

RESEARCH MONOGRAPH . COMPOUND PROFILE

Dihydro-NMN

A reduced-form nicotinamide mononucleotide that bypasses canonical salvage pathway enzymes to elevate cellular NAD⁺ and NADH more rapidly and to a greater extent than its oxidized counterpart NMN, with emerging preclinical evidence in renal cytoprotection, metabolic reprogramming, and anti-proliferative activity.

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AUTHOR	Kodi <i>ac</i> biolabs Research
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ABSTRACT

Dihydronicotinamide mononucleotide (NMNH), also designated reduced nicotinamide mononucleotide or dihydro-NMN, is the 1,4-dihydropyridine analog of beta-nicotinamide mononucleotide (NMN). The compound differs from NMN by a single additional hydrogen at the C-4 position of the nicotinamide ring, converting the aromatic pyridinium to a non-aromatic 1,4-dihydropyridine and conferring distinct biochemical, pharmacokinetic, and pharmacological properties. NMNH was first characterized as a potent nicotinamide adenine dinucleotide (NAD⁺) precursor in mammalian systems in two independent 2021 reports: Zapata-Perez et al. in *The FASEB Journal* demonstrated that NMNH increases NAD⁺ levels to a substantially greater extent and faster than NMN or nicotinamide riboside (NR) across multiple tissues in mice, while Liu et al. in the *Journal of Proteome Research* showed that NMNH potently enhances NAD⁺ and NADH, suppresses glycolysis and the tricarboxylic acid cycle, induces reductive stress, and inhibits cell growth in hepatocellular carcinoma cells. The metabolic pathway of NMNH is mechanistically distinct from that of NMN: NMNH is converted directly to NADH by nicotinamide mononucleotide adenylyltransferase (NMNAT) without requiring nicotinamide phosphoribosyltransferase (NAMPT) or nicotinamide riboside kinase (NRK), the two rate-limiting enzymes of the canonical salvage and Preiss-Handler pathways. The resulting NADH is then oxidized to NAD⁺ by cellular oxidoreductases, producing a net elevation of both reduced and oxidized pyridine dinucleotide pools. In vivo, intraperitoneal administration of NMNH to mice elevates hepatic NAD⁺ approximately five-fold and renal NAD⁺ approximately

two-fold, with significant increases also observed in brain, skeletal muscle, brown adipose tissue, and heart, tissues in which equivalent doses of NMN produce no statistically significant NAD⁺ elevation. The Zapata-Perez et al. study additionally demonstrated that NMNH protects conditionally immortalized proximal tubular epithelial cells against hypoxia and reoxygenation injury, reducing expression of the kidney injury biomarker Kim-1 and the mitochondrial dysfunction marker Tfam, establishing a preclinical basis for renal cytoprotection. The Liu et al. metabolomic analysis revealed that NMNH-treated cells exhibit marked suppression of glycolytic intermediates (glucose-6-phosphate, fructose-1,6-bisphosphate, phosphoenolpyruvate, pyruvate) and tricarboxylic acid cycle intermediates (citrate, alpha-ketoglutarate, succinate, fumarate, malate), accompanied by cell cycle arrest and growth inhibition. The compound induces cellular reductive stress through elevation of the NADH/NAD⁺ ratio, which paradoxically increases reactive oxygen species (ROS) production, linking the reductive stress phenotype to the anti-proliferative activity. NMNH is prepared by chemical reduction of NMN with thiourea dioxide in alkaline aqueous solution or by enzymatic cleavage of NADH with NADH pyrophosphatase (NudC). The compound is supplied as the disodium salt (CAS 108347-85-9) and is commercially available from multiple research chemical suppliers. A first-in-human clinical trial reported in January 2026 indicated that oral NMNH at 500 mg daily for 90 days approximately tripled circulating NAD⁺ levels in healthy adults, though these results remain unpublished and unverified by independent peer review. No regulatory approval exists for NMNH in any jurisdiction; the compound is sold as a dietary supplement or research reagent. This monograph reviews the chemistry, synthesis, and structural distinction from NMN; the NMNAT-

dependent metabolic pathway; the preclinical pharmacology across NAD⁺ elevation, renal cytoprotection, metabolic reprogramming, and anti-proliferative activity; the limited pharmacokinetic data in mice and humans; the emerging clinical evidence; sourcing and quality verification; reconstitution and handling; stack interactions with other NAD⁺ precursors and metabolic modulators; the adverse-event and safety signal including reductive stress and reactive oxygen species concerns; and a comparative assessment of five NAD⁺ precursor candidates against NMNH on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred name: Dihydronicotinamide mononucleotide.

Common abbreviations: NMNH, reduced NMN, dihydro-NMN.

Systematic chemical name (IUPAC): 1-(5-O-phosphono-beta-D-ribofuranosyl)-1,4-dihydropyridine-3-carboxamide.

Chemical Abstracts Service registry numbers: 108347-85-9 (disodium salt). The free acid form does not have a separately registered CAS number in wide commercial use; the disodium salt is the standard commercial and research preparation.

PubChem CID: 440765 (dihydronicotinamide mononucleotide).

Related parent compound: beta-Nicotinamide mononucleotide (NMN), CAS 1094-61-7. NMNH is the 1,4-dihydro reduction product of NMN.

Related dinucleotide: Reduced nicotinamide adenine dinucleotide (NADH), of which NMNH is the mononucleotide fragment produced by pyrophosphatase cleavage of the pyrophosphate bond.

1.2 Structural class and chemistry

NMNH belongs to the class of reduced pyridine nucleotides. The compound consists of a 1,4-dihydronicotinamide moiety linked via a beta-N-glycosidic bond to a D-ribofuranose sugar that is phosphorylated at the 5-prime position. The critical structural distinction from NMN is the reduction state of the nicotinamide ring: NMN contains an aromatic pyridinium ring (oxidized form), whereas NMNH contains a non-aromatic 1,4-dihydropyridine ring (reduced form) bearing an additional hydrogen at C-4. This reduction converts the positively charged pyridinium nitrogen to a neutral tertiary amine and introduces a conjugated diene system in the ring that is responsible for the characteristic ultraviolet absorption at approximately 340 nanometers and the intrinsic fluorescence (excitation approximately 340 nm, emission approximately 460 nm) that distinguishes all dihydronicotinamide species from their oxidized counterparts [1, 2].

Molecular formula: C₁₁H₁₇N₂O₈P (free acid form); C₁₁H₁₅N₂Na₂O₈P (disodium salt).

Molecular weight: 336.24 g/mol (free acid); 380.20 g/mol (disodium salt).

Physical properties: The disodium salt is a white to off-white hygroscopic powder. Freely soluble in water. The compound exhibits characteristic UV absorption maxima at approximately 260 nm (nicotinamide ring) and approximately 340 nm (dihydropyridine chromophore). The 340 nm absorption is diagnostic for the reduced form and is absent in NMN. The compound is fluorescent under UV excitation at 340 nm, emitting at approximately 460 nm; NMN is not fluorescent. This spectroscopic distinction provides a convenient analytical assay for NMNH identity and purity [1].

Stability: NMNH in the solid state as the disodium salt is reported to be stable at ambient temperature for extended periods (up to three years without significant degradation when stored in sealed containers with desiccant). In aqueous solution, the dihydropyridine ring is susceptible to oxidation; solutions should be prepared fresh or stored under inert atmosphere at reduced temperature. The compound is more chemically labile than NMN in solution owing to the oxidation-prone dihydropyridine, and care must be taken to minimize exposure to atmospheric oxygen and light during handling [3].

1.3 Synthesis

NMNH is prepared by two principal methods, both described in the Liu et al. (2021) report [1].

Chemical reduction of NMN: The primary preparative method uses thiourea dioxide (TDO, also known as formamidine sulfinic acid) as the reducing agent. In the published protocol, 340 mg of NMN and 125 mg of TDO are dissolved in 1 mL of 10 percent aqueous ammonia solution, and the reaction mixture is incubated at 40 degrees Celsius for 1 hour. The product is purified by high-performance liquid chromatography (HPLC) on an amide column and recovered by vacuum drying. TDO was selected over classical reducing agents (sodium dithionite, sodium borohydride) because of its stability under standard laboratory storage conditions, its amenability to aqueous solution preparation, its high reduction potential in aque-

ous alkaline media, and its suitability for scalable applications. The reduction is regioselective for the 1,4-position of the nicotinamide ring, producing the biologically active 1,4-dihydro isomer rather than the 1,6- or 1,2-dihydro isomers [1].

Enzymatic cleavage of NADH: The second preparative method uses NADH pyrophosphatase (NudC from *Escherichia coli*) to hydrolyze the pyrophosphate bond of NADH, producing NMNH and adenosine monophosphate (AMP). In the published protocol, 20 mg of NADH and 13 micrograms of NudC are dissolved in 1 mL of water containing 500 mM ammonium acetate and 3 mM magnesium chloride, and the reaction is allowed to proceed to completion. The NMNH product is separated from AMP by HPLC. This method produces NMNH of identical fragmentation pattern and biological activity to the chemically synthesized material, confirming the structural identity of the two preparations [1].

Industrial-scale production for the supplement market employs variants of the chemical reduction method with optimized yields and purification steps, typically achieving greater than 98 percent purity by HPLC [3].

2. Abstract

Dihydronicotinamide mononucleotide (NMNH) is the reduced form of beta-nicotinamide mononucleotide (NMN) and represents a mechanistically distinct NAD⁺ precursor that bypasses the rate-limiting enzymes of canonical NAD⁺ salvage biosynthesis. The compound was characterized as a potent NAD⁺ enhancer in two landmark 2021 publications. Zapata-Perez et al. demonstrated in *The FASEB Journal* that NMNH is metabolized through a nicotinamide riboside kinase (NRK)- and nicotinamide phosphoribosyltransferase (NAMPT)-independent pathway, increasing cellular and tissue NAD⁺ levels to a substantially greater extent than equimolar NMN across multiple organs in mice [2]. Liu et al. reported in the *Journal of Proteome Research* that NMNH elevates both NAD⁺ and NADH in HepG2 hepatocellular carcinoma cells and in mouse liver, with concomitant metabolic reprogramming characterized by suppression of glycolysis and the tricarboxylic acid (TCA) cycle, induction of reductive stress, elevation of reactive oxygen species (ROS), and suppression of cell growth [1].

The metabolic pathway of NMNH proceeds through direct adenylation by nicotinamide mononucleotide adenylyltransferase (NMNAT) isoforms to produce NADH, which is subsequently oxidized to NAD⁺ by cellular oxidoreductases including Complex I of the mitochondrial electron transport chain. This pathway is shorter than the NMN salvage route and independent of the NAMPT bottleneck that constrains NMN-to-NAD⁺ conversion in conditions of NAMPT downregulation or inhibition [1, 2].

In mice, a single intraperitoneal dose of NMNH produces approximately five-fold elevation of hepatic NAD⁺ (compared to approximately 1.5-fold for equimolar NMN), approximately two-fold elevation of renal NAD⁺, and statistically significant NAD⁺ elevation in brain, gastrocnemius muscle, brown adipose tissue, and heart. The hepatic NAD⁺ elevation at 1 hour post-injection is approximately 2.6-fold greater in NMNH-treated than in NMN-treated animals. The renal NAD⁺ elevation forms the basis for the demonstrated cytoprotective activity in proximal tubular epithelial cells subjected to hypoxia and reoxygenation, a model of ischemic acute kidney injury [2].

The anti-proliferative and metabolic reprogramming activities of NMNH are mediated by a distinct mechanism from the cytoprotective NAD⁺ elevation. The elevation of NADH relative to NAD⁺ produces reductive stress, defined as an excess of reducing equivalents relative to oxidizing capacity; this state paradoxically generates ROS through electron leakage from the mitochondrial electron transport chain and from NADPH oxidase, and the resulting oxidative damage contributes to cell cycle arrest and growth suppression. The simultaneous inhibition of glycolysis and the TCA cycle further deprives proliferating cells of biosynthetic intermediates [1].

A first-in-human clinical trial (90-day, double-blind, placebo-controlled, 80 healthy adults, 500 mg NMNH daily) reported in January 2026 that NMNH approximately tripled circulating NAD⁺ levels with no clinically significant adverse events on standard safety laboratory panels. These results remain unpublished in peer-reviewed form and require independent verification [4]. No regulatory agency has approved NMNH for any therapeutic indication. The compound is available as a dietary supplement and as a research reagent from multiple commercial sources.

3. Discovery and Development History

3.1 Context: the NAD⁺ precursor landscape

The recognition that nicotinamide adenine dinucleotide (NAD⁺) declines with age and that this decline contributes to metabolic dysfunction, genomic instability, mitochondrial deterioration, and stem cell senescence has driven a two-decade search for orally bioavailable NAD⁺ precursors [5, 6]. The principal precursors studied through 2020 were nicotinamide (NAM), nicotinic acid (NA, niacin), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN), all of which feed into NAD⁺ biosynthesis through the Preiss-Handler pathway (NA), the salvage pathway (NAM, NR, NMN), or the de novo pathway (tryptophan). Each precursor has limitations: NAM produces dose-limiting flushing through a distinct mechanism from NA but inhibits sirtuins at high concentrations; NA produces pronounced vasodilatory flushing; NR is orally bioavailable but substantially degraded to NAM in the gastrointestinal tract before absorption; and NMN is partially dephosphorylated to NR by CD73 (ecto-5-prime-nucleotidase) at the intestinal brush border before cellular uptake, though direct transport by the Slc12a8 transporter has also been demonstrated [7, 8].

3.2 Identification of reduced NAD⁺ precursors

The recognition that the reduced (dihydro) forms of NAD⁺ precursors might constitute a distinct and potentially superior class of NAD⁺ enhancers emerged from two lines of investigation in 2019 to 2021.

The first was the Giroud-Gerbetant et al. (2019) report identifying dihydronicotinamide riboside (NRH) as a potent NAD⁺ enhancer that increases cellular NAD⁺ concentrations 2.5- to 10-fold within 1 hour, substantially exceeding the capacity of NR at equivalent concentrations [9]. The NRH metabolic pathway was shown to proceed through phosphorylation by adenosine kinase (ADK) to produce NMNH, which is then adenylylated by NMNAT to NADH, which is oxidized to NAD⁺. This finding established NMNH as a central intermediate in the NRH-to-NAD⁺ pathway and motivated direct investigation of NMNH as an NAD⁺ precursor.

The second was the simultaneous and independent characterization of NMNH itself by the Bhatt and Bhatt laboratories (Liu et al., initially deposited as a bioRxiv preprint in November 2020, published in the Journal of Proteome Research in April 2021) and by the Houtkooper laboratory (Zapata-Perez et al., published in The FASEB Journal in March 2021) [1, 2]. These two reports, though conducted independently and using different cell lines, animal models, and analytical methods, reached convergent conclusions: NMNH is a substantially more potent NAD⁺ precursor than NMN in both cellular and animal systems, and it operates through a metabolic pathway that is independent of the NAMPT and NRK enzymes that constrain the canonical salvage route.

3.3 Subsequent research and commercial development

Following the 2021 landmark reports, research on NMNH expanded along three axes. The cytoprotection axis explored renal and potentially cardiac applications of the enhanced NAD⁺ elevation. The anti-proliferative axis explored the metabolic reprogramming and reductive stress phenotype as a potential anti-tumor mechanism. The supplement-commercial axis advanced NMNH into commercial production as a dietary supplement, with multiple manufacturers (EffePharm, UthPeak, Double Wood Supplements, and others) bringing NMNH products to market beginning in approximately 2023 [3, 4].

A protein engineering study by Yang et al. (2023) optimized the NADH pyrophosphatase NudC for efficient biocatalytic production of NMNH, improving the enzymatic synthesis route for scaled manufacturing [10].

The first-in-human clinical trial, conducted with NMNH at 500 mg daily for 90 days in 80 healthy adults, was reported in January 2026 by the sponsoring company. The results indicated approximate tripling of circulating NAD⁺ levels and improvements in subjective quality-of-life measures including emotional well-being and energy levels. The sponsor additionally reported a five-year reduction in biological age as measured by epigenetic clock assays. These results have not been published in a peer-reviewed journal and should be interpreted with caution given the sponsor's commercial interest in the compound [4].

4. Mechanism of Action

NMNH exerts its biological effects through a metabolic pathway that is mechanistically distinct from the canonical NAD⁺ salvage pathway and that produces both NAD⁺ elevation and a concurrent NADH elevation with downstream consequences for cellular redox state, metabolic flux, and proliferative capacity.

4.1 NMNAT-dependent conversion to NADH

The central enzymatic step in NMNH metabolism is the adenylation of NMNH by nicotinamide mononucleotide adenylyltransferase (NMNAT) to produce NADH. Three NMNAT isoforms exist in mammalian cells: NMNAT1 (nuclear), NMNAT2 (cytoplasmic, Golgi-associated), and NMNAT3 (mitochondrial). All three isoforms catalyze the condensation of NMN with ATP to produce NAD⁺ and pyrophosphate; the same enzymes catalyze the condensation of NMNH with ATP to produce NADH and pyrophosphate. The *K_m* values for NMNH have not been reported separately from those for NMN in published NMNAT kinetic studies, but the Liu et al. demonstration that NMNAT mediates the NMNH-to-NADH conversion was established by NMNAT knockdown experiments in which NMNAT silencing abolished NMNH-mediated NAD⁺ and NADH elevation [1].

The resulting NADH is oxidized to NAD⁺ by cellular oxidoreductases, principally Complex I (NADH:ubiquinone oxidoreductase) of the mitochondrial electron transport chain, cytoplasmic lactate dehydrogenase, and other NAD⁺-dependent dehydrogenases operating in the reverse direction. The net effect is elevation of both the NADH and NAD⁺ pools, with the magnitude of NAD⁺ elevation exceeding that produced by equimolar NMN [1, 2].

4.2 Independence from NAMPT and NRK

The NMNH metabolic pathway bypasses two enzymes that constrain the canonical salvage pathway. Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the rate-limiting step of NAM-to-NMN conversion in the salvage pathway; its expression and activity decline with age and are suppressed in multiple pathological

states including obesity, diabetes, and neurodegeneration. Nicotinamide riboside kinase (NRK1/NRK2) catalyzes the phosphorylation of NR to NMN; NRK expression is tissue-variable and is rate-limiting for NR utilization in some tissues [7].

NMNH bypasses both enzymes entirely. The Zapata-Perez et al. report demonstrated that NMNH treatment simultaneously suppresses endogenous NMN synthesis by NAMPT, suggesting that the NMNH pathway actively redirects flux away from the salvage pathway toward direct NADH formation [2]. This bypass mechanism is the principal molecular explanation for the superior NAD⁺ elevation observed with NMNH relative to NMN: the NMNAT step is not rate-limiting in most tissues, whereas the NAMPT and NRK steps are.

4.3 Reductive stress and reactive oxygen species generation

A distinctive feature of NMNH pharmacology is the induction of cellular reductive stress. The elevation of NADH relative to NAD⁺ shifts the cytoplasmic and mitochondrial redox potential toward a more reduced state. This reductive shift has several consequences [1]:

First, increased NADH availability at Complex I of the mitochondrial electron transport chain increases electron flux, and under conditions of high NADH/NAD⁺ ratio, electron leakage from Complex I and Complex III to molecular oxygen increases, generating superoxide anion and downstream reactive oxygen species (hydrogen peroxide, hydroxyl radical). Second, elevated NADH can drive NADPH production through the nicotinamide nucleotide transhydrogenase (NNT), and elevated NADPH can fuel NADPH oxidase-mediated superoxide production. Third, the reductive stress can impair the glutathione and thioredoxin antioxidant systems, which depend on appropriate redox cycling for function.

The net effect is a paradoxical increase in ROS in the context of an overall more reduced cellular environment. This phenomenon has been documented in NMNH-treated HepG2 cells and is proposed as the mechanistic basis for the observed cell cycle arrest and growth inhibition [1].

4.4 Metabolic reprogramming: glycolysis and TCA cycle suppression

The Liu et al. metabolomic analysis demonstrated that NMNH treatment produces a striking suppression of glycolytic and TCA cycle intermediates in HepG2 cells [1]. Glycolytic intermediates (glucose-6-phosphate, fructose-6-phosphate, fructose-1,6-bisphosphate, glyceraldehyde-3-phosphate, 1,3-bisphosphoglycerate, 3-phosphoglycerate, 2-phosphoglycerate, phosphoenolpyruvate, and pyruvate) were uniformly reduced. TCA cycle intermediates (citrate, isocitrate, alpha-ketoglutarate, succinate, fumarate, and malate) were similarly suppressed.

The mechanism of glycolytic suppression is plausibly linked to the elevated NADH/NAD⁺ ratio: multiple glycolytic enzymes (glyceraldehyde-3-phosphate dehydrogenase, lactate dehydrogenase) are NAD⁺-dependent, and a shift toward NADH inhibits their forward reaction. The TCA cycle is similarly constrained by product inhibition at the NAD⁺-dependent dehydrogenases (isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, malate dehydrogenase) when NADH is elevated.

4.5 NAD⁺-dependent signaling consequences

The elevation of NAD⁺ by NMNH is expected to activate the principal NAD⁺-consuming signaling enzymes: the sirtuin family of NAD⁺-dependent protein deacylases (SIRT1 through SIRT7), the poly(ADP-ribose) polymerases (PARP1 and PARP2), and the cyclic ADP-ribose synthases (CD38 and CD157). Sirtuin activation produces downstream effects on mitochondrial biogenesis (SIRT1, SIRT3), genomic stability (SIRT1, SIRT6), inflammatory signaling (SIRT1), and metabolic regulation (SIRT1, SIRT3). PARP activation enhances DNA damage repair. These downstream consequences have been extensively characterized for NMN and NR and are expected to apply to NMNH-mediated NAD⁺ elevation, though direct demonstration of sirtuin and PARP activation by NMNH has not been reported in the published literature [5, 6].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and tissue distribution in mice

The pharmacokinetic characterization of NMNH in published literature is limited to mouse data from the Zapata-Perez et al. (2021) study [2]. Intraperitoneal injection of NMNH at 250 mg/kg in C57BL/6J mice produced the following tissue NAD⁺ elevations at 1 hour post-injection:

Liver: approximately five-fold increase over vehicle control, approximately 2.6-fold greater than the equimolar NMN group. Kidney: approximately two-fold increase, significantly greater than NMN. Brain: significant increase (NMNH group), no significant increase (NMN group). Gastrocnemius muscle: significant increase (NMNH group), no significant increase (NMN group). Brown adipose tissue: significant increase (NMNH group), no significant increase (NMN group). Heart: significant increase (NMNH group), no significant increase (NMN group). The broader tissue distribution of NMNH-mediated NAD⁺ elevation, relative to NMN, is a distinguishing pharmacokinetic feature [2].

Blood NAD⁺ was also significantly elevated in the NMNH group. The time course of NAD⁺ elevation showed peak hepatic levels at approximately 1 hour, sustained elevation at 6 hours, and return toward baseline by 24 hours. NADH levels were concurrently elevated in liver, with the NADH/NAD⁺ ratio remaining elevated at 6 hours [2].

5.2 Oral pharmacokinetics in humans

Human pharmacokinetic data for NMNH are limited to the unpublished 90-day clinical trial reported in January 2026 [4]. Oral NMNH at 500 mg daily approximately tripled circulating NAD⁺ levels over the 90-day treatment period. Detailed pharmacokinetic parameters (C_{max}, T_{max}, AUC, elimination half-life, oral bioavailability) have not been reported. The oral absorption and first-pass metabolism of NMNH in humans are therefore incompletely characterized.

By analogy with NRH, which is phosphorylated to NMNH by adenosine kinase after cellular uptake, orally administered NMNH may be partially dephosphorylated in the gastrointestinal lumen to NRH, absorbed as NRH, and rephosphorylated intracellularly. Alternatively, NMNH may be directly absorbed, as has been demonstrated for NMN via the Slc12a8 transporter, though no NMNH-specific transporter has been identified [8, 9].

5.3 Metabolism

NMNH is metabolized intracellularly by NMNAT to NADH, which enters the general NADH/NAD⁺ metabolic pool. The NADH is oxidized to NAD⁺ by mitochondrial Complex I and by cytoplasmic oxidoreductases. NAD⁺ is subsequently consumed by sirtuins, PARPs, and CD38 in signaling reactions that produce nicotinamide (NAM), which re-enters the salvage pathway [1, 2].

The compound is also susceptible to non-enzymatic and enzymatic oxidation back to NMN in aqueous solution and potentially in plasma, though the rate and significance of this oxidation in vivo have not been quantified.

5.4 Routes of administration

In preclinical research, NMNH has been administered by intraperitoneal injection (the route used in the Zapata-Perez et al. mouse study at 250 mg/kg). In the human clinical trial and in commercial supplement use, the oral route is standard, with capsule formulations of 250 mg and 500 mg available from multiple manufacturers. Intravenous, subcutaneous, and other parenteral routes have not been characterized in published reports.

6. Preclinical Pharmacology

6.1 NAD⁺ and NADH elevation

The primary preclinical pharmacological activity of NMNH is the elevation of intracellular NAD⁺ and NADH pools. In HepG2 human hepatocellular carcinoma cells, NMNH at 50 micromolar produced a three-fold increase in NAD⁺ at 6 hours, whereas NMN at the same concentration produced a two-fold increase. At 1 mM, NMNH produced a five-fold increase in NAD⁺ compared to a two-fold increase with NMN. NADH levels were 2.5-fold higher in NMNH-treated cells than in untreated or NMN-treated cells at equivalent concentrations [1].

In C57BL/6J mice, intraperitoneal NMNH at 250 mg/kg produced hepatic NAD⁺ levels four-fold higher than PBS-treated controls and 1.5-fold higher than NMN-treated animals at the same dose. The kinetic profile showed rapid onset (peak at 1 hour) with sustained elevation (significant at 6 hours) and return toward baseline by 24 hours [2].

6.2 Renal cytoprotection

The Zapata-Perez et al. study demonstrated that NMNH protects conditionally immortalized proximal tubular epithelial cells (ciPTEC) against hypoxia and reoxygenation injury, an in vitro model of ischemic acute kidney injury [2]. NMNH treatment increased NAD⁺ content in ciPTEC cells and reduced expression of kidney injury molecule-1 (Kim-1), a validated biomarker of proximal tubular injury. Expression of mitochondrial transcription factor A (Tfam), a marker of mitochondrial biogenesis, was also modulated, suggesting that NMNH-mediated NAD⁺ elevation supports mitochondrial recovery after hypoxic insult. The cytoprotective effect was greater with NMNH than with NMN at equivalent concentrations, consistent with the superior NAD⁺ elevation.

These findings position NMNH as a candidate renoprotective agent in the context of ischemia-reperfusion injury, acute kidney injury, and potentially chronic kidney disease, though in vivo renal protection studies have not yet been reported [2].

6.3 Anti-proliferative activity and metabolic reprogramming

In HepG2 cells, NMNH induced cell cycle arrest and suppressed cell growth in a concentration-dependent manner. The growth suppression was accompanied by the metabolomic signature of glycolytic and TCA cycle inhibition described in Section 4.4. The anti-proliferative effect was mediated by the combination of reductive stress (elevated NADH/NAD⁺ ratio), ROS generation, and biosynthetic intermediate depletion [1].

The anti-proliferative activity raises the question of whether NMNH-mediated NAD⁺ elevation could paradoxically impair normal tissue homeostasis or whether the effect is selective for highly glycolytic cells (such as cancer cells and rapidly proliferating cells). The Liu et al. study was conducted exclusively in HepG2 cells, a hepatocellular carcinoma cell line with high glycolytic flux. Whether normal hepatocytes, renal epithelial cells, or other non-transformed cell types exhibit the same growth suppression at equivalent NMNH concentrations has not been systematically characterized [1].

6.4 Suppression of endogenous NMN synthesis

An unexpected finding from the Liu et al. study was that NMNH treatment almost completely inhibited endogenous NMN synthesis by NAMPT. The mechanism of this inhibition is not fully elucidated but may involve product feedback (elevated NAD⁺ or NADH inhibiting NAMPT) or substrate competition. The practical implication is that NMNH may redirect cellular NAD⁺ metabolism away from the salvage pathway and toward the NMNAT-direct pathway, potentially altering the steady-state metabolite profile and the balance between NAD⁺ production and consumption [1].

7. Clinical Evidence Base

7.1 First-in-human clinical trial

The sole human clinical study of NMNH reported to date is a 90-day, double-blind, placebo-controlled trial in 80 healthy adult participants at an oral dose of 500 mg NMNH daily [4]. The trial was sponsored by a commercial NMNH manufacturer and the results were communicated in January 2026 through company press materials rather than through peer-reviewed publication.

The reported findings include: approximate tripling of circulating NAD⁺ levels over the 90-day treatment period; improvement in subjective quality-of-life measures for emotional well-being and energy levels; a five-year reduction in biological age as measured by epigenetic clock (DNA methylation-based age estimation); and absence of clinically significant adverse events as assessed by standard safety laboratory panels including blood chemistry, lipid profile, liver function tests, renal function tests, and urinalysis [4].

The limitations of this evidence include: absence of peer-reviewed publication; potential conflict of interest (sponsor is a commercial NMNH vendor); absence of detailed pharmacokinetic parameters; absence of mechanistic biomarker data (sirtuin activity, PARP activity, NADH/NAD⁺ ratio); and absence of independent replication. The reported results are consistent with the preclinical NAD⁺ elevation data but cannot be considered validated until published and independently reproduced.

7.2 Indirect clinical evidence from NMN and NR trials

The clinical evidence for the broader class of NAD⁺ precursors provides indirect support for the expected clinical effects of NMNH. Multiple randomized controlled trials of NMN in humans have demonstrated dose-dependent NAD⁺ elevation, improved insulin sensitivity, increased walking endurance, and increased grip strength in older adults at doses of 250 to 500 mg daily over 6 to 12 weeks [11, 12]. NR has been shown to elevate blood NAD⁺ up to 2.7-fold after a single oral dose and to produce sustained NAD⁺ elevation over 14 days of supplementation [13].

The key open question is whether the superior preclinical NAD⁺ elevation observed with NMNH translates to superior clinical outcomes compared to NMN and NR, or whether the additional NADH elevation and reductive stress phenotype introduce risks that offset the NAD⁺ benefit. This question can only be resolved by head-to-head clinical comparison, which has not been reported.

7.3 Absence of therapeutic indication trials

No clinical trials of NMNH for any specific disease indication (ischemic kidney injury, metabolic disease, cancer, neurodegeneration, or aging) have been reported. The compound is therefore at a substantially earlier stage of clinical development than NMN or NR, both of which have extensive human trial databases.

8. Sourcing and Quality Verification

Research-grade NMNH is available from multiple chemical and supplement suppliers, including MedChemExpress (catalog number HY-145434), Sigma-Aldrich, Cayman Chemical, BioVision, and Bontac Bio-Engineering. The compound is supplied as the disodium salt at purities typically reported as greater than 95 percent by HPLC. Supplement-grade NMNH is available from manufacturers including EffePharm (UthPeak brand), Double Wood Supplements, and MAAC10, in 250 mg and 500 mg capsule formulations.

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

- High-performance liquid chromatography with UV detection at both 260 nm and 340 nm, confirming the presence of the dihydropyridine chromophore and the absence of oxidized NMN contamination
- Mass spectrometry confirmation of molecular weight (337.24 for the $[M+H]^+$ ion of the free acid, or 335.23 for the $[M-H]^-$ ion in negative mode)
- UV-visible spectrophotometry confirming the characteristic dual absorption at 260 nm and 340 nm; the 340/260 nm absorbance ratio provides a rapid purity check specific to the reduced form
- Fluorescence spectroscopy (excitation 340 nm, emission 460 nm) as a confirmatory assay for the dihydropyridine; oxidized NMN does not fluoresce at these wavelengths
- Karl Fischer or loss-on-drying analysis for residual water content (the disodium salt is hygroscopic)

The oxidation state of the nicotinamide ring is the most critical quality attribute for NMNH. Partial oxidation to NMN during storage, handling, or dissolution reduces the effective NMNH content and may confound dose-response interpretations. Investigators should prepare fresh solutions and confirm the 340 nm absorbance immediately before use [1, 3].

9. Reconstitution and Handling

NMNH disodium salt is freely soluble in water at room temperature. Stock solutions for in vitro research are typically prepared at 10 to 100 mM in ultrapure water or in phosphate-buffered saline. For in vivo research, solutions are prepared in phosphate-buffered saline at concentrations appropriate for the injection volume (typically 25 to 50 mg/mL for intraperitoneal injection in mice at 250 mg/kg) [1, 2].

Critical handling considerations for NMNH reflect the oxidation-susceptible dihydropyridine ring:

- Aqueous solutions should be prepared immediately before use when possible. Solutions stored for extended periods should be kept at 2 to 8 degrees Celsius under nitrogen or argon atmosphere in amber or foil-wrapped containers.
- Exposure to atmospheric oxygen accelerates oxidation to NMN. Sparging stock solutions with nitrogen or argon before sealing provides additional protection.
- Exposure to light, particularly ultraviolet light, may accelerate photochemical degradation. Light protection during handling and storage is recommended.
- The compound is stable in the solid state at ambient temperature when stored in sealed, desiccated containers. Manufacturer reports indicate stability for up to three years under these conditions.
- Freeze-thaw cycling of aqueous solutions has not been systematically characterized for NMNH; by analogy with NADH (which tolerates limited freeze-thaw cycles without substantial degradation), single-use aliquoting is recommended to minimize repeated freeze-thaw.
- For cell culture experiments, NMNH should be added to culture media immediately before use and the medium should not be stored with NMNH for extended periods, as oxidation in cell culture conditions (37 degrees Celsius, atmospheric oxygen) may be rapid.
- Confirmation of NMNH integrity by UV absorbance at 340 nm at the time of use is a prudent quality control step, particularly for experiments in which dose-response precision is critical [1].

10. Stack Interactions and Combinations

NMNH interacts with several compound classes through its metabolic pathway and its effects on cellular redox state. Investigators designing combination experiments or supplement stacks should consider the following:

Other NAD⁺ precursors (NMN, NR, NAM, NA): Concurrent administration of NMNH with NMN or NR is pharmacologically partially redundant, as all three compounds converge on NAD⁺ through NMNAT. However, the metabolic routes are distinct (NMNH bypasses NAMPT and NRK), and the combination may produce additive or supra-additive NAD⁺ elevation in tissues where one pathway is rate-limited. The simultaneous NADH elevation from NMNH may shift the net redox state toward reductive stress more than NMN or NR alone, and the combination should be monitored for ROS-related effects. Concurrent administration with NAM is not recommended at high doses, as NAM is a product inhibitor of sirtuins and may attenuate the sirtuin-activating benefit of the elevated NAD⁺ [5, 6].

NRH (dihydronicotinamide riboside): NRH is phosphorylated by adenosine kinase to NMNH as its first metabolic step. Concurrent NMNH and NRH administration is therefore duplicative, as NRH metabolism produces NMNH. The combination is not expected to produce synergy and may increase the risk of reductive stress [9].

Sirtuin activators (resveratrol, SRT1720, honokiol): The combination of NMNH with sirtuin activators is pharmacologically rational, as NMNH provides the NAD⁺ substrate and sirtuin activators increase the catalytic activity of the sirtuins. This combination has been explored for NMN and NR but not specifically for NMNH [5].

PARP inhibitors (olaparib, niraparib, rucaparib): PARP enzymes are major NAD⁺ consumers. PARP inhibitors reduce NAD⁺ consumption and may synergize with NMNH-mediated NAD⁺ elevation to produce greater net NAD⁺ accumulation. This combination has theoretical merit for neuroprotective and cardioprotective applications but has not been studied with NMNH.

CD38 inhibitors (apigenin, quercetin, 78c): CD38 is the principal NAD⁺-consuming ectoenzyme; its expression increases with age and contributes to age-related NAD⁺ decline. CD38 inhibitors reduce NAD⁺ consumption and may synergize with NMNH-mediated NAD⁺ production. The flavonoid CD38 inhibitors apigenin and quercetin are commonly stacked with NMN in supplement formulations; the same rationale applies to NMNH [14].

Antioxidants (N-acetylcysteine, alpha-lipoic acid, coenzyme Q10): Given the reductive stress and ROS generation associated with NMNH, concurrent antioxidant supplementation may attenuate the oxidative component while preserving the NAD⁺ elevation. The interaction has not been studied but is mechanistically plausible.

Metformin: Metformin inhibits Complex I of the mitochondrial electron transport chain, which is the principal site of NADH oxidation to NAD⁺. Concurrent NMNH and metformin may exacerbate NADH accumulation and reductive stress by impairing the oxidation of NMNH-derived NADH. This interaction warrants caution in diabetic patients or research subjects receiving metformin [1].

11. Adverse Events and Safety

11.1 Preclinical safety

No formal preclinical toxicology studies of NMNH have been published in peer-reviewed literature. The mouse studies by Zapata-Perez et al. and Liu et al. used acute or short-term dosing protocols and did not report overt toxicity at the studied doses (250 mg/kg intraperitoneal in mice). No mortality, behavioral changes, or organ-level toxicity were reported [1, 2].

11.2 Human safety data

The 90-day clinical trial at 500 mg NMNH daily in 80 healthy adults reported no clinically significant adverse effects on comprehensive safety laboratory panels, including blood chemistry, lipid profile, liver function, renal function, and urinalysis [4]. Common self-reported side effects from supplement users include mild digestive discomfort (nausea, bloating), nervousness, headache, and fatigue, though these reports are anecdotal and not from controlled trials [3].

11.3 Theoretical safety concerns

Reductive stress: The most distinctive safety concern for NMNH, relative to NMN and NR, is the induction of reductive stress through NADH elevation. Reductive stress has been implicated in cardiac hypertrophy (through protein aggregation in models of desmin-related cardiomyopathy), in exacerbation of ischemia-reperfusion injury (through ROS generation at reperfusion), and in impaired redox signaling. The chronic consequences of sustained NADH elevation from long-term NMNH supplementation are unknown [1].

Reactive oxygen species generation: The paradoxical increase in ROS associated with NMNH-induced reductive stress is a concern for long-term supplementation. While acute ROS elevation may activate beneficial adaptive stress responses (hormesis), chronic ROS elevation contributes to genomic damage, protein oxidation, and lipid peroxidation. The balance between beneficial hormetic signaling and harmful chronic oxidative damage from NMNH has not been characterized [1].

Anti-proliferative activity: The cell cycle arrest and growth suppression observed in HepG2 cells raise the question of whether NMNH at supplement doses could impair normal tissue renewal, wound healing, or immune cell proliferation. The selectivity of the anti-proliferative effect for transformed versus normal cells has not been characterized [1].

Interactions with hepatic and renal conditions: Individuals with pre-existing liver or kidney disease may have altered NMNAT activity, altered NADH oxidation capacity, or altered NAD⁺ metabolism, any of which could modify the response to NMNH. No data on NMNH in these populations exist.

Pregnancy and lactation: No animal reproductive toxicology data and no human pregnancy or lactation data are available. Use in pregnancy and lactation is not recommended in the absence of safety data.

11.4 Regulatory status

NMNH is not approved as a drug or therapeutic agent by any regulatory authority. It is marketed as a dietary supplement in the United States under the Dietary Supplement Health and Education Act (DSHEA) framework and in other jurisdictions under analogous regulations. The regulatory status of NMN, the closest comparator, has been contested: in October 2022, the United States Food and Drug Administration determined that NMN does not qualify as a dietary supplement because it was first studied as a drug. Whether this determination will be extended to NMNH is uncertain [15].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five NAD⁺ precursor candidates against NMNH, evaluated against five competency standards: novelty, effect size (magnitude of NAD⁺ elevation), promising potential (current trajectory and clinical advancement), side-effect profile, and overall validation. The five candidates were selected as the principal NAD⁺ precursors with substantive research programs and, where applicable, human clinical data.

12.1 Nicotinamide Mononucleotide (NMN)

Mechanism: NAD⁺ precursor metabolized through the salvage pathway via NMNAT. NMN is the direct oxidized counterpart of NMNH and the most directly comparable compound. NMN is converted to NAD⁺ by NMNAT in a single enzymatic step, the same enzyme that converts NMNH to NADH.

Novelty: Low. NMN has been studied as an NAD⁺ precursor since the mid-2000s and is the most extensively characterized compound in the class [6].

Effect size: Moderate. NMN produces approximately 1.5- to 2-fold elevation of hepatic NAD⁺ in mice at 250 to 500 mg/kg and approximately 1.5- to 2-fold elevation of blood NAD⁺ in humans at 250 to 500 mg daily over 4 to 12 weeks. NMNH produces approximately five-fold hepatic NAD⁺ elevation in mice at the same dose, a substantial advantage [1, 2, 11].

Promising potential: High. NMN has the most extensive human clinical trial database of any NAD⁺ precursor, with multiple randomized controlled trials demonstrating safety, NAD⁺ elevation, and functional outcomes (insulin sensitivity, walking endurance, grip strength) in healthy and aged adults [11, 12].

Side-effect profile: Favorable. Human trials at doses up to 1200 mg daily for 12 weeks have not reported significant adverse events. No reductive stress or ROS concerns have been identified, as NMN does not substantially elevate NADH [11, 12].

Overall validation: High. The most clinically validated NAD⁺ precursor, with the largest evidence base and the most extensive safety record.

Comparison to NMNH: NMN is the direct chemical and metabolic comparator. NMNH produces substantially greater NAD⁺ elevation in preclinical models (approximately three-fold advantage in liver) but also produces NADH elevation and reductive stress that NMN does not. NMN has a vastly larger clinical evidence base. NMNH has the preclinical potency advantage; NMN has the clinical validation advantage.

12.2 Nicotinamide Riboside (NR)

Mechanism: NAD⁺ precursor metabolized through the salvage pathway via NRK1/NRK2 (phosphorylation to NMN) followed by NMNAT (adenylation to NAD⁺). NR requires two enzymatic steps to reach NAD⁺, compared to one for NMN and one for NMNH [7].

Novelty: Low. NR was characterized as an NAD⁺ precursor by Bieganowski and Brenner in 2004 and has been extensively studied since [7].

Effect size: Moderate. NR produces up to 2.7-fold blood NAD⁺ elevation after a single oral dose in humans and sustained elevation over 14-day supplementation [13]. In mice, hepatic NAD⁺ elevation is approximately 1.5- to 2-fold at comparable doses. The effect size is similar to NMN and substantially less than NMNH in pre-clinical models.

Promising potential: High. NR (as Niagen, marketed by ChromaDex/Tru Niagen) is the most commercially established NAD⁺ precursor supplement. Multiple human trials have demonstrated safety and tolerability at doses up to 2000 mg daily [13].

Side-effect profile: Favorable. Mild gastrointestinal symptoms at high doses. No reductive stress concerns.

Overall validation: High. Second-largest clinical evidence base after NMN.

Comparison to NMNH: NR is metabolized to NMN to NAD⁺ (two steps) or, in its reduced form as NRH, to NMNH to NADH to NAD⁺ (with NMNH as an intermediate). NMNH bypasses the NRK step and produces superior NAD⁺ elevation preclinically. NR has the clinical validation advantage.

12.3 Dihydronicotinamide Riboside (NRH)

Mechanism: Reduced NAD⁺ precursor metabolized by adenosine kinase (ADK) to NMNH, then by NMNAT to NADH, then oxidized to NAD⁺. NRH is the immediate metabolic precursor of NMNH and shares the same downstream pathway [9].

Novelty: Moderate. NRH was characterized as a potent NAD⁺ enhancer by Giroud-Gerbetant et al. (2019) and by Yang et al. (2019), preceding the NMNH characterization by approximately two years [9].

Effect size: High. NRH produces 2.5- to 10-fold NAD⁺ elevation in cells within 1 hour, substantially exceeding NR and NMN. The effect size is comparable to NMNH, consistent with the shared pathway [9].

Promising potential: Moderate. No human clinical trials have been reported. The compound is available as a research reagent but is less commercially developed as a supplement than NMNH.

Side-effect profile: Concerning. A 2022 study by Sonavane et al. demonstrated that NRH promotes a pro-inflammatory phenotype in macrophages, raising safety concerns for chronic supplementation [16]. The same concern may apply to NMNH, as the shared pathway produces the same NADH elevation and potential reductive stress.

Overall validation: Low to moderate. Strong preclinical NAD⁺ elevation data, but the pro-inflammatory macrophage phenotype is a significant concern and no human data exist.

Comparison to NMNH: NRH and NMNH share the same downstream pathway (NRH is phosphorylated to NMNH). The two compounds are expected to produce similar biological effects. NMNH has the advantage of bypassing the ADK phosphorylation step (one fewer enzymatic step) and has more advanced human data (one clinical trial). NRH has the chronological priority in discovery.

12.4 Nicotinic Acid (Niacin, Vitamin B3)

Mechanism: NAD⁺ precursor metabolized through the Preiss-Handler pathway via nicotinic acid phosphoribosyltransferase (NAPRT), nicotinic acid mononucleotide adenyltransferase, and NAD⁺ synthetase. This is a three-step pathway entirely distinct from the salvage pathway [5].

Novelty: None. Niacin has been used as a vitamin and pharmaceutical agent since the 1950s.

Effect size: Moderate. Niacin at pharmacological doses (500 to 2000 mg daily) produces measurable NAD⁺ elevation, but the magnitude has not been directly compared to NMNH in controlled experiments.

Promising potential: Established but limited for NAD⁺ applications. Niacin is a registered pharmaceutical for dyslipidemia (Niacor, Niaspan), but its use as an NAD⁺ precursor is limited by the dose-dependent vasodilatory flushing that constrains patient compliance.

Side-effect profile: Unfavorable for NAD⁺ applications. Dose-dependent flushing, hepatotoxicity at high doses, hyperuricemia, and glucose intolerance limit the use of niacin at the doses required for substantial NAD⁺ elevation [5].

Overall validation: High for the dyslipidemia indication. Moderate for the NAD⁺ precursor application.

Comparison to NMNH: Niacin operates through an entirely different metabolic pathway and does not produce the NADH elevation or reductive stress associated with NMNH. NMNH has the preclinical potency advantage for NAD⁺ elevation. Niacin has the longest clinical history but the least favorable side-effect profile of the NAD⁺ precursors.

12.5 Nicotinamide (NAM, Niacinamide)

Mechanism: NAD⁺ precursor metabolized through the salvage pathway via NAMPT (the rate-limiting enzyme) to NMN, then by NMNAT to NAD⁺ [5].

Novelty: None. Nicotinamide is a B vitamin form used for decades.

Effect size: Low to moderate. NAM is an effective NAD⁺ precursor at low doses but is a product inhibitor of sirtuins: at concentrations above approximately 50 micromolar, NAM binds the sirtuin active site and inhibits deacylation, potentially negating the benefit of the NAD⁺ elevation [5, 6].

Promising potential: Limited for NAD⁺ enhancement applications, precisely because of sirtuin inhibition at the doses required for substantial NAD⁺ elevation.

Side-effect profile: Favorable at low doses. Hepatotoxicity at very high doses (greater than 3 g daily). No flushing (unlike nicotinic acid).

Overall validation: High as a vitamin. Low as a targeted NAD⁺ precursor for aging and metabolic applications due to sirtuin inhibition.

Comparison to NMNH: NMNH produces substantially greater NAD⁺ elevation without sirtuin inhibition (NMNH is not nicotinamide and does not inhibit sirtuins). NMNH bypasses the NAMPT bottleneck that constrains NAM-to-NAD⁺ conversion. NAM has the advantage of the longest safety record and lowest cost of any NAD⁺ precursor.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the NAD⁺ precursor landscape. NMN is the most clinically validated and the direct oxidized counterpart of NMNH, with the largest human trial database but lower preclinical NAD⁺ elevation potency. NR is the most commercially established supplement with a strong safety record but similar potency limitations to NMN. NRH is the most mechanistically similar to NMNH, sharing the same downstream pathway, with comparable preclinical potency but concerning pro-inflammatory signals and no human data. **Niacin** is the oldest NAD⁺ precursor with the worst side-effect profile for chronic supplementation. **Nicotinamide** is the simplest and cheapest precursor but is limited by sirtuin inhibition at effective doses.

NMNH occupies a unique position in this landscape: it is the most potent NAD⁺ enhancer in preclinical models (approximately three- to five-fold advantage over NMN and NR in liver), it bypasses the rate-limiting NAMPT and NRK enzymes, and it has the earliest human clinical data among the reduced-form precursors. Its principal liabilities are the limited clinical evidence (one unpublished trial), the reductive stress and ROS generation that distinguish it from the oxidized precursors, the anti-proliferative activity whose tissue selectivity is uncharacterized, and the regulatory uncertainty.

The critical question for the research-clinical positioning of NMNH is whether the substantially greater NAD⁺ elevation translates to proportionally greater clinical benefit or whether the concurrent NADH elevation and reductive stress phenotype introduce a safety ceiling that limits the therapeutic window. This question is

unanswerable with the current evidence base and will require head-to-head clinical trials with appropriate biomarker monitoring (NAD⁺, NADH, NADH/NAD⁺ ratio, ROS markers, sirtuin activity) to resolve.

13. References

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