental capacity occurs, leading to an increased risk of disease over time.

Nicotinamide Adenine Dinucleotide (NAD^+) in Support of Intrinsic Capacity and Healthy Aging

WHO defines healthy aging as "the process of developing and maintaining the functional ability enabling well-being in older age."[1] Functional ability includes all health-related attributes enabling people to be and do what they value. It is determined by the composite of all physical and mental capacities of an individual, the external experiences that form the context of a person's life, and the interactions between the two. Collectively, these factors define what is known as intrinsic capacity (IC).

Specifically, IC is an indicator of our body's ability to maintain vital functions in the face of stress, whether it is aging, poor diet, lack of sleep, a sedentary lifestyle, or immune stress. It is a direct indicator of health. The better an individual responds to stressors, the more resilient they are, and such, the better their overall health status. The same is the case at the cellular level, and nicotinamide adenine dinucleotide (NAD^+) is a primary factor in cells' IC or resilience.

NAD^+ plays a critical role in maintaining healthy mitochondrial and cellular function, activating DNA repair mechanisms, and helping resist the effects of cellular stressors. It is found in every living cell where it drives cellular energy production in the mitochondria and serves as an important signaling molecule for cellular maintenance and repair. Optimizing healthy mitochondrial function and bolstering cellular maintenance and repair are central to maintaining an individual's IC.

Not surprisingly, NAD^+ depletion has emerged as a fundamental feature of cellular dysfunction and aging, with a growing body of evidence linking its declining levels to aging and a variety of health conditions.

Clinically Proven to Boost NAD^+

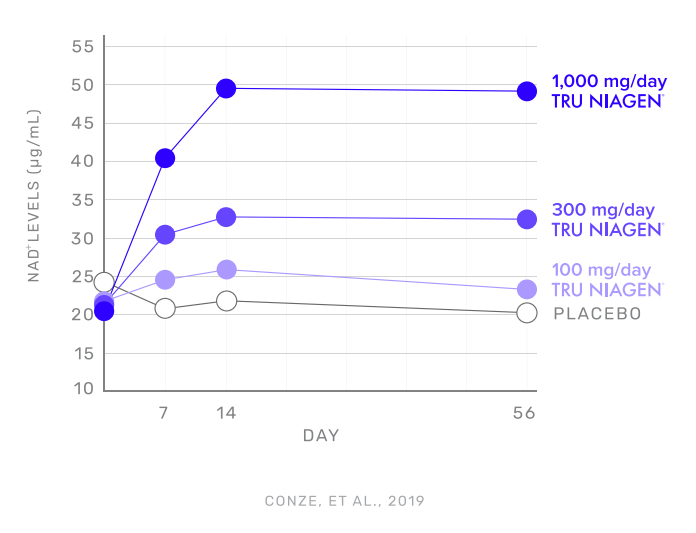
Niagen® nicotinamide riboside (NR) is clinically proven to boost NAD^+, making it an important health optimization tool at the cellular level. By increasing NAD^+, Niagen® promotes mitochondrial health to support the body's natural energy production mechanisms. It has been reviewed and accepted for safety by the leading regulatory bodies in the world, validating it as a trusted key ingredient in Tru Niagen®.

The publication of the first clinical trial of Niagen® in 2016 opened the door to new research assessing NR's ability to address many of the common conditions and challenges associated with aging. With more than 40 registered Niagen® clinical trials and new preclinical studies publishing monthly, NR has gained prominence in the scientific community as a safe and effective way to increase NAD^+ to promote ongoing cellular health over time.

Quick Facts

What Is Niagen® Nicotinamide Riboside?

Niagen® nicotinamide riboside (NR) is the sole active ingredient in Tru Niagen® and Tru Niagen® Pro. It is clinically proven to significantly increase and maintain levels of the essential coenzyme nicotinamide adenine dinucleotide (NAD^+) with continued daily use.[2]*



Niagen®, a nature-identical form of nicotinamide riboside produced by the makers of Tru Niagen® Pro, has twice been successfully reviewed under the FDA's new dietary ingredient (NDI) notification program and has also been successfully notified to the FDA as generally recognized as safe (GRAS).

Supporting Research

Niagen® is a unique form of vitamin B3 proven to safely and effectively increase NAD^+ in humans, as demonstrated by multiple published clinical trials.[2-10]* More than 100 preclinical, peer-reviewed studies have investigated the science behind NR. These studies provide extensive evidence regarding the cellular mechanisms of NR metabolism and the physiological effects of NR supplementation in animal models. At least 40 registered Niagen® clinical trials are now translating this exciting NR research to human health.[11]

To dig into published NR studies, visit **practitioner.truniagen.com** and **aboutnad.com**.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Mechanism Of Action

NR is an NAD^+ precursor that is structurally related to niacin and nicotinamide. It is transported directly into cells via nucleoside transporters, where it is converted to NAD^+ through a unique two-step biosynthetic pathway.[12-14] NR raises intracellular NAD^+ levels with superior pharmacokinetics compared to both niacin, nicotinamide, and nicotinamide mononucleotide (NMN).[3, 13] Research on NMN, a known NR and NAM provitamin and NAD^+ precursor, has also emerged. Multiple studies [12, 13, 15-18] have demonstrated that NMN must be extracellularly converted to NR to increase cellular NAD^+. The phosphate group on NMN is removed by the extracellular enzyme CD73, thereby converting NMN into NR.[16]

By increasing NAD^+ levels, NR promotes mitochondrial health, supporting the body's natural energy production mechanisms and promoting healthy aging.*

Benefits

NAD^+ has been shown to decline with age and metabolic stress.[19-27] Niagen® supports ongoing cellular health by replenishing NAD^+, adding health to years™.* Tru Niagen® Pro:

- **Significantly increases NAD^+***
- **Supports ongoing mitochondrial health***
- **Increases cellular energy production***
- **Supports healthy cellular metabolism***
- **Promotes cellular repair***

Metabolism And Interactions

Clinical pharmacology studies confirm that Niagen® is metabolized similarly to other forms of vitamin B3. Niagen® dose-dependently increases plasma and urinary levels of N'-methyl-4-pyridone-5-carboxamide (Me4PY), and N'-methyl-2-pyridone-5-carboxamide (Me2PY), which are generally considered biomarkers of increased NAD^+ metabolism.[2, 28] Niagen® currently has no known drug interactions. As a novel form of vitamin B3, Niagen® is not anticipated to have any strong drug interactions mediated through cytochrome P450.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Adverse Effects

No serious adverse effects have been attributed to the consumption of Niagen® in double-blind, placebo-controlled clinical trials testing doses as high as 2,000 mg/day for as long as 12 weeks.[2, 5, 6] Nonclinical toxicology studies determined 300 mg/kg/day as the no-observed-adverse-effect-level (NOAEL), and the 1000 mg/kg/day dose was considered the lowest-observed-adverse-effect level (LOAEL).[29]

Mutagenicity, Genotoxicity, Or Toxicity

Bacterial reverse mutation (Ames) assays, in vitro chromosomal aberration assays, and in vivo micronucleus assays showed no elevation of mutagenicity, genotoxicity, or toxicity with Niagen® compared to controls.[29]

What Is Niagen® Nicotinamide Riboside?

Tru Niagen® products contain nicotinamide riboside (NR), a structurally unique, naturally occurring member of the vitamin B3 family (Figure 1).[30] Vitamin B3s serve as cellular building blocks for the essential coenzyme nicotinamide adenine dinucleotide (NAD^+). Vitamin B3 is an essential nutrient that must be consumed at adequate levels in the diet to avoid the deficiency disease pellagra.

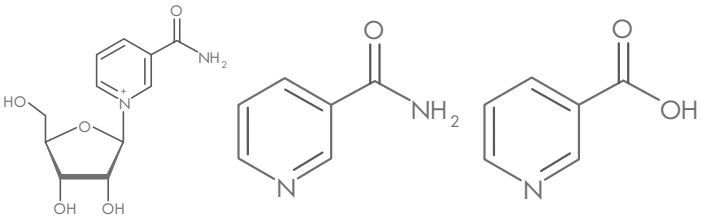


FIGURE 1. NR (LEFT), NAM (MIDDLE), NA (RIGHT)

The recommended daily allowance (RDA) is typically met through the consumption of whole foods such as meats, rice, legumes, and fortified processed foods, such as cereals and whole-grain flours.

While this level of vitamin B3 consumption is sufficient to avoid deficiency disease, vitamin B3 requirements for supporting optimal health have not yet been established. Some scientists have hypothesized that a subclinical NAD^+ deficiency is a common factor in aging—a process marked by a significant decline in NAD^+ levels.[19-22, 31, 32]

Mounting evidence suggests that consuming higher levels of vitamin B3, especially NR, may be beneficial for health optimization and avoiding some of the physiological changes that precede age-associated disease.[33-37] The beneficial effects of NR are mediated through its primary roles as a precursor of NAD^+.

NAD^+: Vital to Cells and Healthy Aging

NAD^+ is an essential coenzyme known for its role in cellular respiration and other metabolic processes. It is found in all living cells, where it and its phosphorylated form, nicotinamide adenine dinucleotide phosphate ($NADP^+$), serve as electron carriers in a wide variety of oxidation-reduction (redox) reactions. These reactions are involved in everything from fatty acid synthesis and the urea cycle to alcohol metabolism and steroid hormone synthesis.

During cellular respiration, the oxidized form of NAD^+ accepts electrons from food metabolites. The reduced form of NAD^+, NADH, then delivers these electrons to the mitochondrial electron transport chain to drive regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) via oxidative phosphorylation.

Beyond its vital role in cellular metabolism, NAD^+ is now known to provide an important link between cell signaling, metabolism, and repair. NAD^+ serves as a substrate for three classes of NAD-consuming enzymes (Figure 2).
NAD^+ signaling impacts a wide variety of cellular activities including DNA repair, regulation of circadian gene expression, and healthy mitochondria maintenance. [38-40]

Healthy cells have regulated signaling (especially nutrient sensing) to ensure they are responding appropriately to external cues. They have effective mitochondria supported by mitochondrial maintenance and repair pathways (e.g., mitophagy, antioxidants, UPRmt) to generate enough cellular energy and limit oxidative stress. Maintaining cellular health leads to physiological benefits at the level of tissues and organs, including limiting senescent cell accumulation, maintaining healthy intracellular communication (i.e., reducing dysregulated inflammation), and keeping a healthy supply of adult stem cells to support tissue regeneration.[41]

Because of its ability to connect cell signaling pathways with cellular energy metabolism, NAD^+ is often described as an energy sensor. NAD^+ levels, which can be influenced by changes in absolute NAD^+/NADH levels or shifts in NAD^+/NADH ratios, help cells modify their behaviors in response to changes in energy and nutrient availability. These signaling pathways are integrated within larger nutrient signaling networks governed by AMPK and mTOR.[42, 43]

Some scientists have hypothesized that NAD-boosting strategies may act as calorie restriction mimetics by activating cellular maintenance enzymes (such as sirtuins) and signaling cells to shift toward the conservation mode associated with low nutrient availability.[5]

This mechanism is conserved in virtually all organisms, from yeast to flies, to worms, rodents, primates, and humans, and is linked to both increased lifespan and healthspan.[44]

NAD^+-Consuming Enzymes

Sirtuins. The seven mammalian sirtuins (SIRTs) localize throughout the cell, where they deacetylate target proteins in a NAD-dependent manner.[44] By post-translationally modifying target proteins such as SOD2 (a free radical scavenger) and PGC-1α (the master regulator of mitochondrial biogenesis), sirtuins can direct a wide range of cellular behaviors in response to changes in NAD^+ levels. Furthermore, SIRTs play a significant role in inflammation.
SIRT1 suppresses the activity of NF-□β, which downregulates COX-2 and iNOS production and upregulates the expression of antioxidant genes known to suppress inflammation.
And SIRT2, 6, and 7 suppress the NF-□β signaling pathway.[46]

PARPs. Poly(ADP-ribose) polymerases (PARPs) modify their target substrates by adding one or more ADP-ribose (ADPR) moieties derived from the consumption of NAD^+. Although mammals express seventeen different PARPs with a range of emerging functions, most research has focused on PARP1 and its role in DNA repair.[47] Additionally, PARPs affect immune cell maturation and differentiation and regulate the expression of cytokines, chemokines, and other inflammatory mediators.[48]

NADases. These NAD-consuming enzymes degrade large quantities of NAD^+. Cyclic ADP-ribose (cADPR) synthases, including CD38 and CD157, are integral cell membrane proteins that convert NAD^+ into ADPR and small amounts of cADPR second messengers involved in calcium signaling. Because they can degrade large quantities of NAD^+, these enzymes are hypothesized to be drivers of age-associated changes in NAD^+ levels.[49, 50] A more recently discovered NADase called SARM1 is thought to drive NAD^+ depletion and axonal degeneration in injured neurons.[51]

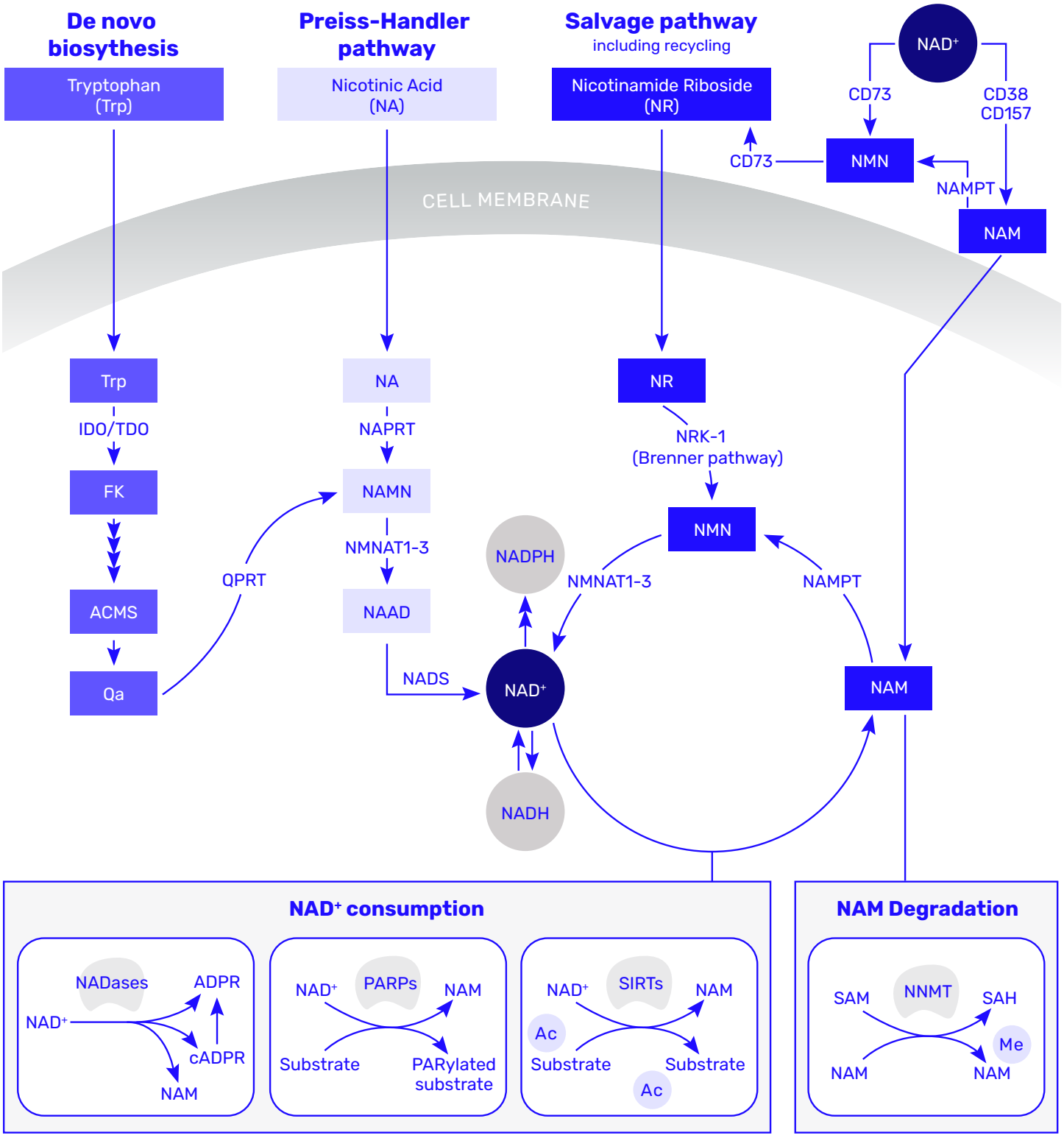


FIGURE 2. CONSUMPTION AND BIOSYNTHESIS OF NAD+

Figure adapted from Fang, E.F., et al., NAD(+) in Aging: Molecular Mechanisms and Translational Implications. Trends Mol Med, 2017. 23(10): p. 899-916.

NAD⁺ Declines With Age And Disease

Once thought to be a conserved cellular resource, NAD⁺ levels have recently been demonstrated to decline with age, metabolic stress, and in conditions of injury and disease. These findings have been highlighted in recent review articles. They are summarized in Table 1.[33-37] Observed declines in NAD⁺ levels have reignited scientists' interest in NAD's role in human health and have inspired new investigations into NAD-boosting therapies.

TABLE 1. NAD⁺ DECLINE IN MAMMALS

**Observed in human tissues Values for "% of normal" represent the approximate percentage of NAD⁺ observed compared to a young or healthy control. These have been estimated from graphs when not stated in the cited reference. In most cases, a decrease in NAD⁺ cannot be distinguished from a shift in the NAD⁺/NADH ratio.*

Table based on data from Yoshino, J., et al. NAD(⁺) Intermediates: The Biology and Therapeutic Potential of NMN and NR. Cell Metab, 2018. 27(3): p. 513-528.

CONDITION	TISSUE	% OF NORMAL	REFERENCES
Aging	Muscle	30-85%	49, 52-58
	Liver	40-90%	21, 49, 53, 55, 56,
	Adipose	55-75%	49, 53
	Brain	35-90%	22, 60-62
	Pancreas	80-85%	53
	Spleen	35-40%	49
	Heart	30-70%	59, 63
	Kidney	15-98%	56, 59, 64
	Lung	20-25%	59
	Cerebrospinal Fluid	86%	19*
	Skin	40-50%	20*
	Blood Plasma	15-92%	19*, 32*
	Testes	100%	63
Obesity	Liver	85-100%	24, 53, 65-67
	Adipose	15-20%	53
	Muscle	80-100%	53, 68
Overnutrition	Muscle	66%	26*
	Liver	100%	69
	Blood Plasma	46%	25*
Duchenne Muscular Dystrophy	Muscle	45-75%	70, 71
Noise Injury	Cochlea	40-50%	72
Heart Failure	Heart	70%	73
Alcohol Injury	Liver	55-75%	27
Liver Regeneration	Liver	60-70%	74
Ataxia Telangiectasia	Brain	40%	75
Axonal Degeneration	Nerve	30%	76
	Brain	53%	77
	Eye	64%	78
Alzheimer's Disease	Brain	50%	79
Cockayne's Syndrome (CS)	Brain	40-60%	61
Type 2 Diabetes	Liver	63-67%	53, 67
	WAT	43%	53
	Muscle	98%	53
Congenital Malformations	Plasma	19%	80*
	Blood Serum	57-80%	80
Non-Alcoholic Fatty Liver Disease	Liver	25-80%	21, 24, 81
Disease (NAFLD)			
Cataract	RBC	68%	82*

*Observed in human tissues Values for "% of normal" represent the approximate percentage of NAD⁺ observed compared to a young or healthy control. These have been estimated from graphs when not stated in the cited reference. In most cases, a decrease in NAD⁺ cannot be distinguished from a shift in the NAD⁺/NADH ratio.

NAD^+ Biosynthesis

Ongoing NAD^+ biosynthesis is supported by the nutritional intake of NAD^+ precursors. Dietary NAD^+ precursors include the amino acid tryptophan and vitamin B3s, niacin and nicotinamide. Although NR is naturally found in trace amounts in cow milk, an eight-ounce serving of milk contains less than a few hundred micrograms of NR—more than 1,000 times less than the amount found in a single recommended serving of Tru Niagen® Pro.[83]

Multiple biosynthetic pathways support NAD^+ synthesis (Figure 2 on page 10)

De Novo Pathway. The de novo biosynthesis pathway converts the amino acid tryptophan into NAD^+ through eight enzymatic steps. Because intermediates of this pathway feed into other metabolic processes, the conversion of tryptophan to NAD^+ is less efficient than the other pathways.[84] Approximately 60 mg tryptophan is required to generate the same NAD^+ as 1 mg of niacin.[85]

Preiss-Handler Pathway. The Preiss-Handler pathway converts dietary NA into NAD^+ through three enzymatic steps.

Salvage Pathway. The salvage pathway recycles NAM, the byproduct of NAD-consuming reactions, back into NAD^+ through two enzymatic steps. The salvage pathway is also responsible for converting dietary NAM into NAD^+.

NR Pathway (Brenner). In 2004, Dartmouth scientists led by Dr. Charles Brenner, now Alfred E. Mann chair of the new Department of Diabetes & Cancer Metabolism at City of Hope National Medical Center in California, discovered that eukaryotic cells possess a unique pathway to convert NR into NAD^+.[14] Dietary NR can enter cells through nucleoside transporters.[12, 13] Once inside the cell, nicotinamide riboside kinases (NRKs) phosphorylate NR to create nicotinamide mononucleotide (NMN). NMN is then converted to NAD^+ through the second step of the salvage synthesis pathway.

NMN, NAD^+, and NADH have also been promoted as NAD-boosting strategies, either through oral supplements or intravenous delivery. However, the ability of cells to use these molecules to boost intracellular NAD^+ pools combined with a general lack of rigorous clinical safety data have limited the usefulness of these molecules as approaches for increasing NAD^+ in the human body.

Nicotinamide Mononucleotide (NMN). NMN's safety and efficacy are only just beginning to be established through human clinical trials, and it has not yet achieved New Dietary Ingredient (NDI) or GRAS status. So far, only one study has been published, demonstrating the tolerability of single doses of NMN but does not show its effects on NAD^+ levels in the body.[86] Because of its negatively charged phosphate group, NMN cannot enter cells without first being converted to NR by dephosphorylation. One research group has claimed to identify an NMN transporter, which appears to be primarily expressed in the mouse small intestine. However, other researchers have yet to replicate the results, and the presence of an NMN transporter in other tissues has not been established.[87] In contrast, multiple studies from different research groups have been published, demonstrating that NMN must be extracellularly converted to NR to support intracellular NAD^+ synthesis.[12, 13, 15, 88] In mice, loss of NRK activity affects both NR and NMN's ability to boost NAD^+ levels—a result that would only be expected if NMN is converted to NR before entering the cell.[13, 15]

Nicotinamide Adenine Dinucleotide (NAD^+/NADH). Although NAD^+ and NADH have been the subject of a handful of clinical studies, a lack of rigorous toxicology, pharmacokinetic, and clinical safety data has raised questions about their use in humans. Only one study published to date has investigated the metabolic fate and pharmacokinetic properties of intravenously administered NAD^+ in humans.[89] During digestion, orally administered NAD^+ breaks down into smaller precursors. At the same time, oral NADH degrades into unidentified metabolites that are not metabolized by the body in the same way as either NAD^+ or NAM.[90] The size and instability of these molecules also limit their value as supplements. A briefing document issued by the FDA opined that NAD^+ is unlikely to remain stable under ordinary storage conditions.[91] During a clinical study, researchers had to split a single 250 mg dose of NAD^+ into two 125 mg capsules to make them easier for patients to swallow.[92]

NR Is A Unique NAD⁺ Precursor

In addition to using a novel pathway to synthesize NAD⁺, NR has several unique features that differentiate it from the other vitamin B3s. Most notably, NR does not cause the same uncomfortable flushing response commonly triggered by high-dose NA supplementation. NA induces flushing through activation of the G-protein coupled receptor GPR109A.[93] NR does not interact with this receptor and has not been shown to cause flushing in clinical trials of doses as high as 2,000 mg/day.[2-10, 94]

Pharmacokinetics. When tested head-to-head in mice, NR, NA, and NAM showed distinct pharmacokinetic properties, increasing various hepatic NAD⁺ metabolites to different degrees and over different time scales. Specifically, NR increased NAD⁺ more effectively than NA and stimulated production of ADPR—the product of NAD-consuming enzymatic reactions—more effectively than NAM.[3] This last finding is consistent with in vitro experiments showing that NAM is a potent inhibitor of sirtuin activity.[95, 96]

More recent research supports an emerging theme in which the different NAD⁺ biosynthetic pathways respond uniquely to age and stress. The enzyme nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the rate-limiting step of the salvage pathway that converts NAM to NAD⁺. NAMPT levels have been shown to decrease with age in both mice and humans.[21, 54] In contrast, expression of the NRK enzymes, which catalyze the first step of the NR pathway, has been shown to increase under metabolic stress conditions. In two different mouse models of heart failure, NRK2 expression increased while NAMPT expression decreased.[73, 97] A similar shift in NRK2 expression was observed in human samples from heart failure patients versus healthy human controls.[73] Increased NRK1 and NRK2 expression has also been observed in injured mouse and rat neurons.[18, 98]

Bioavailability. Some questions have been raised over the oral bioavailability of NR. Many of these concerns stem from a single preclinical pharmacokinetic study tracking the metabolic fate of isotopically labeled NR.[99] The study's authors concluded that most orally administered NR was metabolized to NAM in the liver and delivered to systemic tissues as NAM rather than NR. Some NR is expected to be metabolized to NAM in the liver during first-pass metabolism to support the enhanced hepatic NAD⁺ flux observed after NR supplementation.[3] However, this one study does not represent the final word on the bioavailability of oral NR.

Indeed, a growing body of preclinical evidence demonstrates that oral NR and NAM are not physiologically equivalent. Some oral NR is delivered to tissues without change. Notably, oral NR supplementation rescues deficits in skeletal muscle function caused by the loss of NAMPT activity, demonstrating that NR can elicit physiological benefits without the need for NAM salvage pathway activity.[54] Oral NR has also been shown to significantly increase NAD⁺ in the failing mouse heart and promote hematopoietic stem cell expansion in mice—benefits that oral NAM could not replicate.[73, 100]

Endogenous Requirement. The uniqueness of NR compared to NAM is further underscored by a recent study examining the consequences of losing the ability to synthesize NAD⁺ from NR.[69] The researchers created mice lacking NRK enzyme activity. Their liver cells became less resilient to metabolic stress caused by a high-fat diet and were predisposed to developing nonalcoholic fatty liver disease. NAM supplementation could not fully compensate for the inability to use NR to make NAD⁺. Although more research is needed to fully understand NR's unique properties compared to other precursors, this study suggests that under conditions of metabolic stress, cells specifically seek out and require NR to maintain NAD⁺ levels.

Preclinical Findings

More than 100 peer-reviewed preclinical studies have investigated the science behind NR. These studies have characterized the biochemical pathway converting NR to NAD^+ and have provided important information about the pharmacokinetic and physiological effects of NR supplementation (recently reviewed by Katsyuba & Auwerx.[33] Together, these studies show that NR supplementation can support the health and resiliency of aging and metabolically challenged cells.

Mechanistically, NR has been shown to support mitochondrial function in many different types of cells and tissues. Loss of mitochondrial efficiency is recognized as a hallmark of aging and is associated with physiological decline and disease in metabolically active tissues such as the brain, heart, liver, and skeletal muscle.[41, 101-104] In addition to increasing cellular NAD^+ availability for energy production, NR supplementation promotes mitochondrial health by bolstering mitochondrial repair pathways that counteract and mend the oxidative damage induced by overactive and stressed mitochondria. NR has been shown to upregulate mitochondrial autophagy (i.e., mitophagy), stimulate the mitochondrial unfolded protein response (UPRmt), and activate the free radical scavenger superoxide dismutase (SOD).[23, 24, 55, 57, 100, 105, 106]

Together, these activities help maintain the respiratory capacity and energy-generating efficiency of metabolically stressed mitochondria.

Numerous studies have reported promising physiological outcomes of NR supplementation in rodent models of aging, metabolic stress, and a variety of disease states. The wide-ranging effects of nutritionally boosting NAD^+ make sense given the fundamental importance of NAD^+ for healthy cellular metabolism, energy production, and healthy aging. Consistent with NR's ability to support mitochondrial health, many of NR's preclinical benefits have been demonstrated in metabolically active cells and tissues.

NAD^+ and the Intrinsic Capacity Domains

Five IC domains that represent key research areas focused on NAD^+ and its impact on cellular function and health: cognition, locomotion, sensory, psychological, and vitality.

Each cover a core set of functions collectively reflecting the needs required to add health to years™ through improvements in healthspan - i.e., the ability to move, think, see, hear, remember, and recover.[107]

Preclinical studies in animal models [23, 24, 27, 54, 55] demonstrate that increasing NAD^+ status provides benefits well beyond the prevention of pellagra, including improvements in basic cellular processes to support the health of a wide variety of tissues under stress.

The benefits of nutritionally boosting NAD^+ make sense given the fundamental importance of NAD^+ for healthy cellular metabolism, energy production, and the wide-ranging physiologic stresses we all face in the modern world.

INTRINSIC CAPACITY DOMAIN	SUBDOMAINS	PHYSIOLOGICAL OUTCOMES
Cognition	• Memory • Intelligence • Problem Solving	Improves cognition in models of Alzheimer's disease[79, 106, 109, 109]
		Ameliorates neurodegenerative disease symptoms [61, 75, 110]
		Reduces brain inflammation and improves cognition in diabetic mice [111, 112]
Locomotion	• Muscle Function • Muscle Strength • Muscle Repair & Recovery • Excercise Performance • Balance • Gait	Improves muscle strength and endurance in aged mice [57]
		Improves muscle function in models of muscular dystrophy [57, 113, 114]
		Enhances the effects of exercise training on aerobic performance [115]
		Improves pectoralis muscle weight, length, width, and depth in chicks[116]
Sensory	• Hearing • Vision • Neuropathies (e.g. peripheral neuropathy, diabetic neuropathy)	Opposes chemotherapy-induced peripheral neuropathy [117, 118]
		Protects against noise-induced and age-related hearing loss [72, 119, 120]
		Protects against light-induced retinal degeneration [121]
		Protects against axon loss in model of optic nerve degeneration [122]
Psychological	• Mood • Emotional Vitality	Improves alcohol-induced depressive behavior [123]
		Corrects social deficits and fearful/anxiety-like behaviors in autistic mice [124]

continued page 16

These studies and more are available on the Tru Niagen® NAD+ Education Hub. This practitioner-exclusive database contains published clinical trials, preclinical studies, and review articles detailing the ability of NAD^+ and NR to support human health.

To request access, visit **Practitioner.TruNiagen.com**

INTRINSIC CAPACITY DOMAIN	SUBDOMAINS	PHYSIOLOGICAL OUTCOMES
Vitality	• Energy Metabolism • Cardio-respiratory Function • Inflammation & Immuity • Hormonal Function • Fertility & Reproduction	Protects the liver against fibrosis and non-alcoholic fatty liver disease [21, 24, 125-127]
		Counteracts the metabolic consequences of high-fat diet [23]
		Opposes type 2 diabetes and diabetic neuropathy [67]
		Counteracts liver damage induced by alcohol [27]
		Improves symptoms of mitochondrial myopathy [128, 129]
		Promotes liver regeneration after partial hepatectomy [74]
		Supports metabolic health of postpartum mothers and offspring [130]
		Preserves cardiac function in models of heart failure [73, 97, 105, 131]
		Promotes ongoing health and proliferation of hematopoietic stem cells [100]
		Restores "younger" clock function,, circadian mitochondrial function, and circadian behaviors in old mice [132]
		Inhibits endothelial inflammation and improved nitric oxide-dependent function [88]
		Reduces viral replication in a murine hepatitis virus (MHV) infection model [133]
		Reduces gene expressions of proinflammatory cytokines [10]
		Increases live birth rate, ovulatory potential, and oocyte quantity and quality [134]
Numerous studies have reported promising physiological outcomes of NR supplementation for aging, metabolic stress, and a variety of disease states in rodent models. The broad effects of nutritionally boosting NAD^+ makes sense given the fundamental importance of NAD^+ for healthy aging, cellular metabolism, and energy production. Consistent with NR's ability to support mitochondrial health, many of NR's preclinical benefits have been demonstrated in metabolically active cells and tissues.		
* Source for IC domains: [107]		

These studies and more are available on the Tru Niagen® NAD+ Education Hub. This practitioner-exclusive database contains published clinical trials, preclinical studies, and review articles detailing the ability of NAD^+ and NR to support human health.

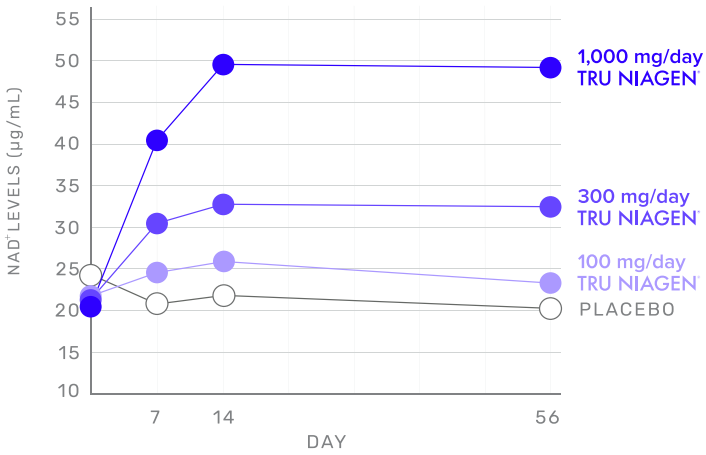
To request access, visit **Practitioner.TruNiagen.com**

Clinical Evidence

Several clinical trials of Niagen® NR have been published to date. These studies consistently show that Niagen® is well-tolerated and significantly increases NAD^+ levels in human blood and blood cells. Clinical pharmacology studies demonstrate that Niagen® increases NAD^+ levels in a dose-dependent manner. On average, consumption of 100 mg, 300 mg, and 1000 mg Niagen® increases blood NAD^+ by 22%, 51%, and 142%, respectively. These new elevated NAD^+ levels are reached after approximately two weeks and are maintained with continued once daily (q.d.) supplementation (Figure 3).[2]

The first clinical trial established the safety and efficacy of single-dose NR supplementation.[3] Initial studies of daily Niagen® supplementation demonstrated the tolerability of chronic Niagen® supplementation at doses as high as 2,000 mg/day for as long as 12 weeks.[6] These trials also provided exciting preliminary evidence for the potential of Niagen® to support both cardiovascular and liver health.[5, 6] More recent clinical studies are now beginning to investigate the effect of Niagen® on NAD^+ in tissues beyond blood. Niagen® has been shown to statistically significantly increase multiple NAD^+ metabolites in human skeletal muscle, indicating that it effectively enhances NAD^+ turnover in this tissue.[7, 8] No attributable serious adverse events have been reported in any Niagen® clinical studies, and daily Niagen® supplementation is not associated with changes in either LDL cholesterol or plasma homocysteine.[2]

In the first of its kind to date, a multi-collaborator Phase II clinical trial examined the effect of a proprietary blend of nutrients aimed at mitochondrial health, including Niagen® NR, on the recovery time of mild-to-moderate COVID-19 patients. The study, conducted at the Umraniye Teaching and Research Hospital in Istanbul, Turkey, and led by researchers from Sweden, China and the UK, compared the effect of a daily nutritional cocktail (termed "combined metabolic cofactor supplementation" or CMCS) plus the standard of care (SOC) in Turkey (hydroxychloroquine) to the SOC plus placebo. After 14 days, the investigators found on average, the SOC +



CONZE, ET AL., 2019

FIGURE 3. EFFECT OF DAILY NIAGEN® SUPPLEMENTATION ON NAD^+ LEVELS

CMCS recovered nearly 30% faster (6.6 days) than the SOC + placebo group (9.3 days). The CMCS group also experienced an improvement in liver function relative to the placebo group[135] (Altay). The CMCS consisted of Niagen NR, along with L-serine, L-carnitine and N-acetylcysteine. This collection of nutrients has been shown to positively impact mitochondrial and liver function[9] and is currently being studied in a Phase III trial for nonalcoholic fatty liver disease (NAFLD). The breakthrough findings from this Phase II trial are consistent with the results from preclinical studies on NR and coronavirus, as well as the clinical studies demonstrating an anti-inflammatory effect of supplemental NR.

More than 40 ongoing and published Niagen® clinical trials are currently registered, with new clinical trials added regularly.[11] 14 of these trials are sponsored by the National Institutes of Health (NIH). To see the most up-to-date list of registered clinical trials, visit **clinicaltrials.gov** and search for "nicotinamide riboside."

Niagen® Dosage And Administration

Niagen®, a branded NR produced by the makers of Tru Niagen® nutraceuticals, has twice been successfully reviewed under the FDA's new dietary ingredient (NDI) notification program, and has also been successfully notified to the FDA as generally recognized as safe (GRAS). Niagen® has undergone rigorous toxicological testing using FDA accepted and internationally standardized protocols.[29] Published clinical trials support safety for up to 2,000 mg/day for up to 12 weeks.[6] Niagen® is bioavailable after oral administration and is clinically proven to increase NAD^+ levels in a dose-dependent manner (Figure 4).[2, 3]

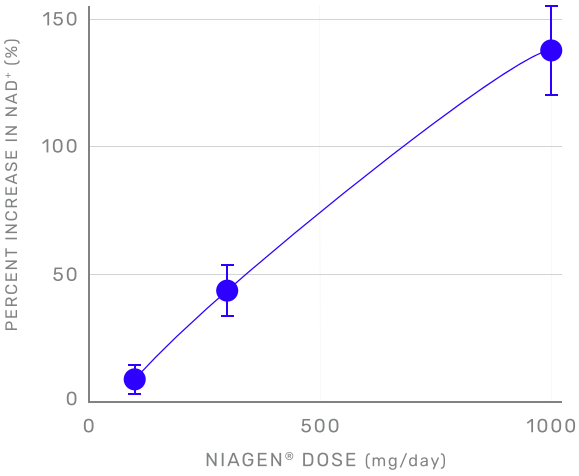


FIGURE 4. ESTIMATED NIAGEN® DOSE RESPONSE

This Niagen® dose-response curve was generated using quadratic least squares fit of empirical clinical data. Clinical data show the average effect of eight weeks of daily supplementation of 100 mg, 300 mg, and 1000 mg Niagen® in 96 subjects (error bars represent standard error). Clinical data was originally reported in Conze, D., C. Brenner, and C.L. Kruger, Safety and Metabolism of Long-term Administration of NIAGEN (nicotinamide riboside chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults. Sci Rep, 2019. 9(1): p. 9772.

Interactions

Niagen® currently has no known drug interactions. As a form of vitamin B3, Niagen® is not anticipated to have any strong drug interactions mediated through cytochrome P450. In an unpublished in vitro analysis of human liver, NR did not have any inhibitory effects on CYP2C8 and CYP3A4, nor did it induce expression of CYP1A2, CyP2B6, CYP3A4, or CYP2C8 in cultured human hepatocytes.

Clinical Pharmacology

Pharmacokinetic analyses demonstrate that the body metabolizes Niagen® as a form of vitamin B3.[2, 3] An eight-week randomized, placebo-controlled trial of 140 overweight but otherwise healthy adults published in the Nature journal Scientific Reports reported the mean concentrations of NAD^+ metabolites in urine and plasma. N'-methylnicotinamide (MeNAM) and N'-methyl-4-pyridone-3-carboxamide (Me2Py) was significantly elevated in blood and urine in a dose-dependent manner after daily ingestion of 100 mg, 300 mg, or 1000 mg Niagen®. Normal metabolism of NAM and NAD^+ in humans also leads to the production of these metabolites, and they are generally considered to be biomarkers of increased NAD^+ metabolism.[28] Additional clinical trials have supported these pharmacological findings.[3-6, 8]

Nonclinical Toxicology

A safety assessment of NR published in the journal Human and Experimental Toxicology demonstrated the safety of orally administered Niagen® at intake levels of 0 mg, 300 mg, 1000 mg, and 3000 mg/kg/day for 90 consecutive days.[29] Administration of NAM, which has been used clinically in humans for more than 40 years, was administered at 1260 mg/kg/day as a positive control. Administration of Niagen® at 300 mg/kg/day did not result in treatment-related adverse effects in any of the measured parameters. A slight decrease (8%) in body weight measured on day 90 was considered adaptive. The no-observed-adverse-effect-level (NOAEL) was determined to be 300 mg/kg/day. Niagen® administration at 1000 mg/kg/day resulted in mild treatment-related organ weight changes, and changes in neutrophils, alanine aminotransferase, and triglycerides in female rats. Liver effects at 1000 mg/kg/day were considered treatment-

related but mild and potentially adaptive. The 1000 mg/kg/day dose was considered the lowest-observed-adverse-effect level (LOAEL). Adverse effects at 3000 mg/kg/day included treatment-related organ weight changes in liver, kidneys, testes, epididymides, and ovaries; decreased food consumption; decreased body weight; and increases in clinical chemical parameters related to hepatocyte function. Similar adverse effects were noted for animals receiving NAM, which has been administered safely at high doses to humans to treat various health concerns for more than 40 years.[29]

Mutagenicity And Genotoxicity

Bacterial reverse mutation (Ames) assays were performed in compliance with the Organization for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practices (GLP) and Guideline No. 471. Niagen® was not cytotoxic at any of the doses tested and did not increase the number of mutation colonies in any tester strain, compared to the vehicle control. To test for genotoxicity of Niagen®, in vitro chromosomal aberration assays were performed in compliance with the OECD Principles of PLG, Guideline No. 473. Niagen® was not cytotoxic to ex vivo human peripheral blood lymphocytes at any concentration tested. In vivo micronucleus assays were performed in compliance with the OECD Principles of GLP, Guideline No. 474. No mortalities or clinical signs of toxicity were observed in any of the rats receiving Niagen®.[29]

Supply, Storage and Handling

Niagen® NR is available in different products, including Tru Niagen® and Tru Niagen® Pro capsules. Tru Niagen® is supplied in capsules containing 300 mg Niagen®. Tru Niagen® Pro is available in 300 mg or 500 mg per capsule formulations. Niagen® is also available in a powder form as Tru Niagen® stick pack. Each Tru Niagen® stick pack delivers 300 mg Niagen® NR and a good source of fiber (3 g inulin). Containers, capsules, and stick packs should be stored in a cool, dry place protected from heat, moisture, and bright light.

To learn more about Tru Niagen® products, visit **practitioner.truniagen.com**.

Product Usage & Recommendations

Tru Niagen® labeling recommends one capsule daily for a total of 300 mg/day. Tru Niagen® Pro delivers 300 mg or 500 mg of Niagen® with one capsule consumed daily, or as recommended by the healthcare provider. These instructions allow healthcare professionals to have more flexibility in providing their patients with daily dose recommendations that are customized to patient needs.
Tru Niagen® products can be taken morning or evening, with or without food. They are not associated with stomach upset or any other serious adverse reactions.

Have additional questions?

Please email us at **practitioner@truniagen.com**

References

1. *Organization, W.H., World Report on Ageing and Health. 2015: World Health Organization.*
2. *Conze, D., C. Brenner, and C.L. Kruger, Safety and Metabolism of Long-term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults. Sci Rep, 2019. 9(1): p. 9772.*
3. *Trammell, S.A., et al., Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nat Commun, 2016. 7: p. 12948.*
4. *Airhart, S.E., et al., An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. PLoS One, 2017. 12(12): p. e0186459.*
5. *Martens, C.R., et al., Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults. Nat Commun, 2018. 9(1): p. 1286.*
6. *Dollerup, O.L., et al., A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. Am J Clin Nutr, 2018.*
7. *Elhassan, Y.S., et al., Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD(+) Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures. Cell Rep, 2019. 28(7): p. 1717-1728 e6.*
8. *Remie, C.M.E., et al., Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. Am J Clin Nutr, 2020.*
9. *Zhang, C., et al., The acute effect of metabolic cofactor supplementation: a potential therapeutic strategy against non-alcoholic fatty liver disease. Mol Syst Biol, 2020. 16(4): p. e9495.*
10. *Zhou, B., et al., Boosting NAD Level Suppresses Inflammatory Activation of PBMCs in Heart Failure. Journal of Clinical Investigation, 2020.*
11. *ClinicalTrials.gov. [cited 2020 September 9]; Available from: https://clinicaltrials.gov/ct2/results?cond=&term=nicotinamide &state=&city=&dist=.*
12. *Nikiforov, A., et al., Pathways and subcellular compartmentation of NAD biosynthesis in human cells: from entry of extracellular precursors to mitochondrial NAD generation. J Biol Chem, 2011. 286(24): p. 21767-78.*
13. *Ratajczak, J., et al., NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. Nat Commun, 2016. 7: p. 13103.*
14. *Bieganowski, P. and C. Brenner, 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): p. 495-502.*
15. *Fletcher, R.S., et al., Nicotinamide riboside kinases display redundancy in mediating nicotinamide mononucleotide and nicotinamide riboside metabolism in skeletal muscle cells. Mol Metab, 2017. 6(8): p. 819-832.*
16. *Grozio, A., et al., CD73 protein as a source of extracellular precursors for sustained NAD+ biosynthesis in FK866-treated tumor cells. J Biol Chem, 2013. 288(36): p. 25938-49.*
17. *Sociali, G., et al., Antitumor effect of combined NAMPT and CD73 inhibition in an ovarian cancer model. Oncotarget, 2016. 7(3): p. 2968-84.*
18. *Vaur, P., et al., Nicotinamide riboside, a form of vitamin B3, protects against excitotoxicity-induced axonal degeneration. FASEB J, 2017. 31(12): p. 5440-5452.*
19. *Guest, J., et al., Changes in oxidative damage, inflammation and [NAD(H)] with age in cerebrospinal fluid. PLoS One, 2014. 9(1): p. e85335.*
20. *Massudi, H., et al., Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. PLoS One, 2012. 7(7): p. e42357.*
21. *Zhou, C.C., et al., Hepatic NAD(+) deficiency as a therapeutic target for non-alcoholic fatty liver disease in ageing. Br J Pharmacol, 2016. 173(15): p. 2352-68.*
22. *Zhu, X.H., et al., In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. Proc Natl Acad Sci U S A, 2015. 112(9): p. 2876-81.*
23. *Canto, C., et al., The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. Cell Metab, 2012. 15(6): p. 838-47.*
24. *Gariani, K., et al., Eliciting the mitochondrial unfolded protein response by nicotinamide adenine dinucleotide repletion reverses fatty liver disease in mice. Hepatology, 2016. 63(4): p. 1190-204.*
25. *Seyedsadjadi, N., et al., High protein intake is associated with low plasma NAD+ levels in a healthy human cohort. PLoS One, 2018. 13(8): p. e0201968.*
26. *Seyssel, K., et al., Regulation of energy metabolism and mitochondrial function in skeletal muscle during lipid overfeeding in healthy men. J Clin Endocrinol Metab, 2014. 99(7): p. E1254-62.*
27. *Wang, S., et al., Nicotinamide riboside attenuates alcohol induced liver injuries via activation of SirT1/PGC-1alpha/mitochondrial biosynthesis pathway. Redox Biol, 2018. 17: p. 89-98.*
28. *Mrochek, J.E., et al., Metabolic response of humans to ingestion of nicotinic acid and nicotinamide. Clin Chem, 1976. 22(11): p. 1821-7.*
29. *Conze, D.B., J. Crespo-Barreto, and C.L. Kruger, Safety assessment of nicotinamide riboside, a form of vitamin B3. Hum Exp Toxicol, 2016.*
30. *Jacobson, M.K. and E.L. Jacobson, Vitamin B3 in Health and Disease: Toward the Second Century of Discovery. Methods Mol Biol, 2018. 1813: p. 3-8.*
31. *Zhang, M. and W. Ying, NAD(+) Deficiency Is a Common Central Pathological Factor of a Number of Diseases and Aging: Mechanisms and Therapeutic Implications. Antioxid Redox Signal, 2018.*
32. *Clement, J., et al., The Plasma NAD+ Metabolome is Dysregulated in 'normal' Ageing. Rejuvenation Res, 2018.*
33. *Katsyuba, E. and J. Auwerx, Modulating NAD(+) metabolism, from bench to bedside. EMBO J, 2017. 36(18): p. 2670-2683.*
34. *Fang, E.F., et al., NAD(+) in Aging: Molecular Mechanisms and Translational Implications. Trends Mol Med, 2017. 23(10): p. 899-916.*
35. *Rajman, L., K. Chwalek, and D.A. Sinclair, Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence. Cell Metab, 2018. 27(3): p. 529-547.*
36. *Verdin, E., NAD(+) in aging, metabolism, and neurodegeneration. Science, 2015. 350(6265): p. 1208-13.*
37. *Yoshino, J., J.A. Baur, and S.I. Imai, NAD(+) Intermediates: The Biology and Therapeutic Potential of NMN and NR. Cell Metab, 2018. 27(3): p. 513-528.*
38. *Surjana, D., G.M. Halliday, and D.L. Damian, Role of nicotinamide in DNA damage, mutagenesis, and DNA repair. J Nucleic Acids, 2010. 2010.*

39. Nakahata, Y. and Y. Bessho, The Circadian NAD(+) Metabolism: Impact on Chromatin Remodeling and Aging. Biomed Res Int, 2016. 2016: p. 3208429.
40. Canto, C. and J. Auwerx, Targeting sirtuin 1 to improve metabolism: all you need is NAD(+)? Pharmacol Rev, 2012. 64(1): p. 166-87.
41. Lopez-Otin, C., et al., The hallmarks of aging. Cell, 2013. 153(6): p. 1194-217.
42. Carroll, B. and V.I. Korolchuk, Nutrient sensing, growth and senescence. FEBS J, 2018. 285(11): p. 1948-1958.
43. Galluzzi, L., et al., Metabolic control of autophagy. Cell, 2014. 159(6): p. 1263-76.
44. Hwangbo, D.S., et al., Mechanisms of Lifespan Regulation by Calorie Restriction and Intermittent Fasting in Model Organisms. Nutrients, 2020. 12(4).
45. Zhang, N. and A.A. Sauve, Regulatory Effects of NAD(+) Metabolic Pathways on Sirtuin Activity. Prog Mol Biol Transl Sci, 2018. 154: p. 71-104.
46. Mendes, K.L., D.F. Lelis, and S.H.S. Santos, Nuclear sirtuins and inflammatory signaling pathways. Cytokine Growth Factor Rev, 2017. 38: p. 98-105.
47. Bock, F.J. and P. Chang, New directions in poly(ADP-ribose) polymerase biology. FEBS J, 2016. 283(22): p. 4017-4031.
48. Bai, P. and L. Virag, Role of poly(ADP-ribose) polymerases in the regulation of inflammatory processes. FEBS Lett, 2012. 586(21): p. 3771-7.
49. Camacho-Pereira, J., et al., CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. Cell Metab, 2016. 23(6): p. 1127-1139.
50. Chini, E.N., et al., The Pharmacology of CD38/NADase: An Emerging Target in Cancer and Diseases of Aging. Trends Pharmacol Sci, 2018. 39(4): p. 424-436.
51. Essuman, K., et al., The SARM1 Toll/Interleukin-1 Receptor Domain Possesses Intrinsic NAD(+) Cleavage Activity that Promotes Pathological Axonal Degeneration. Neuron, 2017. 93(6): p. 1334-1343 e5.
52. Gomes, A.P., et al., Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell, 2013. 155(7): p. 1624-38.
53. Yoshino, J., et al., Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. Cell Metab, 2011. 14(4): p. 528-36.
54. Frederick, D.W., et al., Loss of NAD Homeostasis Leads to Progressive and Reversible Degeneration of Skeletal Muscle. Cell Metab, 2016. 24(2): p. 269-82.
55. Mouchiroud, L., et al., The NAD(+)/Sirtuin Pathway Modulates Longevity through Activation of Mitochondrial UPR and FOXO Signaling. Cell, 2013. 154(2): p. 430-41.
56. Yaku, K., K. Okabe, and T. Nakagawa, Simultaneous Measurement of NAD Metabolome in Aged Mice Tissue Using Liquid Chromatography Tandem-Mass Spectrometry (LC/MS/MS). Biomed Chromatogr, 2018.
57. Zhang, H., et al., NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. Science, 2016. 352(6292): p. 1436-43.
58. Das, A., et al., Impairment of an Endothelial NAD(+)-H2S Signaling Network Is a Reversible Cause of Vascular Aging. Cell, 2018. 173(1): p. 74-89 e20.
59. Braidy, N., et al., Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats. PLoS One, 2011. 6(4): p. e19194.
60. Stein, L.R. and S. Imai, Specific ablation of Nampt in adult neural stem cells recapitulates their functional defects during aging. EMBO J, 2014. 33(12): p. 1321-40.
61. Scheibye-Knudsen, M., et al., A high-fat diet and NAD(+) activate Sirt1 to rescue premature aging in cockayne syndrome. Cell Metab, 2014. 20(5): p. 840-55.
62. Braidy, N., et al., Mapping NAD(+) metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence. Biogerontology, 2014. 15(2): p. 177-98.
63. North, B.J., et al., SIRT2 induces the checkpoint kinase BubR1 to increase lifespan. EMBO J, 2014. 33(13): p. 1438-53.
64. Guan, Y., et al., Nicotinamide Mononucleotide, an NAD(+) Precursor, Rescues Age-Associated Susceptibility to AKI in a Sirtuin 1-Dependent Manner. J Am Soc Nephrol, 2017. 28(8): p. 2337-2352.
65. 65. Wang, X., et al., The Inhibitory Effects of Purple Sweet Potato Color on Hepatic Inflammation Is Associated with Restoration of NAD(+) Levels and Attenuation of NLRP3 Inflammasome Activation in High-Fat-Diet-Treated Mice. Molecules, 2017. 22(8).
66. Escande, C., et al., Deleted in breast cancer-1 regulates SIRT1 activity and contributes to high-fat diet-induced liver steatosis in mice. J Clin Invest, 2010. 120(2): p. 545-58.
67. Trammell, S.A., et al., Nicotinamide Riboside Opposes Type 2 Diabetes and Neuropathy in Mice. Sci Rep, 2016. 6: p. 26933.
68. Frederick, D.W., et al., Increasing NAD synthesis in muscle via nicotinamide phosphoribosyltransferase is not sufficient to promote oxidative metabolism. J Biol Chem, 2015. 290(3): p. 1546-58.
69. Sambeat, A., et al., Endogenous nicotinamide riboside metabolism protects against diet-induced liver damage. Nat Commun, 2019. 10(1): p. 4291.
70. Chalkiadaki, A., et al., Muscle-specific SIRT1 gain-of-function increases slow-twitch fibers and ameliorates pathophysiology in a mouse model of duchenne muscular dystrophy. PLoS Genet, 2014. 10(7): p. e1004490.
71. Ryu, K.W., et al., Metabolic regulation of transcription through compartmentalized NAD(+) biosynthesis. Science, 2018. 360(6389).
72. Brown, K.D., et al., Activation of SIRT3 by the NAD(+) precursor nicotinamide riboside protects from noise-induced hearing loss. Cell Metab, 2014. 20(6): p. 1059-68.
73. Diguet, N., et al., Nicotinamide Riboside Preserves Cardiac Function in a Mouse Model of Dilated Cardiomyopathy. Circulation, 2017.
74. Mukherjee, S., et al., Nicotinamide adenine dinucleotide biosynthesis promotes liver regeneration. Hepatology, 2017. 65(2): p. 616-630.
75. Fang, E.F., et al., NAD(+) Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. Cell Metab, 2016. 24(4): p. 566-581.
76. Gerdts, J., et al., SARM1 activation triggers axon degeneration locally via NAD(+) destruction. Science, 2015. 348(6233): p. 453-7.
77. Park, J.H., et al., Nicotinamide mononucleotide inhibits post-ischemic NAD(+) degradation and dramatically ameliorates brain damage following global cerebral ischemia. Neurobiol Dis, 2016. 95: p. 102-10.

References

78. *Li, Y., et al., Corneal Denervation Causes Epithelial Apoptosis Through Inhibiting NAD+ Biosynthesis. Invest Ophthalmol Vis Sci, 2019. 60(10): p. 3538-3546.*
79. *Hou, Y., et al., NAD(+) supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. Proc Natl Acad Sci U S A, 2018.Shi, H., et al., NAD Deficiency, Congenital Malformations, and Niacin Supplementation. N Engl J Med, 2017. 377(6): p. 544-552.*
80. *Shi, H., et al., NAD Deficiency, Congenital Malformations, and Niacin Supplementation. N Engl J Med, 2017. 377(6): p. 544-552.*
81. *Salomone, F., et al., Silibinin Restores NAD(+) Levels and Induces the SIRT1/AMPK Pathway in Non-Alcoholic Fatty Liver. Nutrients, 2017. 9(10).*
82. *Koenekoop, R.K., et al., Mutations in NMNAT1 cause Leber congenital amaurosis and identify a new disease pathway for retinal degeneration. Nat Genet, 2012. 44(9): p. 1035-9.*
83. *Trammell, S.A., et al., Nicotinamide Riboside Is a Major NAD+ Precursor Vitamin in Cow Milk. J Nutr, 2016. 146(5): p. 957-63.*
84. *Bogan, K.L. and C. Brenner, Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. Annu Rev Nutr, 2008. 28: p. 115-30.*
85. *Council, N.R., Recommended Dietary Allowances: 10th Edition. 1989: Washington, DC.*
86. *Irie, J., et al., Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men. Endocr J, 2019.*
87. *Grozio, A., et al., Slc12a8 is a nicotinamide mononucleotide transporter. Nature metabolim, 2019. 1: p. 47-57.*
88. *Mateuszuk, L., et al., Reversal of endothelial dysfunction by nicotinamide mononucleotide via extracellular conversion to nicotinamide riboside. Biochem Pharmacol, 2020: p. 114019.*
89. *Grant, R., et al., A Pilot Study Investigating Changes in the Human Plasma and Urine NAD+ Metabolome During a 6 Hour Intravenous Infusion of NAD. Front Aging Neurosci, 2019. 11: p. 257.*
90. *Kimura, N., et al., Comparison of metabolic fates of nicotinamide, NAD+ and NADH administered orally and intraperitoneally; characterization of oral NADH. J Nutr Sci Vitaminol (Tokyo), 2006. 52(2): p. 142-8.*
91. *FDA Briefing Document: Pharmacy Compounding Advisory Committee (PCAC) Meeting. 2017.*
92. *Kline, N.S., et al., Controlled evaluation of nicotinamide adenine dinucleotide in the treatment of chronic schizophrenic patients. Br J Psychiatry, 1967. 113(500): p. 731-42.*
93. *Tunaru, S., et al., Characterization of determinants of ligand binding to the nicotinic acid receptor GPR109A (HM74A/ PUMA-G). Mol Pharmacol, 2005. 68(5): p. 1271-80.*
94. *Dollerup, O.L., et al., Effects of nicotinamide riboside on endocrine pancreatic function and incretin hormones in obese, non-diabetic men. J Clin Endocrinol Metab, 2019.*
95. *Bitterman, K.J., et al., Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast sir2 and human SIRT1. J Biol Chem, 2002. 277(47): p. 45099-107.*
96. *Sauve, A.A. and V.L. Schramm, Sir2 regulation by nicotinamide results from switching between base exchange and deacetylation chemistry. Biochemistry, 2003. 42(31): p. 9249-56.*
97. *Xu, W., et al., Lethal Cardiomyopathy in Mice Lacking Transferrin Receptor in the Heart. Cell Rep, 2015. 13(3): p. 533-545.*
98. *Sasaki, Y., T. Araki, and J. Milbrandt, Stimulation of nicotinamide adenine dinucleotide biosynthetic pathways delays axonal degeneration after axotomy. J Neurosci, 2006. 26(33): p. 8484-91.*
99. *Liu, L., et al., Quantitative Analysis of NAD Synthesis-Breakdown Fluxes. Cell Metab, 2018. 27(5): p. 1067-1080 e5.*
100. *Vannini, N., et al., The NAD-Booster Nicotinamide Riboside Potently Stimulates Hematopoiesis through Increased Mitochondrial Clearance. Cell Stem Cell, 2019. 24(3): p. 405-418 e7.*
101. *Johri, A. and M.F. Beal, Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther, 2012. 342(3): p. 619-30.*
102. *Brown, D.A., et al., Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. Nat Rev Cardiol, 2017. 14(4): p. 238-250.*
103. *103. Boengler, K., et al., Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue. J Cachexia Sarcopenia Muscle, 2017. 8(3): p. 349-369.*
104. *Wei, Y., et al., Nonalcoholic fatty liver disease and mitochondrial dysfunction. World J Gastroenterol, 2008. 14(2): p. 193-9.*
105. *Smyrnias, I., et al., Cardioprotective Effect of the Mitochondrial Unfolded Protein Response During Chronic Pressure Overload. Journal of the American College of Cardiology, 2019. 73(14): p. 1795-1806.*
106. *106. Sorrentino, V., et al., Enhancing mitochondrial proteostasis reduces amyloid-beta proteotoxicity. Nature, 2017. 552(7684): p. 187-193.*
107. *Cesari, M., et al., Evidence for the Domains Supporting the Construct of Intrinsic Capacity. J Gerontol A Biol Sci Med Sci, 2018. 73(12): p. 1653-1660.*
108. *Gong, B., et al., Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-gamma coactivator 1alpha regulated beta-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. Neurobiol Aging, 2013. 34(6): p. 1581-8.*
109. *Xie, X., et al., Nicotinamide ribose ameliorates cognitive impairment of aged and Alzheimer's disease model mice. Metab Brain Dis, 2018.*
110. *Fragola, G., et al., Deletion of Topoisomerase 1 in excitatory neurons causes genomic instability and early onset neurodegeneration. Nat Commun, 2020. 11(1): p. 1962.*
111. *Lee, H.J. and S.J. Yang, Supplementation with Nicotinamide Riboside Reduces Brain Inflammation and Improves Cognitive Function in Diabetic Mice. Int J Mol Sci, 2019. 20(17).*
112. *Joshi, U., et al., Targeting sirtuin activity with nicotinamide riboside reduces neuroinflammation in a GWI mouse model. Neurotoxicology, 2020.*
113. *Ryu, D., et al., NAD+ repletion improves muscle function in muscular dystrophy and counters global PARylation. Sci Transl Med, 2016. 8(361): p. 361ra139.*
114. *Thomasson, R., et al., Alteration of performance in a mouse model of Emery-Dreifuss muscular dystrophy caused by A-type lamins gene mutation. Human Molecular Genetics, 2019.*
115. *Crisol, B.M., et al., NAD(+) precursor increases aerobic performance in mice. Eur J Nutr, 2019.*
116. *Gonzalez, J.M. and A.R. Jackson, In ovo feeding of nicotinamide riboside affects broiler pectoralis major muscle development. Translational Animal Science, 2020.*

117. *Hamity, M.V., et al., Nicotinamide riboside, a form of vitamin B3 and NAD+ precursor, relieves the nociceptive and aversive dimensions of paclitaxel-induced peripheral neuropathy in female rats. Pain, 2017. 158(5): p. 962-972.*
118. *Hamity, M.V., et al., Nicotinamide riboside relieves paclitaxel-induced peripheral neuropathy and enhances suppression of tumor growth in tumor-bearing rats. Pain, 2020.*
119. *Okur, M.N., et al., Short-term NAD(+) supplementation prevents hearing loss in mouse models of Cockayne syndrome. NPJ Aging Mech Dis, 2020. 6: p. 1.*
120. *Han, S., et al., Nicotinamide riboside protects noise-induced hearing loss by recovering the hair cell ribbon synapses. Neurosci Lett, 2020. 725: p. 134910.*
121. *Zhang, X., et al., Systemic Treatment With Nicotinamide Riboside Is Protective in a Mouse Model of Light-Induced Retinal Degeneration. Invest Ophthalmol Vis Sci, 2020. 61(10): p. 47.*
122. *Kitaoka, Y., et al., Axonal Protection by Nicotinamide Riboside via SIRT1-Autophagy Pathway in TNF-Induced Optic Nerve Degeneration. Mol Neurobiol, 2020.*
123. *Jiang, Y., et al., Nicotinamide riboside alleviates alcohol-induced depression-like behaviours in C57BL/6J mice by altering the intestinal microbiota associated with microglial activation and BDNF expression. Food Funct, 2019.*
124. *Gerasimenko, M., et al., Nicotinamide riboside supplementation corrects deficits in oxytocin, sociability and anxiety of CD157 mutants in a mouse model of autism spectrum disorder. Scientific Reports, 2020. 10: p. 10035.*
125. *Han, X., et al., Nicotinamide riboside exerts protective effect against aging-induced NAFLD-like hepatic dysfunction in mice. PeerJ, 2019. 7: p. e7568.*
126. *Pham, T.X., et al., Nicotinamide riboside, an NAD+ precursor, attenuates the development of liver fibrosis in a diet-induced mouse model of liver fibrosis. Biochim Biophys Acta Mol Basis Dis, 2019.*
127. *Jiang, R., et al., Nicotinamide riboside protects against liver fibrosis induced by CCl4 via regulating the acetylation of Smads signaling pathway. Life Sci, 2019.*
128. *Cerutti, R., et al., NAD(+)-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. Cell Metab, 2014. 19(6): p. 1042-9.*
129. *Khan, N.A., et al., Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO Mol Med, 2014. 6(6): p. 721-31.*
130. *Ear, P.H., et al., Maternal Nicotinamide Riboside Enhances Postpartum Weight Loss, Juvenile Offspring Development, and Neurogenesis of Adult Offspring. Cell Rep, 2019. 26(4): p. 969-983 e4.*
131. *Vignier, N., et al., Rescue of biosynthesis of nicotinamide adenine dinucleotide (NAD+) protects the heart in cardiomyopathy caused by lamin A/C gene mutation. Hum Mol Genet, 2018.*
132. *Levine, D.C., et al., NAD(+) Controls Circadian Reprogramming through PER2 Nuclear Translocation to Counter Aging. Mol Cell, 2020.*
133. *Heer, C.D., et al., Coronavirus infection and PARP expression dysregulate the NAD Metabolome: an actionable component of innate immunity. bioRxiv, 2020: p. 2020.04.17.047480.*
134. *Yang, Q., et al., Increasing ovarian NAD(+) levels improve mitochondrial functions and reverse ovarian aging. Free Radic Biol Med, 2020. 156: p. 1-10.*
135. *Altay, O., et al., Combined metabolic cofactor supplementation accelerates recovery in mild-to-moderate COVID-19. MedRxiv, 2020.*