

RESEARCH MONOGRAPH . COMPOUND PROFILE

Nicotinamide-Riboside

A naturally occurring pyridine nucleoside form of vitamin B3 that serves as a direct precursor to nicotinamide adenine dinucleotide (NAD+) through the nicotinamide riboside kinase pathway, distinguished from other NAD+ precursors by direct cellular uptake, absence of flushing, and a growing clinical evidence base in aging, neurodegeneration, and cardiovascular function.

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ABSTRACT

Nicotinamide riboside (NR) is a pyridine nucleoside form of vitamin B₃ and a direct biosynthetic precursor to nicotinamide adenine dinucleotide (NAD⁺), the essential redox cofactor and sirtuin/PARP cosubstrate whose decline with aging is implicated in mitochondrial dysfunction, genomic instability, neurodegeneration, and metabolic disease. First identified as an NAD⁺ precursor in yeast by Bieganowski and Brenner in 2004 [1], NR is phosphorylated by the conserved nicotinamide riboside kinases NRK1 and NRK2 to nicotinamide mononucleotide (NMN), which is subsequently adenylylated by nicotinamide mononucleotide adenylyltransferases (NMNATs) to yield NAD⁺. This two-step pathway is independent of the Preiss-Handler and de novo biosynthetic routes and constitutes a distinct salvage mechanism for NAD⁺ repletion.

The compound attracted broad scientific attention following the 2012 demonstration by Canto, Houtkooper, Auwerx, and colleagues that dietary NR supplementation in mice activates SIRT1 and SIRT3, enhances mitochondrial oxidative metabolism, and protects against high-fat-diet-induced obesity and metabolic dysfunction [2]. Subsequent preclinical work established NR-mediated NAD⁺ repletion as protective in mouse models of dilated cardiomyopathy [3], noise-induced hearing loss, Alzheimer-like neurodegeneration, Parkinson disease [4], hepatic steatosis, muscular dystrophy, and age-related stem cell decline. In each case, the proposed mechanism centers on restoration of NAD⁺-dependent sirtuin and poly(ADP-ribose) polymerase activity in metabolically stressed tissues.

Translation to humans began with the Trammell et al. (2016) pharmacokinetic study demonstrating dose-dependent elevation of the blood NAD⁺ metabolome after single oral doses of 100, 300, and 1,000 mg in healthy volunteers [5]. The Martens et al. (2018) crossover trial in healthy middle-aged and older adults confirmed that chronic NR supplementation at 1,000 mg daily for six weeks is well tolerated, elevates whole-blood NAD⁺ by approximately 60 percent, and produces a trend toward reduced systolic blood pressure and aortic stiffness [6]. The Conze, Brenner, and Kruger (2019) eight-week randomized trial in 140 healthy overweight adults established dose-dependent (100, 300, 1,000 mg daily) and sustained NAD⁺ elevation with no detectable adverse effect on hepatic, renal, or lipid parameters [7]. The Elhassan et al. (2019) study demonstrated that NR augments the aged human skeletal muscle NAD⁺ metabolome and induces anti-inflammatory transcriptomic signatures [8]. More recently, the NADPARK trial (Brakedal et al. 2022) showed that NR at 1,000 mg daily for 30 days is well tolerated in newly diagnosed Parkinson disease patients, increases cerebral NAD levels measured by phosphorus magnetic resonance spectroscopy, and is associated with altered cerebral metabolism and mild clinical improvement in a subset of responders [4]. The NR-SAFE trial (2023) extended the safety assessment to 3,000 mg daily for 30 days in Parkinson disease patients, confirming tolerability and up to five-fold blood NAD⁺ elevation without methyl donor depletion [9].

Despite consistent pharmacodynamic evidence that oral NR elevates NAD⁺ in blood, muscle, and brain, clinically meaningful efficacy endpoints have proven elusive in most completed trials. NR has not demonstrated significant effects on insulin sensitivity, whole-body glucose metabolism, or skeletal muscle mitochondrial bioenergetics in randomized controlled trials in obese or older

adults [10, 11]. Cognitive endpoints have not reached significance in trials of mild cognitive impairment [12]. The compound is therefore positioned as a well-tolerated NAD⁺ repletion agent with strong preclinical rationale, consistent pharmacodynamic activity, and an incomplete clinical efficacy record that awaits adequately powered Phase 2 and Phase 3 trials in disease-specific populations.

Nicotinamide riboside chloride is marketed as the dietary supplement Niagen (ChromaDex/Niagen Bioscience) and has received Generally Recognized as Safe (GRAS) status from the United States Food and Drug Administration for use as a vitamin B₃ source in foods [13], as well as two successful New Dietary Ingredient notifications for use in dietary supplements. The compound is not approved as a drug for any indication. This monograph reviews the chemistry, biosynthetic pathway, molecular pharmacology, pharmacokinetics, preclinical and clinical evidence, sourcing, handling, stack interactions, adverse-event profile, and a comparative assessment of five NAD⁺ precursor and booster candidates against NR on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred name: Nicotinamide riboside.

Synonyms: NR, 1-(beta-D-ribofuranosyl)nicotinamide, nicotinamide beta-ribose, SRT647 (early research code). The compound is frequently referred to in the commercial literature by the trademarked ingredient name Niagen (ChromaDex/Niagen Bioscience).

Chemical Abstracts Service registry numbers: 1341-23-7 (free base/zwitterionic form), 23111-00-4 (nicotinamide riboside chloride, the commercially manufactured salt form). The chloride salt is the standard commercial and research preparation.

International Union of Pure and Applied Chemistry name: 3-carbamoyl-1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyridin-1-ium. The compound is formally a pyridinium cation with a beta-D-ribofuranosyl substituent at the ring nitrogen.

PubChem Compound Identifier: CID 439924.

1.2 Structural class and chemistry

Nicotinamide riboside is a pyridine nucleoside consisting of a nicotinamide (3-carbamoylpyridine) moiety connected through a beta-N-glycosidic bond to a D-ribofuranose sugar. It belongs to the vitamin B3 family (niacin vitamers), which also includes nicotinic acid (niacin), nicotinamide (niacinamide), and nicotinamide mononucleotide (NMN). Among these vitamers, NR is distinguished by the presence of the intact ribose sugar without the 5-prime phosphate group that characterizes NMN.

Molecular formula: C₁₁H₁₅N₂O₅⁺ (cationic form); C₁₁H₁₅ClN₂O₅ (chloride salt).

Molecular weight: 255.25 g/mol (cationic form); 290.70 g/mol (chloride salt).

Physical properties: White to off-white crystalline powder (as the chloride salt). Freely soluble in water; soluble in methanol and ethanol; sparingly soluble in apolar organic solvents. The chloride salt is hygroscopic and should be stored with desiccant. Decomposition occurs at temperatures above 130 degrees Celsius. Degradation in aqueous solution follows pseudo-first-order kinetics and is accelerated by alkaline pH and elevated temperature, with the degradation rate approximately doubling for every 10 degree Celsius increase [14].

Stereochemistry: The ribose sugar adopts the D-configuration with defined stereochemistry at C-1 prime (beta), C-2 prime (R), C-3 prime (R), C-4 prime (S). The compound is supplied as a single stereoisomer. The glycosidic bond is in the beta configuration, placing the nicotinamide ring equatorial to the ribose ring.

1.3 Synthesis

Commercial-scale synthesis of nicotinamide riboside chloride proceeds through several established routes. The original chemical synthesis involves glycosylation of nicotinamide with an appropriately protected ribofuranose donor (typically 1-O-acetyl-2,3,5-tri-O-benzoyl-beta-D-ribofuranose) under Lewis acid catalysis, followed by global deprotection and salt formation with hydrochloric acid [15]. Enzymatic and chemoenzymatic routes have also been developed, including purine nucleoside phosphorylase-catalyzed transglycosylation and nicotinamidase-coupled biosynthetic approaches. Microbial fermentation routes using engineered *Escherichia coli* strains have been reported for large-scale production from nicotinamide or 3-cyanopyridine feedstocks [16]. ChromaDex (now Niagen Bioscience) has developed proprietary manufacturing processes for the commercial Niagen ingredient. The chloride salt is the standard commercial form, though tartrate and malate salt forms have also been described in the patent literature. Quality specifications for commercial material typically require greater than 98 percent purity by high-performance liquid chromatography, with characterization by nuclear magnetic resonance spectroscopy and mass spectrometry confirmation of molecular identity.

2. Abstract

Nicotinamide riboside (NR) is a naturally occurring pyridine nucleoside vitamin B3 vitamer that functions as a direct precursor to nicotinamide adenine dinucleotide (NAD⁺) through the nicotinamide riboside kinase (NRK) salvage pathway. The compound was identified as an NAD⁺ precursor and nutrient in 2004 by Bieganowski and Brenner, who demonstrated that NR is phosphorylated by the conserved kinases NRK1 and NRK2 to nicotinamide mononucleotide (NMN), establishing a Preiss-Handler-independent route to NAD⁺ in fungi and humans [1].

NAD⁺ is an essential cofactor in cellular redox reactions, serving as an electron carrier in glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation. Beyond its redox role, NAD⁺ is a consumed cosubstrate for three families of signaling enzymes: the sirtuins (SIRT1 through SIRT7), the poly(ADP-ribose) polymerases (PARPs), and the cyclic ADP-ribose synthases (CD38/CD157). Tissue NAD⁺ concentrations decline with aging, obesity, and metabolic stress, and this decline is causally linked in animal models to mitochondrial dysfunction, impaired DNA repair, stem cell exhaustion, and neurodegeneration [17]. NR supplementation restores NAD⁺ levels in multiple tissues and reverses or attenuates these age-associated phenotypes in preclinical models.

The principal preclinical demonstrations include protection against high-fat-diet-induced obesity and metabolic dysfunction through SIRT1/SIRT3 activation and enhanced mitochondrial biogenesis in mice [2]; preservation of cardiac function in a mouse model of dilated cardiomyopathy [3]; rescue of age-related muscle stem cell decline through activation of the mitochondrial unfolded protein response [18]; neuroprotection in mouse models of Alzheimer disease and noise-induced hearing loss; and improvement of Parkinson disease-relevant phenotypes in patient-derived induced pluripotent stem cell dopaminergic neurons [19].

Human translation has established that oral NR at doses of 100 to 3,000 mg daily is well tolerated, dose-dependently elevates blood NAD⁺ and related metabolites, and produces consistent pharmacodynamic effects on the NAD⁺ metabolome in healthy volunteers, overweight adults, older adults, and patients with Parkinson disease [4, 5, 6, 7, 9]. Clinical efficacy on disease-specific endpoints has been more limited: modest trends toward reduced blood pressure and arterial stiffness in

older adults [6, 20], anti-inflammatory transcriptomic signatures in aged skeletal muscle [8], altered cerebral metabolism in Parkinson disease [4], and improved walking distance in peripheral artery disease [21] have been reported, but several trials have failed to demonstrate effects on insulin sensitivity, skeletal muscle mitochondrial function, or cognitive outcomes [10, 11, 12]. The compound is commercially available as a dietary supplement (Niagen) with GRAS status and is not approved as a drug for any indication.

3. Discovery and Development History

3.1 Identification as an NAD⁺ precursor

Nicotinamide riboside was known as a chemical entity for decades before its biological significance was recognized. The compound had been identified in milk and other biological matrices, but its role as a vitamin and NAD⁺ precursor was not established until the 2004 publication by Bieganowski and Brenner in *Cell* [1]. Working in *Saccharomyces cerevisiae*, Bieganowski and Brenner demonstrated that NR supports the growth of yeast strains auxotrophic for NAD⁺ biosynthesis through a pathway independent of both the de novo (from tryptophan) and the Preiss-Handler (from nicotinic acid) routes. They identified the genes NRK1 (YNL129W) and NRK2 (encoding nicotinamide riboside kinases) as necessary and sufficient for the phosphorylation of NR to NMN, establishing a previously unrecognized salvage pathway to NAD⁺. The human orthologs NMRK1 and NMRK2 were shown to be functional, confirming the conservation of the pathway.

3.2 Preclinical development as a metabolic intervention

The translational potential of NR was catalyzed by the 2012 publication by Canto, Houtkooper, Auwerx, and colleagues in *Cell Metabolism* [2]. This study demonstrated that dietary NR supplementation (400 mg/kg/day in chow) in C57BL/6J mice on a high-fat diet increased hepatic and muscle NAD⁺ content, activated SIRT1 (nuclear) and SIRT3 (mitochondrial) deacetylase activity, enhanced mitochondrial biogenesis and oxidative metabolism, improved insulin sensitivity, and reduced body weight gain. The effect was comparable in magnitude to the metabolic benefits of caloric restriction and exercise, positioning NR as a potential calorie-restriction mimetic.

Subsequent preclinical studies from multiple laboratories extended these findings. The Zhang et al. (2016) study in *Science* demonstrated that NAD⁺ repletion with NMN (a downstream metabolite of NR) improved age-related muscle stem cell function through activation of the mitochondrial unfolded protein response [18]. The Diguët et al. (2018) study in *Circulation* showed that NR supplementation preserves cardiac function and reduces cardiac remodeling in a mouse model of di-

lated cardiomyopathy through NAD⁺-dependent normalization of mitochondrial protein acetylation [3]. The Brown et al. (2014) study demonstrated protection against noise-induced hearing loss in mice. The Gong et al. (2013) study in PLoS ONE showed neuroprotective effects in a model of Alzheimer disease.

3.3 Commercial development

ChromaDex, Inc. (Irvine, California; subsequently reorganized as Niagen Bioscience) licensed the intellectual property surrounding NR from Dartmouth College (where Charles Brenner held his initial academic appointment) and from Cornell University. ChromaDex developed the proprietary manufacturing process for nicotinamide riboside chloride under the trade name Niagen and obtained New Dietary Ingredient (NDI) notification acceptance from the U.S. Food and Drug Administration in 2015 and 2017, followed by GRAS notification acceptance (GRN 000635) in 2016 [13]. The European Food Safety Authority (EFSA) subsequently evaluated nicotinamide riboside chloride as a novel food ingredient and issued a positive safety opinion. The compound is marketed globally as a dietary supplement under the Tru Niagen brand and through licensed ingredient partnerships. ChromaDex has also pursued pharmaceutical development pathways, with investigator-initiated and company-sponsored clinical trials in aging, cardiovascular disease, and neurodegeneration.

3.4 Current clinical development status

As of the most recent monograph revision, NR has been evaluated in over 30 registered clinical trials spanning healthy aging, obesity, type 2 diabetes, heart failure, Parkinson disease, Alzheimer disease, mild cognitive impairment, peripheral artery disease, acute kidney injury, COVID-19, and long COVID. No registration trial for a drug indication has been completed or submitted. The compound remains positioned as a dietary supplement with an expanding but inconclusive clinical evidence base for disease-specific applications.

4. Mechanism of Action

Nicotinamide riboside functions as a substrate for the NAD⁺ salvage pathway rather than as a receptor ligand. Its mechanism of action is therefore metabolic rather than pharmacodynamic in the classical receptor-binding sense: NR is converted to NAD⁺, and the elevated NAD⁺ pool activates downstream enzymatic consumers that mediate the observed biological effects.

4.1 The NRK pathway

The rate-limiting step in NR utilization is its phosphorylation by the nicotinamide riboside kinases NRK1 and NRK2 (gene names NMRK1 and NMRK2). NRK1 is ubiquitously expressed and has a K_m of approximately 0.088 mM for NR with ATP as co-substrate [22]. NRK2 expression is restricted primarily to skeletal and cardiac muscle and has a K_m of approximately 0.19 mM. Both enzymes produce nicotinamide mononucleotide (NMN) as the direct product. NMN is subsequently adenylylated by the nicotinamide mononucleotide adenylyltransferases (NMNAT1, NMNAT2, NMNAT3; localized to the nucleus, cytoplasm/Golgi, and mitochondria, respectively) to yield NAD⁺. The two-step pathway (NR to NMN to NAD⁺) is rapid and does not require the intermediate formation of nicotinic acid mononucleotide (NaMN) or passage through the Preiss-Handler pathway, distinguishing it from nicotinic acid metabolism [1].

NRK1 and NRK2 exhibit functional redundancy in unchallenged tissues, as demonstrated by knockout studies in myotubes [22]. However, NRK2 is transcriptionally upregulated under conditions of metabolic stress, including energy depletion and sarcoplasmic reticulum dysfunction, suggesting a stress-responsive role in NAD⁺ salvage that extends beyond basal homeostasis [23].

4.2 Cellular uptake

A distinguishing feature of NR relative to NMN is its ability to enter cells without prior dephosphorylation. NMN, which carries a 5-prime phosphate group, must be dephosphorylated to NR by the ectoenzyme CD73 (5-prime nucleotidase) before cellular uptake in most tissues, though a dedicated NMN transporter (SLC12A8) has

been reported in the small intestine [24]. NR enters cells through equilibrative nucleoside transporters (ENTs), which are broadly expressed across tissues. This direct cellular uptake is one basis for the argument that NR is a more efficient NAD⁺ precursor on a molar basis than NMN, though the clinical significance of this distinction remains debated.

4.3 NAD⁺-dependent signaling

The downstream consequences of NR-mediated NAD⁺ elevation are mediated by three principal families of NAD⁺-consuming enzymes:

Sirtuins (SIRT1 through SIRT7). The sirtuins are NAD⁺-dependent protein deacetylases (deacetylases, desuccinylases, demalonylases, and others) that regulate metabolic adaptation, stress resistance, inflammation, circadian rhythm, and genomic stability. SIRT1 (nuclear/cytoplasmic) deacetylates PGC-1α, FOXO transcription factors, p53, NF-κB, and other targets to promote mitochondrial biogenesis, fatty acid oxidation, gluconeogenesis, antioxidant defense, and anti-inflammatory gene expression. SIRT3 (mitochondrial) deacetylates components of the electron transport chain and the tricarboxylic acid cycle to enhance oxidative metabolism and reduce reactive oxygen species production. NAD⁺ is a rate-limiting cosubstrate for sirtuin catalytic activity; the K_m of SIRT1 for NAD⁺ (approximately 100 to 200 micromolar) is within the physiological concentration range, making sirtuin activity directly responsive to fluctuations in cellular NAD⁺ [25].

Poly(ADP-ribose) polymerases (PARP1, PARP2). The PARPs consume NAD⁺ to synthesize poly(ADP-ribose) chains on target proteins in response to DNA damage. PARP1 is a major consumer of cellular NAD⁺ and is activated by single-strand and double-strand DNA breaks. In aging tissues with accumulated DNA damage, chronic PARP activation depletes NAD⁺ and creates a vicious cycle of NAD⁺ insufficiency and impaired sirtuin function. NR supplementation restores the NAD⁺ pool and partially rescues sirtuin activity even in the context of ongoing PARP activation [17].

CD38/CD157. CD38 is an ectoenzyme and intracellular NADase that hydrolyzes NAD⁺ to produce cyclic ADP-ribose and nicotinamide. CD38 expression increases with aging and inflammation, and CD38-mediated NAD⁺ consumption is a major driver of age-related NAD⁺ decline in multiple tissues [26]. NR supplementation can

partially offset CD38-mediated NAD⁺ depletion, though the magnitude of repletion depends on the balance between NRK-mediated synthesis and CD38-mediated degradation.

4.4 Metabolomic signature

A notable pharmacodynamic finding from the Trammell et al. (2016) study is that NR supplementation elevates not only NAD⁺ but also nicotinic acid adenine dinucleotide (NAAD) in blood [5]. NAAD is not an expected intermediate in the NRK pathway and its appearance suggests metabolic interconversion between the salvage and Preiss-Handler pathways. The rise in NAAD has been proposed as a sensitive biomarker of effective NAD⁺ repletion and has been confirmed in subsequent clinical trials.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Nicotinamide riboside is absorbed from the gastrointestinal tract after oral administration. The Trammell et al. (2016) study in *Nature Communications* demonstrated that single oral doses of 100, 300, and 1,000 mg of NR (as nicotinamide riboside chloride) produce dose-dependent increases in blood NAD⁺ and related metabolites in healthy human volunteers [5]. Peak elevation of blood NAD⁺ occurs approximately 8 hours after a single oral dose, reflecting the kinetics of absorption, cellular uptake, phosphorylation, and adenylation rather than simple pharmacokinetic C_{max}.

Recent evidence from Liu et al. (2018) using isotope-labeled NAD⁺ precursors in mice demonstrated that orally administered NR is substantially metabolized in the gut and liver, with a significant fraction converted to nicotinamide (NAM) before reaching systemic circulation [27]. The intact NR that reaches the portal circulation is phosphorylated by hepatic NRK1 and contributes to hepatic NAD⁺ synthesis, while the NAM fraction enters the conventional salvage pathway through nicotinamide phosphoribosyltransferase (NAMPT). The relative contribution of intact NR versus NAM-derived NAD⁺ to total systemic NAD⁺ elevation in humans remains an area of active investigation.

5.2 Distribution

NR and its metabolites distribute broadly. The compound crosses the blood-brain barrier, as demonstrated by the NADPARK trial, in which oral NR at 1,000 mg daily for 30 days increased cerebral NAD levels measured by phosphorus-31 magnetic resonance spectroscopy in a subset of Parkinson disease patients [4]. NR-derived NAD⁺ elevation has been confirmed in skeletal muscle biopsy tissue in older adults [8], in peripheral blood mononuclear cells, and in whole blood across multiple trials. The volume of distribution and plasma protein binding of intact NR have not

been formally characterized in human pharmacokinetic studies, as the compound is rapidly metabolized and the pharmacodynamic endpoint (tissue NAD⁺ elevation) is the relevant measure rather than plasma NR concentration.

5.3 Metabolism

NR is metabolized through multiple parallel pathways. The intended pathway is phosphorylation by NRK1/NRK2 to NMN and subsequent adenylation to NAD⁺. However, NR is also a substrate for purine nucleoside phosphorylase, which cleaves the glycosidic bond to release nicotinamide and ribose. The nicotinamide produced by this cleavage enters the NAMPT-dependent salvage pathway (nicotinamide to NMN to NAD⁺) or is methylated by nicotinamide N-methyltransferase (NNMT) to N-methyl-nicotinamide, which is excreted renally. The methylation pathway has raised theoretical concern about methyl donor depletion (consumption of S-adenosylmethionine) at high NR doses, but the NR-SAFE trial at 3,000 mg daily did not demonstrate clinically significant methyl donor depletion or elevation of homocysteine above clinically relevant thresholds [9].

5.4 Elimination

The metabolic products of NR are eliminated primarily through renal excretion. N-methyl-nicotinamide, N-methyl-2-pyridone-5-carboxamide (2-PY), and N-methyl-4-pyridone-3-carboxamide (4-PY) are the principal urinary metabolites. Urinary excretion of these methylated metabolites increases dose-dependently with NR supplementation and serves as an additional biomarker of NR utilization [5, 7].

5.5 Routes of administration

Oral administration is the standard route for NR supplementation and clinical investigation. The compound is supplied as capsules or tablets containing nicotinamide riboside chloride, typically in 125 mg, 250 mg, or 300 mg unit doses. Intravenous NAD⁺ and intravenous NR preparations have been evaluated in pilot studies, with intravenous routes producing higher peak plasma levels but also higher rates of adverse effects including nausea, diarrhea, muscle cramping, and dizziness [28]. Sublingual and intranasal routes have not been formally evaluated.

5.6 Dose-response relationship

The Conze et al. (2019) study established a clear dose-response for blood NAD⁺ elevation: 100 mg daily increased whole-blood NAD⁺ by 22 percent, 300 mg daily by 51 percent, and 1,000 mg daily by 142 percent at steady state over 8 weeks [7]. The Trammell et al. (2016) study reported up to 2.7-fold elevation of blood NAD⁺ after a single 1,000 mg dose in a pilot participant [5]. The NR-SAFE trial at 3,000 mg daily reported up to five-fold blood NAD⁺ elevation [9]. Whether higher NAD⁺ elevation translates to proportionally greater clinical benefit is unknown and is a critical open question for dose optimization in disease-specific applications.

6. Preclinical Pharmacology

6.1 Metabolic protection

The foundational preclinical study is the Canto et al. (2012) demonstration that NR supplementation (400 mg/kg/day) in C57BL/6J mice on a high-fat diet activates SIRT1 and SIRT3, increases mitochondrial content and oxidative capacity in liver and muscle, improves insulin sensitivity, reduces hepatic steatosis, and protects against diet-induced obesity [2]. The metabolic protection was comparable in magnitude to the effects of resveratrol (a SIRT1 activator) and exercise. Mitochondrial morphology analysis revealed increased mitochondrial number and altered cristae structure consistent with enhanced oxidative capacity.

6.2 Cardiac protection

Diguet et al. (2018) demonstrated that NR supplementation preserves left ventricular ejection fraction and reduces cardiac hypertrophy and fibrosis in a mouse model of dilated cardiomyopathy induced by conditional cardiomyocyte-specific deletion of Serum Response Factor [3]. The mechanism involved NAD⁺-dependent normalization of mitochondrial protein acetylation (SIRT3 target proteins) and stabilization of mitochondrial membrane potential. Protection was observed both prophylactically and after the onset of cardiac dysfunction.

6.3 Neuroprotection

Multiple preclinical models have demonstrated NR-mediated neuroprotection. The Schondorf et al. (2018) study in Cell Reports used patient-derived induced pluripotent stem cells differentiated into dopaminergic neurons from GBA-N370S Parkinson disease patients and demonstrated that NR treatment corrected mitochondrial dysfunction, lysosomal deficits, and alpha-synuclein accumulation through NAD⁺/sirtuin-dependent mechanisms [19]. Brown et al. (2014) demonstrated protection against noise-induced hearing loss and spiral ganglion neurite degeneration in mice treated with NR prior to noise exposure. Gong et al. (2013) reported that NR delays the progression of Alzheimer-like phenotypes in the Tg2576 mouse model.

6.4 Stem cell rejuvenation

Zhang et al. (2016) demonstrated in Science that NAD⁺ repletion (using NMN, the direct downstream metabolite of NR) rejuvenates aged muscle stem cells by activating the mitochondrial unfolded protein response (UPR-mt) and prohibitin signaling [18]. The aged satellite cells showed improved self-renewal capacity, enhanced regenerative potential after injury, and extended lifespan when transplanted into aged mice. These findings have been extended to NR itself in subsequent studies showing activation of UPR-mt in muscle stem cells of aged mice supplemented with NR.

6.5 Anti-inflammatory effects

NR supplementation reduces circulating inflammatory cytokines in multiple pre-clinical models. The mechanism involves SIRT1-mediated deacetylation and inactivation of the NF-kappaB p65 subunit, suppressing transcription of pro-inflammatory genes including tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6. SIRT3-mediated deacetylation of mitochondrial superoxide dismutase 2 (SOD2) reduces mitochondrial reactive oxygen species production, further attenuating the NLRP3 inflammasome activation that contributes to age-related chronic inflammation [17].

7. Clinical Evidence Base

7.1 Healthy volunteer and aging studies

The Martens et al. (2018) crossover trial (Nature Communications) randomized 24 lean, healthy middle-aged and older adults (55 to 79 years) to NR 500 mg twice daily (1,000 mg total) or placebo for six weeks in a 2 x 6-week crossover design [6]. NR was well tolerated, increased whole-blood NAD⁺ by approximately 60 percent, and produced a non-significant trend toward reduced systolic blood pressure (minus 2 mmHg) and carotid-femoral pulse wave velocity (a measure of aortic stiffness). The study was underpowered for cardiovascular endpoints and was designed primarily as a safety and pharmacodynamic trial.

A subsequent study by Martens and colleagues (2022, Frontiers in Cardiovascular Medicine) evaluated NR at 500 mg twice daily for 3 months in middle-aged and older adults with elevated systolic blood pressure [20]. This trial reported a significant reduction in casual systolic blood pressure and improved vascular endothelial function measured by brachial artery flow-mediated dilation.

7.2 Obesity and metabolic health

Dollerup et al. (2018) conducted a 12-week randomized, placebo-controlled trial of NR 1,000 mg twice daily (2,000 mg total) in 40 obese, insulin-resistant men [10]. NR did not improve insulin sensitivity (measured by hyperinsulinemic-euglycemic clamp), whole-body glucose metabolism, resting energy expenditure, or plasma lipids. A small but statistically significant reduction in hepatic lipid content was observed, though the clinical significance was uncertain.

Remie et al. (2020) conducted a randomized, double-blind, placebo-controlled, crossover trial of NR 1,000 mg daily for 6 weeks in 13 healthy overweight or obese adults [11]. NR supplementation modestly altered body composition (decreased fat mass, increased fat-free mass) and increased skeletal muscle acetylcarnitine concentrations but did not affect muscle mitochondrial respiration, hepatic lipid content, cardiac function, blood pressure, or substrate oxidation.

7.3 Skeletal muscle and aging

Elhassan et al. (2019) conducted an open-label study of NR 1,000 mg daily for 21 days in 12 older men (aged 70 to 80 years) [8]. Muscle biopsy demonstrated significant augmentation of the skeletal muscle NAD⁺ metabolome (NAD⁺, NAAD, NMN, and other intermediates). Transcriptomic analysis revealed upregulation of anti-inflammatory pathways and downregulation of energy metabolism and mitochondrial pathways. Circulating interleukin-6 was significantly reduced. Skeletal muscle mitochondrial bioenergetics (assessed by high-resolution respirometry) were not significantly altered.

7.4 Parkinson disease

The NADPARK trial (Brakedal et al. 2022, Cell Metabolism) was a double-blind Phase 1 trial in 30 newly diagnosed, treatment-naïve Parkinson disease patients randomized to NR 1,000 mg daily or placebo for 30 days [4]. NR was well tolerated. A subset of NR-treated participants showed increased cerebral NAD levels (measured by phosphorus-31 magnetic resonance spectroscopy), and these NAD responders exhibited altered cerebral glucose metabolism (measured by fluorodeoxyglucose positron emission tomography) and mild improvement on the Movement Disorder Society Unified Parkinson Disease Rating Scale. The clinical improvement was variable across participants and did not reach significance in the intention-to-treat analysis.

The NR-SAFE trial (2023, Nature Communications) evaluated high-dose NR (1,500 mg twice daily, 3,000 mg total) for 30 days in 20 Parkinson disease patients [9]. The trial confirmed safety and tolerability at this dose, demonstrated up to five-fold blood NAD⁺ elevation, and showed no evidence of methyl donor depletion (homocysteine, folate, and vitamin B12 remained within normal limits). A dose-optimization trial (N-DOSE, NCT05589766) is ongoing to determine the optimal NR dose for Phase 2 efficacy studies in Parkinson disease.

7.5 Cognitive impairment and Alzheimer disease

A randomized, placebo-controlled trial of NR in older adults with mild cognitive impairment evaluated NR supplementation for effects on cognition and Alzheimer disease biomarkers [12]. NR significantly increased blood NAD⁺ concentrations and was well tolerated, but did not significantly alter cognitive performance or cere-

brospinal fluid Alzheimer disease biomarkers over the study period. A 2025 publication by Wu et al. (Alzheimer's and Dementia: Translational Research and Clinical Interventions) examined NR effects on cognitive and Alzheimer disease biomarkers in older adults with subjective cognitive decline and mild cognitive impairment, reporting exploratory signals that require confirmation in larger trials.

7.6 Peripheral artery disease

The NICE trial (2024, Nature Communications) evaluated NR with and without resveratrol in patients with peripheral artery disease [21]. NR supplementation improved six-minute walk distance, a clinically meaningful functional endpoint. Resveratrol did not add additional benefit. The trial provides one of the more promising disease-specific efficacy signals for NR to date.

7.7 Heart failure

A Phase 1 safety and tolerability trial of NR in patients with heart failure with reduced ejection fraction demonstrated safety and tolerability of oral NR at doses up to 2,000 mg daily, with evidence of NAD⁺ metabolome augmentation in peripheral blood mononuclear cells [29]. Larger efficacy trials in heart failure are in planning or early enrollment.

7.8 Long COVID

A double-blind, placebo-controlled trial evaluated NR at 2,000 mg daily in 58 participants with long COVID, randomized 2:1 to NR for 20 weeks or placebo for 10 weeks followed by NR for 10 weeks [30]. Results demonstrated NAD⁺ metabolome elevation. Efficacy on symptom recovery and cognitive endpoints from this trial has been published in eClinicalMedicine (Lancet family).

8. Sourcing and Quality Verification

Nicotinamide riboside chloride is commercially available from multiple sources in both consumer-supplement and research-grade forms.

Consumer-grade supplement sources: Tru Niagen (Niagen Bioscience/ChromaDex) is the principal branded consumer product, available in 150 mg, 300 mg, and multi-capsule configurations. The Niagen ingredient has NDI and GRAS notification acceptance from the FDA and is manufactured under current Good Manufacturing Practice (cGMP) conditions. Multiple third-party supplement brands license the Niagen ingredient or source nicotinamide riboside chloride from alternative manufacturers.

Research-grade sources: Nicotinamide riboside chloride is supplied by major chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, Cayman Chemical, MedChemExpress, Toronto Research Chemicals, BocSciences, others) at greater than 98 percent purity by HPLC. Supply is in milligram to multi-gram quantities. Pricing is moderate to high relative to other NAD⁺ precursors, typically \$100 to \$500 per gram of high-purity research material.

Quality verification considerations: Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (255.25 for the cationic form, [M]⁺ ion)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) for structural confirmation
- Karl Fischer analysis or loss-on-drying for residual water content (the chloride salt is hygroscopic)
- Residual solvent analysis if the compound was obtained from chemical synthesis
- Heavy metal analysis (arsenic, cadmium, lead, mercury) for material intended for in vivo research

The nicotinamide riboside chloride market includes both authentic and potentially adulterated material. Third-party analytical testing (by Janoshik Analytical, Eurofins, NSF International, or equivalent accredited laboratories) is recommended for material from unfamiliar suppliers. Certificates of analysis from the supplier should be verified against independent analytical results, particularly for the chloride salt form, as nicotinamide (a much less expensive compound) has been reported as an adulterant in lower-quality preparations.

9. Reconstitution and Handling

Nicotinamide riboside chloride is supplied as a crystalline powder and is freely soluble in water at room temperature. For in vitro research applications, stock solutions are typically prepared at 10 to 100 mM in phosphate-buffered saline, cell culture medium, or dimethyl sulfoxide. Aqueous stock solutions should be prepared fresh or stored at minus 20 degrees Celsius in single-use aliquots; the compound degrades in aqueous solution at room temperature and at alkaline pH through hydrolysis of the glycosidic bond, releasing nicotinamide and ribose [14].

For in vivo research in rodents, NR is typically administered by oral gavage (dissolved in water or saline) or incorporated into rodent chow at concentrations of 400 mg/kg body weight/day (the dose used in the Canto et al. 2012 study) or equivalent. The compound is stable in dry rodent chow stored at room temperature for the duration of typical feeding studies (weeks to months) but should not be exposed to elevated humidity or temperature.

For human studies, the compound is administered as oral capsules (the Niagen formulation is the most commonly used clinical-grade material). No reconstitution is required for oral capsule administration. Storage at controlled room temperature (15 to 25 degrees Celsius) in sealed containers with desiccant is appropriate for the solid and capsule forms. Light protection is not strictly required but is reasonable practice for long-term storage.

Investigators should note that nicotinamide riboside chloride is hygroscopic and should be weighed and handled under low-humidity conditions. Exposure to high humidity results in weight gain from water absorption, which can introduce dosing errors if the material is weighed after moisture uptake. Desiccant storage and rapid handling under dry conditions are recommended.

10. Stack Interactions and Combinations

Nicotinamide riboside interacts with several compound classes through its role as an NAD⁺ precursor and through its downstream effects on sirtuin and PARP activity. Investigators and supplement users should consider the following interactions:

Other NAD⁺ precursors (nicotinamide, nicotinic acid, NMN, tryptophan). Co-administration of NR with other NAD⁺ precursors produces potentially additive NAD⁺ elevation but also additive flux through the methylation pathway (NNMT-mediated conversion of nicotinamide to N-methyl-nicotinamide), which theoretically increases methyl donor consumption. The clinical significance of this concern is low at standard supplement doses but may become relevant at high combined doses. NR plus nicotinic acid co-administration would introduce flushing risk from the nicotinic acid component.

Sirtuin activators (resveratrol, SRT1720, pterostilbene). The combination of NR with sirtuin activators is pharmacologically rational: NR provides the NAD⁺ cosubstrate and the sirtuin activator enhances allosteric activation of SIRT1. The NRPT (nicotinamide riboside plus pterostilbene) combination product (Basis, by Elysium Health) was evaluated in a clinical trial and demonstrated sustained NAD⁺ elevation [31]. The NICE trial evaluated NR with and without resveratrol for peripheral artery disease, finding no additional benefit from resveratrol [21].

PARP inhibitors (olaparib, niraparib, rucaparib, talazoparib). PARP inhibitors reduce NAD⁺ consumption by blocking PARP catalytic activity. Theoretically, the combination of a PARP inhibitor with NR could synergistically increase NAD⁺ availability, but this combination has not been evaluated in clinical studies and raises complex considerations in the oncology setting where PARP inhibitors are used therapeutically.

CD38 inhibitors (apigenin, luteolin, quercetin, 78c). CD38 is a major NADase whose expression increases with aging. Inhibition of CD38 reduces NAD⁺ degradation, and the combination with NR (which increases NAD⁺ synthesis) could theoretically produce greater net NAD⁺ elevation than either approach alone. Preclinical studies support this rationale, but clinical data are absent.

Metformin. Metformin activates AMP-activated protein kinase (AMPK), which increases NAMPT expression and NAD⁺ biosynthesis through the salvage pathway. The combination with NR could produce additive NAD⁺ elevation through complementary mechanisms (increased salvage synthesis via NAMPT plus direct NRK-mediated synthesis from NR). No clinical interaction data are available.

CYP enzyme interactions. NR is not known to be a significant substrate, inhibitor, or inducer of cytochrome P450 enzymes. The Conze et al. (2019) trial did not identify drug interactions at doses up to 1,000 mg daily [7]. Formal drug-drug interaction studies have not been conducted.

Methylation-dependent compounds. High-dose NR produces increased nicotinamide, which is methylated by NNMT to N-methyl-nicotinamide. This methylation consumes S-adenosylmethionine (SAM). Co-administration of NR with other compounds that consume SAM (creatine synthesis at high doses, phosphatidylcholine synthesis) could theoretically deplete the methyl donor pool. The NR-SAFE trial at 3,000 mg daily did not demonstrate clinically significant methyl donor depletion [9], but prudence suggests monitoring homocysteine in individuals on very high combined methylation-demanding regimens.

11. Adverse Events and Safety

11.1 Common adverse events

Oral NR at doses of 100 to 3,000 mg daily has been well tolerated across all published clinical trials. The most commonly reported adverse events, generally occurring at rates similar to placebo, include:

- Mild gastrointestinal symptoms (nausea, bloating, diarrhea): reported in 5 to 15 percent of participants across trials, typically transient and self-limiting
- Headache: reported in 3 to 8 percent of participants
- Fatigue: reported in 2 to 5 percent of participants
- Pruritus and skin flushing: reported rarely and at substantially lower rates than with nicotinic acid (niacin), which produces prostaglandin-mediated cutaneous vasodilation. NR does not interact with the GPR109A receptor responsible for niacin flush

11.2 Laboratory safety parameters

The Conze et al. (2019) eight-week trial in 140 subjects demonstrated no significant differences between NR and placebo groups in hepatic transaminases (ALT, AST), renal function markers (creatinine, blood urea nitrogen), serum lipids (total cholesterol, LDL, HDL, triglycerides), fasting glucose, or serum potassium [7]. Plasma homocysteine was unchanged. Some changes in hematological parameters were observed from baseline but did not differ between NR and placebo groups.

11.3 High-dose safety

The NR-SAFE trial at 3,000 mg daily for 30 days in Parkinson disease patients reported no moderate or severe adverse events and no significant difference in mild adverse events between NR and placebo groups [9]. Serum homocysteine showed a slight initial rise in NR recipients but remained within normal laboratory reference ranges, and methyl donor pool integrity was maintained (folate and vitamin B12 unchanged).

11.4 Serious adverse events

In the mild cognitive impairment trial, three serious adverse events were reported: a urinary tract infection, dizziness/transient ischemic attack, and exacerbation of a chronic gait disorder [12]. These were judged unrelated or possibly related to the study drug by the investigators. No pattern of serious adverse events attributable to NR has emerged across the published trial literature.

11.5 Theoretical concerns

Methyl donor depletion. The metabolism of NR-derived nicotinamide through NNMT consumes SAM. At very high doses or in individuals with pre-existing methylation deficiency (folate deficiency, MTHFR polymorphism), this could theoretically contribute to hyperhomocysteinemia. Current clinical data do not support this concern at doses up to 3,000 mg daily, but monitoring is prudent in high-dose, long-duration applications.

Tumor promotion. NAD⁺ is required for rapidly dividing cells, and theoretical concern has been raised that NAD⁺ boosting could promote growth of pre-existing tumors. Preclinical data are mixed: some models show NR-mediated tumor promotion, while others show no effect or protection. Clinical data are insufficient to resolve this question. The concern is theoretical and has not been substantiated in human supplementation studies, but caution is warranted in individuals with active malignancy.

Interaction with circadian rhythm. NAD⁺ levels oscillate with circadian periodicity, driven by NAMPT transcription under CLOCK/BMAL1 control. Exogenous NR supplementation could theoretically disrupt this oscillation. The clinical significance is unknown; timing of NR administration relative to the circadian cycle has not been systematically studied.

11.6 Regulatory safety assessments

The FDA accepted GRAS notification GRN 000635 for nicotinamide riboside chloride at intended use levels in foods corresponding to dietary exposures of up to approximately 145 mg/person/day at the 90th percentile [13]. A 90-day subchronic toxicity study in rats at doses up to 300 mg/kg body weight/day demonstrated no treatment-related adverse effects. EFSA has issued a positive safety opinion for NR chloride as a novel food ingredient in the European Union.

12. Comparative Assessment

This section presents a structured comparative assessment of five NAD⁺ precursor and booster candidates against nicotinamide riboside, evaluated against five competency standards: novelty, effect size (pharmacodynamic NAD⁺ elevation and clinical endpoints), promising potential (clinical trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal alternative strategies for NAD⁺ repletion or boosting with substantive preclinical or clinical evidence.

12.1 Nicotinamide Mononucleotide (NMN)

Mechanism: NMN is the direct phosphorylated product of NR and the immediate precursor to NAD⁺ in the NRK pathway. Exogenous NMN is dephosphorylated to NR by CD73 at the cell surface, taken up as NR, and rephosphorylated intracellularly, though a dedicated intestinal NMN transporter (SLC12A8) has been reported [24]. NMN therefore converges with NR on the same intracellular pathway.

Novelty: Low. The mechanism is identical to NR at the intracellular level. The distinction is at the level of cellular uptake (NMN requires dephosphorylation in most tissues; NR does not).

Effect size: Preclinical NAD⁺ elevation in mice is comparable to NR at equivalent doses. Clinical evidence in humans is growing: Yoshino et al. (2021) demonstrated that NMN at 250 mg daily for 10 weeks improved muscle insulin sensitivity in prediabetic women [32], an endpoint that NR has not achieved in comparable trials. However, head-to-head clinical comparisons of NR and NMN at equivalent molar doses have not been conducted.

Promising potential: Moderate to high. NMN has attracted substantial commercial and research interest. Multiple clinical trials are ongoing. The compound is sold as a dietary supplement, though its U.S. regulatory status has been complicated by the FDA's determination that NMN was investigated as a drug before being marketed as a supplement, leading to enforcement actions against NMN supplement products.

Side-effect profile: NMN has demonstrated tolerability comparable to NR in published trials. No significant safety concerns have been identified at doses up to 1,250 mg daily. The side-effect profile appears similar to NR.

Overall validation: Moderate. The preclinical evidence base is extensive and comparable to NR. The clinical evidence base is smaller than NR but growing, with some disease-specific endpoints (muscle insulin sensitivity) that NR has not achieved.

Comparison to NR: NMN and NR are mechanistically convergent at the intracellular level. NR has the advantages of a larger clinical trial database, established GRAS and NDI status, and clearer regulatory pathway in the United States. NMN has the advantage of one positive insulin sensitivity trial and a higher molecular weight (334.22 versus 255.25 for the cationic form) that delivers fewer molar equivalents per milligram. The two compounds are more similar than different, and definitive superiority claims for either are not supported by current evidence.

12.2 Nicotinic Acid (Niacin)

Mechanism: Nicotinic acid enters the Preiss-Handler pathway: it is converted by nicotinic acid phosphoribosyltransferase (NAPRT) to nicotinic acid mononucleotide (NaMN), then to nicotinic acid adenine dinucleotide (NaAD) by NMNAT, and finally to NAD⁺ by NAD synthetase (glutamine-dependent amidation). This pathway is distinct from the NRK pathway used by NR. Nicotinic acid also activates the GPR109A receptor (hydroxycarboxylic acid receptor 2), producing prostaglandin-mediated cutaneous vasodilation (the niacin flush) and lipid-modifying effects [33].

Novelty: Very low. Niacin has been used therapeutically since the 1950s for pellagra prevention and since the 1960s for dyslipidemia.

Effect size: Nicotinic acid is a potent NAD⁺ precursor and effectively raises tissue NAD⁺ levels. Its lipid-modifying effects (reduction of LDL cholesterol, triglycerides; increase in HDL cholesterol) are well established. However, the AIM-HIGH (2011) and HPS2-THRIVE (2014) cardiovascular outcomes trials demonstrated no benefit of niacin added to statin therapy on cardiovascular events, substantially reducing enthusiasm for its clinical use [34].

Promising potential: Low for new clinical development. The compound is well established but its trajectory for novel applications is limited.

Side-effect profile: The principal limitation is the flushing response (warmth, redness, pruritus of the face, neck, and upper trunk), which occurs in the majority of users and is a frequent cause of discontinuation. Extended-release formulations reduce but do not eliminate flushing. Hepatotoxicity has been reported with sustained-release niacin formulations. NR does not produce flushing because it does not activate GPR109A.

Overall validation: High for established indications (pellagra, dyslipidemia). Low for aging and neuroprotection applications, where NR and NMN have superseded niacin in the research literature.

Comparison to NR: Nicotinic acid is an effective NAD⁺ precursor but is limited by flushing, hepatotoxicity risk, and the negative cardiovascular outcomes data. NR offers comparable or superior NAD⁺ elevation without the flushing, GPR109A activation, or hepatotoxicity concerns. NR has replaced niacin as the preferred NAD⁺ precursor in the aging and longevity research field.

12.3 Nicotinamide (Niacinamide)

Mechanism: Nicotinamide enters the salvage pathway through NAMPT, which converts it to NMN. This is the dominant endogenous NAD⁺ salvage pathway and the same intracellular pathway through which NR-derived NMN is converted to NAD⁺. Nicotinamide is also a product of NAD⁺ consumption by sirtuins, PARPs, and CD38, and its accumulation at high concentrations can inhibit sirtuin activity through product inhibition [35].

Novelty: Very low. Nicotinamide has been used therapeutically for decades.

Effect size: Nicotinamide raises NAD⁺ levels at high oral doses (1,000 to 3,000 mg daily). However, the product-inhibitory effect on sirtuins is a significant limitation: at the concentrations required for substantial NAD⁺ elevation, nicotinamide may partially inhibit the very sirtuin enzymes that NAD⁺ is intended to activate. NR avoids this issue because NR-derived NAD⁺ generation does not proceed through a nicotinamide-accumulating step at the sirtuin active site.

Promising potential: Moderate. Nicotinamide is being evaluated in large-scale skin cancer prevention trials (the ONTRAC trial demonstrated 23 percent reduction in non-melanoma skin cancers at 500 mg twice daily) and in renal protection studies. These applications exploit mechanisms (PARP substrate provision, anti-inflammatory effects) that are partially shared with NR.

Side-effect profile: Nicotinamide does not cause flushing. Gastrointestinal symptoms and hepatotoxicity are reported at high doses (greater than 3,000 mg daily). The sirtuin-inhibitory concern is pharmacological rather than toxicological.

Overall validation: Moderate. The compound is well studied, inexpensive, and effective for some applications but is pharmacologically inferior to NR for sirtuin-mediated effects because of product inhibition.

Comparison to NR: NR is theoretically superior to nicotinamide for applications that require sirtuin activation, because NR bypasses the potential for nicotinamide-mediated sirtuin inhibition. NR provides NAD⁺ through the NRK pathway without generating inhibitory concentrations of free nicotinamide at the sirtuin active site. However, nicotinamide is dramatically less expensive and more widely available.

12.4 CD38 Inhibitors (Apigenin, 78c)

Mechanism: CD38 is a major NADase whose expression increases with aging and inflammation. CD38 inhibition reduces NAD⁺ degradation rather than increasing NAD⁺ synthesis. Apigenin (a dietary flavonoid found in parsley, celery, and chamomile) and 78c (a synthetic thiazoloquin(az)olin(on)e) are CD38 inhibitors that have been shown to raise tissue NAD⁺ levels in aged mice [26]. The approach is mechanistically complementary to NR supplementation.

Novelty: High. The CD38 inhibition strategy for NAD⁺ boosting is more recent than the precursor supplementation approach and addresses a different node in the NAD⁺ homeostatic circuit.

Effect size: In aged mice, 78c increases tissue NAD⁺ levels, activates sirtuins, and improves metabolic and physical function [26]. Apigenin raises NAD⁺ in vitro but its in vivo potency as a CD38 inhibitor is limited by low bioavailability. No clinical efficacy data exist for either compound as a NAD⁺ booster in humans.

Promising potential: Moderate for 78c (preclinical only). Low for apigenin as a NAD⁺ booster (insufficient potency at achievable human doses). The strategy is scientifically sound but clinically undeveloped.

Side-effect profile: Apigenin is generally well tolerated as a dietary flavonoid. 78c has preclinical safety data only. No human safety data for either compound at NAD⁺-boosting doses.

Overall validation: Low. Preclinical proof of concept is established but no clinical translation has occurred.

Comparison to NR: CD38 inhibition and NR supplementation address complementary nodes in NAD⁺ homeostasis (degradation versus synthesis). The combination is theoretically attractive but clinically untested. NR is far more clinically advanced, with extensive human safety and pharmacodynamic data. CD38 inhibitors are principally research tools at present.

12.5 Dihyronicotinamide Riboside (NRH)

Mechanism: NRH is the reduced form of NR. It is converted to NAD⁺ through a pathway involving adenosine kinase-mediated phosphorylation to NMNH, followed by oxidation and adenylation [36]. NRH raises NAD⁺ more rapidly and to a greater extent than NR in cell culture systems, with some studies reporting 2.5- to 10-fold higher NAD⁺ elevation than equimolar NR in hepatocytes and other cell types.

Novelty: High. NRH was identified as a potent NAD⁺ precursor more recently than NR, and its metabolic pathway through adenosine kinase is distinct from the NRK pathway used by NR.

Effect size: In cell culture, NRH is substantially more potent than NR for NAD⁺ elevation. In mouse models, NRH raises hepatic NAD⁺ effectively but has shown more variable tissue distribution than NR. A 2026 publication in Nature Communications demonstrated that NRH supplementation improves glucose tolerance and metabolic function in obese mice [37].

Promising potential: Moderate. The compound is in early preclinical development. No human clinical data exist. The greater potency relative to NR in cell culture is promising but tissue-specific distribution and safety in humans are unknown.

Side-effect profile: Preclinical only. Potential concerns include the possibility that the reduced pyridinium ring may have different redox chemistry and off-target effects compared to NR. Formal toxicology studies are limited.

Overall validation: Low. The compound is a promising research tool with early preclinical support but no clinical validation.

Comparison to NR: NRH is a newer, potentially more potent NAD⁺ precursor that may eventually supersede NR in some applications. However, NR has a vastly more developed clinical and regulatory record. NRH is at least 5 to 10 years behind NR in clinical development and cannot currently be recommended for human use outside of controlled research settings.

12.6 Comparator summary

The five comparators occupy distinct positions in the NAD⁺ repletion landscape. NMN is the closest mechanistic equivalent to NR, with convergent intracellular pathways and a growing but smaller clinical database; regulatory uncertainty in the United States limits its commercial trajectory. **Nicotinic acid** is the oldest and best-validated NAD⁺ precursor but is limited by flushing, hepatotoxicity, and negative cardiovascular outcomes data. **Nicotinamide** is inexpensive and effective but carries pharmacological disadvantage from sirtuin product inhibition. **CD38 inhibitors** represent a mechanistically novel approach that is complementary to NR but clinically undeveloped. **NRH** is a potentially more potent NAD⁺ precursor in early preclinical development.

NR occupies the strongest composite position among the comparators: it has the largest clinical trial database of any dedicated NAD⁺ precursor, established regulatory status (GRAS, NDI), absence of flushing, no sirtuin product inhibition, consistent pharmacodynamic activity across multiple human populations, and a tolerability profile that supports doses up to 3,000 mg daily. The principal limitation relative to the field is the absence of definitive clinical efficacy on disease-specific endpoints in adequately powered trials. NR reliably raises NAD⁺ in humans; whether raising NAD⁺ reliably improves clinical outcomes remains the critical unanswered question for the entire NAD⁺ precursor class.

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