UTHEVER®

Youth Forever, To Be World's Best NMN

Clinical-Backed NMN

NMN White Paper

Key Points

1. The level of NAD+ gradually declines with aging, leading to changes in metabolism and an increase in susceptibility to disease.
2. NMN can effectively improve intracellular NAD+ levels and is the preferred choice over mainstream NAD+ precursors due to its obvious advantages.
3. Extensive research has demonstrated that supplementing with the appropriate amount of NMN can increase NAD+ levels, thereby alleviating the onset and progression of various age-related diseases.
4. NMN, a safe and effective nutritional supplement, has gained widespread recognition and application globally in the food, dietary supplement, and cosmetic industries.

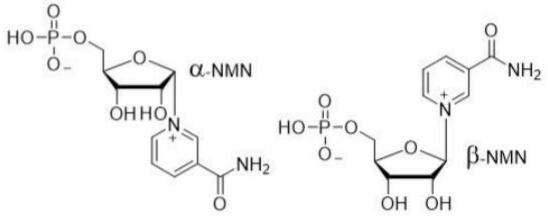
NMN as a natural bioactive agent

Nicotinamide Mononucleotide (NMN), is a derivative of vitamin B3, which has important physiological functions on human cells. It can be naturally synthesized in cells or obtained from a variety of plant and animal food sources[1], as listed in Table 1.

Table 1. NMN content in food

Food Types	Name	NMN Content (mg/100g)
Vegetables	Edamame	0.47-1.88
	Broccoli	0.25-1.12
	Cucumber	0.56-0.65
	Cabbage	0.0-0.9
Fruits	Avocado	0.36-1.6
	Tomato	0.26-0.3
Meat	Beef	0.06-0.42
Seafood	Shrimp	0.22

NMN is a bioactive nucleotide formed by the reaction between a nucleoside comprising nicotinamide and ribose and a phosphate group[2]. There are two types of differential isomers of NMN: α and β. Only β-type NMN was found to be biologically active and can increase intracellular NAD+ levels[3].



Restoring NAD+: therapeutic approaches and health impacts

Aging is associated with decreased nicotinamide adenine dinucleotide (NAD+) levels that promote or exacerbate aging-related diseases. Thus, restoring NAD+ levels has emerged as a intervention method to prevent and alleviate aging-related diseases and restore health and vigor during the aging process. Approaches promote tissue NAD+ levels and are beneficial for health. These include improved tissue and organ function, protection from cognitive decline, improved metabolic health, reduced inflammation, and increased physiological benefits, such as increased physical activity, which may collectively extend patient health-span and potentially lifespan[66], as illustrated in Figure 1.

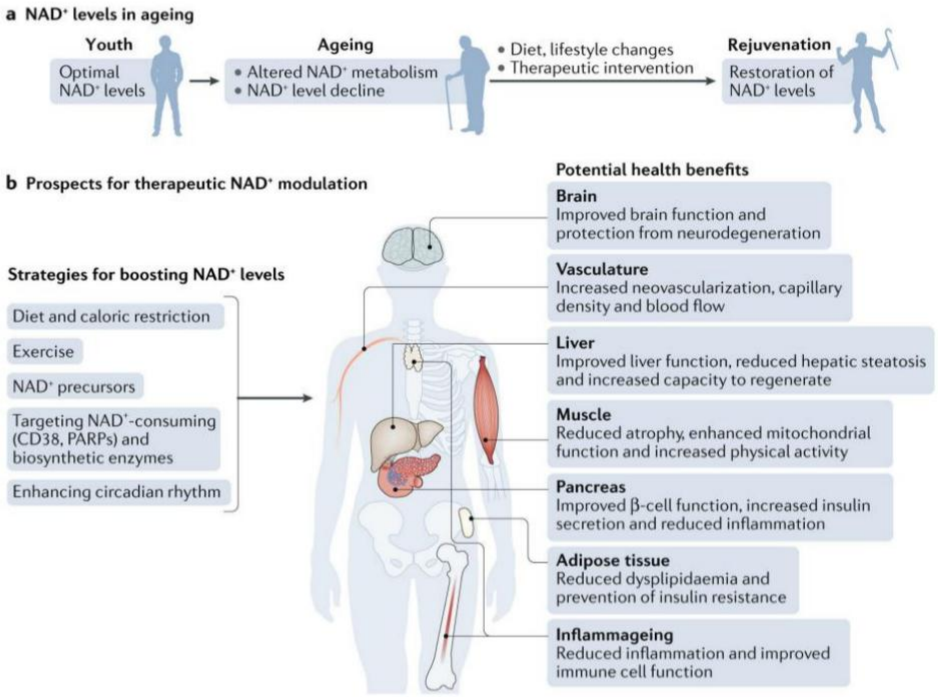


Figure 1. NAD+ levels and their impact on health

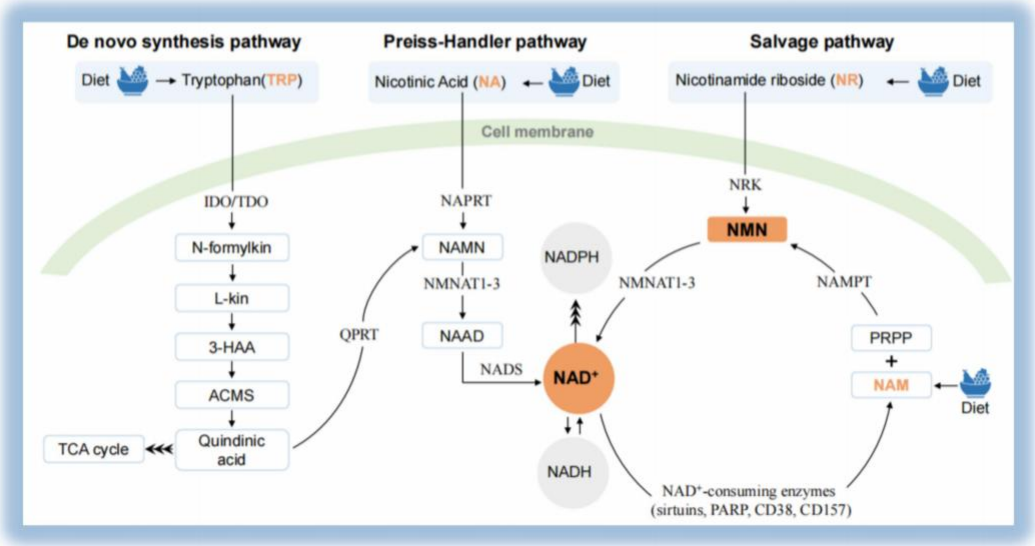
Relationship and difference between NMN and other NAD+ precursors

Nicotinamide Adenine Dinucleotide (NAD) exists in 2 forms, the oxidized (NAD+) and reduced (NADH) forms, in which NAD+ accepts a hydride ion to become NADH. The conversion process is crucial for the central carbon metabolism as NAD+ serves as a coenzyme for redox reactions, making it a vital component of energy metabolism [4-7]; in addition, it is an essential cofactor for nonredox enzymes such as sirtuins and poly(adenosine diphosphate-ribose) polymerases (PARPs) [8-10]. It is also critical for maintaining tissue and metabolic homeostasis for healthy aging.

There have been extensive reviews of the relationship between NAD+ and the 9 aging hallmarks, namely genomic instability[11], telomere attrition [12], epigenetic alterations [13], loss of proteostasis[14], deregulated nutrient sensing[15], mitochondrial dysfunction [16], cellular senescence[17], stem cell exhaustion[18], and altered intercellular communication [19]. Aging is accompanied by a gradual decline of NAD+ concentration across multiple human tissues, including skin, blood, liver, muscle, and brain [20-21]. Many factors, including DNA damage, chronic inflammation, oxidative stress [22], and increased NAD+-consuming enzyme activities [23], have also been shown to accelerate NAD+ degradation. Lowering the concentrations of NAD+ in cells or tissue results in decreased energy production within mitochondria, which contributes to the development of aging and a range of age-related disorders, including atherosclerosis, arthritis, hypertension, cognitive decline, diabetes, and cancer [24-26].

The NAD+ biosynthesis pathways include the de novo synthesis pathway, Preiss-Handler pathway, and salvage pathway [8], as illustrated in Figure 1. Among the 3 pathways, the de novo biosynthetic pathway is the most indirect mechanism contributing to system-wide NAD+, with most NAD+ coming from the salvage pathway[20,27].

Figure 2. NAD+ levels are maintained by 3 independent pathways



Comparison of NAD+ Precursors in the Salvage Pathway

Niacinamide (NAM) is catalyzed by NAMPT to generate NMN, and then NMN is catalyzed by NMNAT to generate NAD+. During the conversion of NAM into NAD+, it is limited by NAMPT rate-limiting enzymes, and only a small part of NAM is involved in the synthesis of NAD+, which cannot effectively improve the level of NAD+. Moreover, NAM has certain limitations in intake, and excessive administration will inhibit the activity of Sirtuins and cause liver poisoning. So it is not recommended as an ingredient for NAD+ supplements.

Nicotinamide ribose (NR) will be converted into NAM in large quantities in the human digestive system after oral administration, and then participate in the synthesis of NMN, and still cannot escape the restriction of rate-limiting enzyme NAMPT, which reduces the conversion efficiency.

Nicotinamide mononucleotides (NMN) can not only bypass the restriction of NAMPT but also can be directly converted into NAD+ in one step with the help of the transporter Slc12a8, which results in the most direct and effective precursor of NAD+. Therefore, it can be used as the first choice to enhance NAD+.

Functions of NMN

NMN is an effective precursor for NAD+ biosynthesis, and in vitro/in vivo studies have demonstrated that NMN supplementation increases NAD+ concentration and could mitigate aging-related disorders such as oxidative stress, DNA damage, neurodegeneration, and inflammatory responses.
Details are described in table 2.

Model	NMN dose	Potential health benefits
C57BL/6, G3 Terc -/-, SIRT2-/-, Sirt2$^{flox/flox}$ and NG2-Cre^{ERT34} Mice	Intraperitoneal injection: 10 mg/kg body weigh	Restored nuclear entry of Sirt2 and rejuvenated aged oligodendrocyte progenitor cells; Enhanced new myelin generation in aged central nervous system[28]
C57BL/6 wild-type mice and Sirt3- deficient mouse	Intraperitoneal injection: 500 mg/kg body weight	Improved stress resistance against acetaminophen-induced liver injury, restored Nrf2-mediated adaptive homeostasis; Restored liver redox homeostasis via the Sirt3–Nrf2 axis and protected aged liver from oxidative stress-induced injury[29]
Aged 4 wk male C57BL/6J mice	Oral administration: 400 mg/kg body weight	Increased brain NAD+ levels in mice after 45 min oral intervention[30]
Middle cerebral artery occlusion mouse	Intraperitoneal injection: 300 and 2000 mg/kg body weight	NMN accumulated earlier than NAD in the brain, reduced cerebral infarction at 24 h post-middle cerebral artery occlusion; Protected from acute ischemic stroke injury[31]
Aged 5–6 wk male Kunming mice	Intraperitoneal injection: 300, 400 and 500 mg/kg body weight	Modulated GABA and glutamate production by increasing GABAA receptor α2 and glutamic acid decarboxylase 65/67 expression; Enhanced immune system by boosting nitric oxide secretion and IL-1β expression[32]
STZ-induced diabetic C57BL/6J mice	Oral administration: 500 mg/kg body weight	Significantly increased body and testis weight and number of sperm in STZ-induced diabetic mice[33]
Aged (16 mo) male C57BL/6J mice	Intraperitoneal injection: 500 mg/L	Improved the intestinal structural and functional decline; the potential mechanism was boosting the NAD+ pool and activating the SIRT3/6-mediated signaling pathway with regard to antioxidant, anti-inflammatory, and barrier function[34]
C57BL/6 mice	Oral administration: 500 mg/kg body weight	Prevented lung physiological decline and pulmonary fibrosis; Improved respiratory system function[33]
Aged 7 wk female ICR mice	Intraperitoneal injection: 250 mg/kg body weight	Blocked UVB-induced photodamage in mice, maintaining normal structure and amount of collagen fibers, normal thickness of epidermis and dermis, reducing the production of mast cells, and maintaining complete organized skin structure[35]
Aged (7–10 wk) C57BL/6 mice	Intraperitoneal injection: 250 and 500 mg/kg body weight	Increased NAD+ levels, SIRT1 protein expression, and heme oxygenase-1 expression; Exerted neuroprotective effects on photoreceptors after retinal detachment and oxidative injury[36]
ICR mice	Intraperitoneal injection: 200 mg/kg body weight	Improved the quality of oocytes from naturally aged mice by recovering NAD+ levels; Increased ovulation of aged oocytes but also enhanced their meiotic competency and fertilization ability by maintaining the normal spindle/chromosome structure and the dynamics of the cortical granule component ovastacin[37]
Aged 3 and 24 mo male C57BL/6J mice	Intraperitoneal injection: 500 mg/kg body weight	Protected vascular system by changing miRNA expression profile[38]
Aged 3 and 24 mo male C57BL/6 mice	Intraperitoneal injection: 500 mg/kg body weight	Restored youthful expression levels in 204 genes; Promoted SIRT1 activation in the neurovascular unit; Protected neurovascular function[39]
Aged 3 wk male Sprague Dawley rat	Intraperitoneal injection: 20 mg/kg body weight	Alleviated Al-induced bone injuries by decreasing bone loss, suppressed oxidative stress as well as inhibited thioredoxininteracting protein-NOD-like receptor pyrin domain containing 3 inflammasome pathway and proinflammatory cytokine production[40]
Aged (24 and 3 mo) male Wistar rats	Intraperitoneal injection: 100 mg/kg body weight	Reversed aging-induced learning and memory impairment; Improved mitochondrial function in the brains of aged animals; Reduced apoptosis in the brains of aged animals[41]

Aged (18 mo) C57BL/6J mice	Oral administration: 400 mg/kg body weight	**Increased endurance; Improved blood flow in elderly mice by increasing capillary density[42]**
Aged (24 mo) C57BL/6 male mice	Intraperitoneal injection: 500 mg/kg body weight	**Reversed aging-induced cerebrovascular endothelial dysfunction; Restored NAD+ and mitochondrial energetics and reduced mtROS; Improved cognitive performance in NMN treated aged mice[43]**
Male Long-Evans rats (decompensated hemorrhagic model)	Oral administration: 400 mg/kg body weight	**Reduced lactic acidosis and serum IL-6 levels, increased NAD+ levels, and prevented mitochondrial dysfunction in both liver and kidney; Mitigated inflammation, improved cellular metabolism, and promoted survival following hemorrhagic shock[44]**
Aged (6 mo old) APP(swe)/PS1(DE9) double transgenic (Alzheimer disease model) mice	Subcutaneous injection: 100 mg/kg body weight for 28 d	**Reduced inflammatory responses, synaptic loss, amyloid plaque burden and β-amyloid production by inhibition of JNK activation[45]**
Middle cerebral artery occlusion CD1 mice	Intraperitoneal injection: 300 mg/kg body weight	**Decreased mortality, brain infarction, edema, apoptosis, and hemorrhage via protecting blood–brain-barrier integrity[46]**
Collagenase-induced intracerebral hemorrhage CD1 mice	Intraperitoneal injection: 300 mg/kg body weight	**Reduced brain edema, brain cell death, oxidative stress, neuroinflammation, intercellular adhesion molecule-1 expression, microglia activation and neutrophil infiltration in brain hemorrhagic area by suppressing neuroinflammation/ oxidative stress[47]**
Male cardiac-specific FXN-knockout mice and male SIRT3-knockout/FKN knockout mice	Intraperitoneal injection: 500 mg/kg body weight	**Improved cardiac functions, reduced energy waste and improved energy utilization in FXN-knockout mice but not in SIRT3- knockout/FKN-knockout mice[48]**
Cardiac-specific deficiency of Klf4 C57BL/6J mice	Intraperitoneal injection: 500 mg/kg body weight for 3 or 5 d	**Preserved mitochondrial ultrastructure, reduced ROS, and prevented cell death in the heart; Protected the mutant mice from pressure overload-induced heart failure[49]**
Aged (26–28 mo) C57Bl/6 male mice	Oral administration: 300 mg/kg body weight	**Restored SIRT1 activity and reversed age-related arterial dysfunction by decreasing oxidative stress[50]**
C57BL/6N male mice	Oral administration: 100 and 300 mg/kg body weight	**Suppressed body weight gain; Improved eye function, healthy plasma lipid profile, insulin sensitivity, physical activity, energy metabolism, and other physiopathologies; Enhanced mitonuclear protein imbalance and mitochondrial oxidative metabolism in skeletal muscles[51]**
High-fat diet-fed aged C57BL6/J female mice	Intraperitoneal injection: 500 mg/kg body weight	**Increased liver citrate synthase activity and triglyceride accumulation; Improved glucose tolerance, NAD+ levels of muscle and liver[52]**
Transverse aortic constriction-stressed mice, male conditional knockout mice	Intraperitoneal injection: 500 mg/kg body weight	**Improved mitochondrial function and protected mice from heart failure[53]**
Aged 3 mo osteoporotic male C57BL/6 mice	Oral administration: 31.25, 62.5, 125, 250 and 500 mg/kg body weight	**Dramatically ameliorated the hippocampal CA1 injury and significantly improved neurological outcome; Prevented the increase in PAR formation and NAD+ catabolism[54]**
Male Wistar rats (Alzheimer disease model)	Intraperitoneal injection: 500 mg/kg body weight	**Improved cognitive function and energy metabolism, ameliorated neuron survival, reduced ROS accumulation[17]**
APP(swe)/PS1(DE9) double transgenic (Alzheimer disease model) mice	Subcutaneous injection: 100 mg/kg body weight	**Decreased brain APP levels and increases brain mitochondrial function; Reversed cognitive deficits[55]**

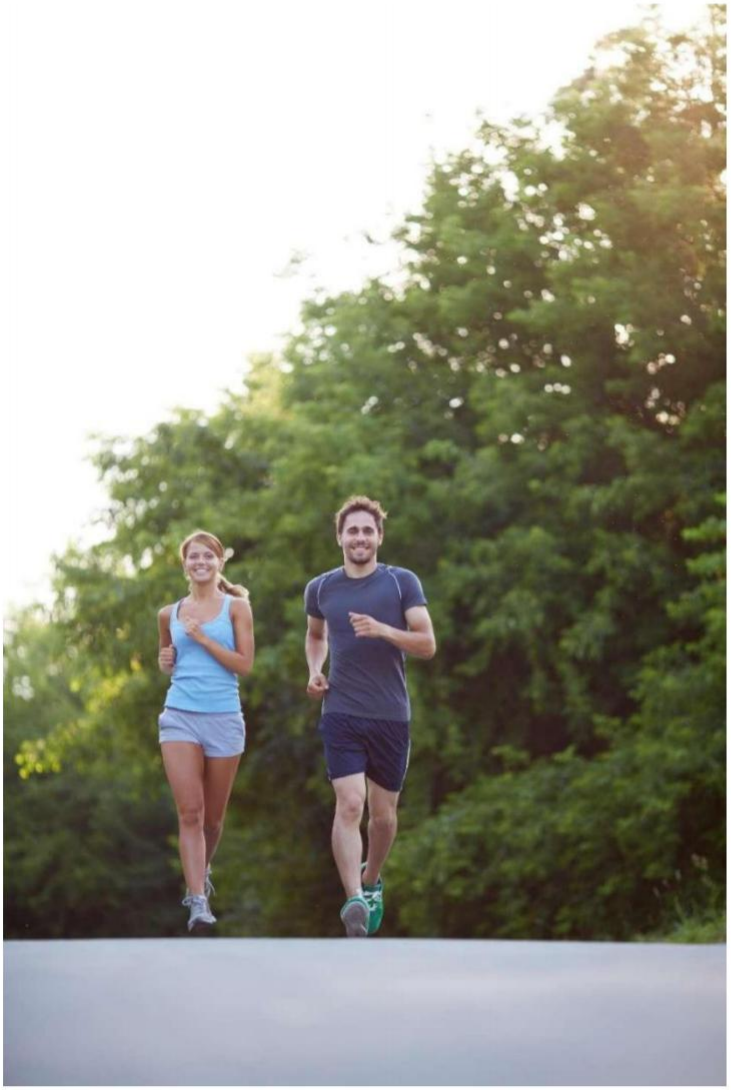
Table 2. Preclinical studies in mouse models using NAD+ boosting strategies (NMN intervention)

Safety and dosage of NMN

For the past few years, researchers have started to assess the safety and effects of NMN supplementation in humans to determine whether the effects observed in cells and animal models can be translated to humans.

Published human clinical data suggest that NMN is relatively safe and has shown some beneficial effects as a supplement, which has been summarized in Table 3.

Dosage recommendation



Existing human clinical trials suggest that oral NMN administration is generally safe when taken in doses between 150 and 900mg per day, and although only a limited number of indicators were studied, the results suggest that NMN has potential as an antiaging agent.

Table 3. The safety and antiaging effects of NMN in human clinical trials

Registration number	Design	Dose & duration	Indicators	Outcome
UMIN000021309	Nonblinded, nonrandomized, non–placebo-controlled study; 10 healthy men aged 40–60y	Oral administration: 100, 250 or 500 mg for5 h	Clinical parameters, ophthalmic parameters, sleep quality score, serum parameters, NMN metabolites levels in plasma	↑NMN metabolites (2-PY and 4-PY) in plasma and bilirubin levels; ↓creatinine, chloride, and glucose levels within the normal ranges in serum; No significant changes in ophthalmic examination and sleep quality score; Single oral administration of NMN up to 500 mg is safe and well-tolerated in healthy men without causing any significant deleterious effects[56]
jRCTs041200034	Double-blind, randomized, placebo-controlled study; 30 healthy volunteers aged 20–65 y	Oral administration: 250 mg daily for 12 wk	Adverse events, clinical parameters, blood and urine biochemical parameters, body composition, skeletal muscle mass, bone mineral mass, NAD+, and amino acid metabolome of blood	↑NAD^+ and NAMN levels but not NMN; Pulse rate is strongly correlated with the increase in NAD^+ level; No obvious adverse effects, and no significant changes in other indicators; Oral administration of NMN is safe[57]
/	Double-blind, block randomized, placebo controlled study; 32 overweight or obese adults aged 55–80 y	Oral administration: 1000 mg once daily or twice daily for 14 d	NMN, NAD+, and NAD+ metabolome in blood and urine	1000 mg once or twice daily regimens were safe and associated with substantial dose related increases in blood NAD^+ levels and its metabolome[58]
NCT03151239	Double-blind, randomized, placebo-controlled study; 25 postmenopausal and prediabetic women aged 55–75 y	Oral administration: 250 mg daily for 10 wk	NMN metabolites and NAD+ in plasma, PBMCs, and skeletal muscle; body composition and basal metabolic variables; skeletal muscle insulin sensitivity and signaling; skeletal muscle global transcriptome profile	NAD^+ and NMN metabolites in plasma; ↑ NMN metabolites in skeletal muscle but not NMN; ↑muscle insulin sensitivity, insulin signaling[59]
ChiCTR2000035138	Double-blind, randomized, placebo-controlled study; 48 healthy recreationally trained runners aged 27–50 y	Oral administration: 300, 600 or 1200mg daily for 6 wk	Body composition and cardiopulmonary function	↑aerobic capacity, enhanced O_2 utilization of skeletal muscle; ↑VT in a dose-dependent manner; No obvious adverse symptoms and abnormal ECG[60]
UMIN000036321	Double-blind, randomized, placebo-controlled study; 42 healthy old men aged 65 y	Oral administration: 250 mg daily for 12 wk	Clinical characteristics, blood and urine biochemical parameters, body composition, skeletal muscle mass, segmental lean	↑NAD^+ and NAD^+ metabolite levels in blood, improved muscle strength and performance, and no obvious adverse effects were observed[61]
UMIN000038097	Double-blind, randomized, placebo-controlled study; 108 overweight or obese adults aged 65 y	Oral administration: 250 mg daily for 12 wk	body composition, muscle mass, bone mass, sleep quality, fatigue, physical performances	NMN intake in the afternoon is more effective in improving lower limb function and reducing drowsiness in older adults[62]
NCT04228640	Oral administration: 300 mg NMN/d for 60 d	Oral administration: 300 mg NMN/d for 60d	Blood cellular NAD serum, six minutes walking endurance test, blood pressure, pulse pressure, SF-36 questionnaire, adverse events; blood biochemical parameters, HOMA-IR	NAD^+/NADH levels in the serum, SF-36 score, minute walking endurance, and HOMAIR index; ↓blood pressure, pulse pressure, and blood glucose; All test data did not have any statistically significant changes. However, the increase in NAD^+ /NADH levels in serum and the improvement in overall health and walking endurance were clinically significant[64]
UMIN000043084	Double-blind, randomized, placebo-controlled study; 31 healthy participants aged 20–65 y	Oral administration: 1250 mg NMN/d for 4 wk	Safety evaluation of NMN oral administration in healthy adult men and women	Did not cause changes exceeding physiological variations (including anthropometry,hematological, biochemical, urine, and body composition)[65]
/	Nonblinded, nonrandomized, non–placebo-controlled study; 8 healthy men aged 45–60 y	Oral administration: 300 mg daily for 90 d	The telomere length of the PBMC	↑ telomere length of PBMC, which may be the potential molecular mechanisms of NMN for extending lifespan[63]

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UMIN000045347	nonblinded, non-randomized, non-placebo controlled ; 17 postmenopausal women Age 50-80 y	Oral administration: 300 mg daily for 8wk	Sleep-related parameters, including sleep quality score (e.g., PSQI), sleep latency, total sleep time, sleep efficiency, wake after sleep onset (WASO), and number of nighttime awakenings; subjective fatigue scores, and clinical safety indicators	↑ **Sleep quality scores (PSQI improvement);** ↓ **Sleep latency;** ↓ **Fatigue scores;** **No significant changes in routine biochemical parameters;** **No serious adverse events reported**[67]
UMIN000047134	Open-label, single-arm exploratory research Ten healthy subjects Age 20-70 y	NMN 300 mg administered intravenously via drip infusion (5 mL/min) dissolved in 100 mL saline	NAD^+ metabolism (NAD^+, NADH), SIRT1 activity, gene expression markers (NAMPT, NANOG, p16), lipid and glucose metabolism, comprehensive organ function parameters , hematological profiles, inflammatory markers, urinalysis, vital signs, and clinical safety assessments.	↑ **NAD^+ levels in blood cells;** ↓ **Triglyceride levels;** ↑ **NAMPT mRNA expression;** ↓ **p16 mRNA expression;** **No significant changes in glucose metabolism, cholesterol levels, hematological parameters, organ function markers, or vital signs;** **No significant activation of SIRT1;** **No adverse events observed**[68]
jRCTs051190002	Prospective, placebo-controlled, double-blind study 14 men with diabetes Age ≥65 y	Oral administration: NMN 250 mg daily for 24wk	Safety, Grip strength, Walking speed, Exploratory indicators (Frailty status, Retinal parameters)	**No significant improvement in grip strength;** **No significant improvement in walking speed;** **No significant changes in metabolic parameters;** ↑ **Trend toward improved frailty status (not statistically significant);** **No significant changes in retinal parameters;** **No serious adverse events observed**[69]
NCT04823260	Double-blind, randomized, placebo-controlled 80 healthy participants Age 40-65 y	Oral administration: NMN 300 mg, 600 mg, and 900 mg daily for 60 d	Blood NAD^+ levels, Physical performance, Blood glucose, Insulin resistance (HOMA-IR), SF-36 score,body composition, safety assessments	↑ **NAD^+ levels in blood;** ↑ **Physical performance (6-minute walking distance);** ↑ **General health scores (SF-36 improvement);** ↓ **Blood glucose levels (mild reduction);** ↓ **Insulin resistance (HOMA-IR improvement);** **No significant changes in body weight or BMI;** **No significant changes in liver or kidney function markers;** **No serious adverse events observed**[70]
UMIN000045205	Double-blind, randomized, placebo-controlled 36 healthy middle-aged and elderly subjects Age 40-65 y	Oral administration: NMN 250 mg daily for 12wk	Arterial stiffness,Blood NAD^+ levels,NAD^+-related metabolites,Blood pressure, Vascular-related parameters, Glucose metabolism, Lipid profile, safety assessments	↑ **NAD^+ levels in blood;** ↓ **Arterial stiffness;** **No significant changes in blood pressure;** **No significant changes in glucose metabolism or lipid profile;** **No clinically significant changes in liver or kidney function;** **No serious adverse events observed**[71]
/	Double-blind, randomized, placebo-controlled 30 overweight or obese subjects Over 45 y	Oral administration: NMN 1000 mg daily for 28 d	Arterial stiffness, Blood NAD^+ levels, Blood pressure, Vascular-related parameters, Glucose metabolism, Lipid profile, Body weight, Muscle performance, Safety assessments	↑ **Blood NAD^+ levels** ↓ **Body weight** ↓ **Total cholesterol, LDL cholesterol, non-HDL cholesterol** ↓ **Diastolic blood pressure; ↔ Systolic blood pressure** **No clinically significant changes in liver or kidney function** **No serious adverse events observed**[72]
UMIN000047042	Non-double-blind, non-randomized, non-placebo controlled 11 healthy subjects Age 20-65 y	Oral administration: NMN 250 mg daily for 12wk	Blood NAD^+ levels, Plasma NMN, Insulin, Glucose metabolism, Lipid profile, Body weight, Liver function, Adiponectin/Leptin, Safety assessments	↑ **Plasma NAD^+ levels** ↑ **Plasma NMN levels** ↑ **Postprandial insulin levels** **No adverse symptoms observed**[73]
UMIN000047871	Double-blind, randomized, placebo-controlled 60 healthy subjects age from 65-75 y	Oral administration: NMN 250 mg daily for 12wk	Stepping test,Physical performance,Blood NAD-related metabolites,Body composition,Sleep quality,Safety assessments	↑ **Blood NAD^+, NAM, 2-PY, 4-PY, NaMN, NaR** ↓ **4-m walking time** ↑ **Sleep quality** **No serious adverse events; blood biochemistry and hematology unchanged**[74]

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jRCTs031180242	Single center, single arm, open label 11 healthy middle aged men	Oral administration: NMN 250 mg daily for 8wk	PBMC NAD^+ levels, NAD+-related metabolites, Glucose metabolism / Insulin, Body composition, Blood pressure, Ophthalmic parameters, Sleep quality, Safety assessments	**↑ PBMC NAD^+ levels** **↓ Postprandial insulin in subgroup with above-mean insulin AUC** **No serious adverse events; mild transient elevations in AST/ALT/g-GTP in some participants; overall safe and tolerable[75]**
NCT05038488	Placebo-controlled, randomized, parallel group, doubleblind trial 42 adults, ≥18 y, hospitalized with COVID-19 and AKI	Oral administration: NMN 2000 mg daily for 14 d	serum creatinine, Markers of AKI,Blood NAD^+ levels and metabolites,Inflammation markers,Clinical indices of disease severity,Safety assessments	**↑ Blood NAD^+ levels** **↑ NAD^+ metabolites** **Serum creatinine, cystatin C, BUN: No significant differences vs placebo** **AKI markers (NGAL, KIM-1): No significant differences** **Inflammatory markers (CRP, IL-6, TNF-α): No significant differences** **Clinical indices (WHO ordinal scale, mSOFA): No significant differences** **no clinically meaningful changes in liver enzymes, blood counts, or glucose[76]**
/	Single-arm, pre-post intervention study, 15 healthy Japanese women aged between 40 and 50 years	Oral administration: NMN 500 mg daily for 12wk	Hair density and growth,Hair shaft diameter and cuticle condition (SEM),Hair metabolomics ,Hair hormone levels ,Subjective assessments	**↑ Anagen hair elongation density** **↑ Hair diameter** **↓ Total hair density, vellus hair, terminal hair density** **↑ Hair metabolite changes** **Hair hormone levels (cortisol, testosterone, progesterone unchanged)** **↑ Subjective hair quality (elasticity, gloss, volume improved)** **↓ Fatigue and perceived hair loss** **no major safety issues reported[77]**

NMN production process

In the chemical synthesis process, using nicotinamide ribose salt as the initial raw material, NMN is synthesized through two main reaction steps.

Enzyme catalyzed synthesis method uses 2 enzymes to catalyze NR to synthesize NMN. The production method is mild and the production efficiency is high.

The biological fermentation synthesis method uses niacinamide and glucose as raw materials, and uses cell factory to biosynthesize NMN. If the chassis cells and fermentation process are optimized well, the production cost can be greatly reduced.

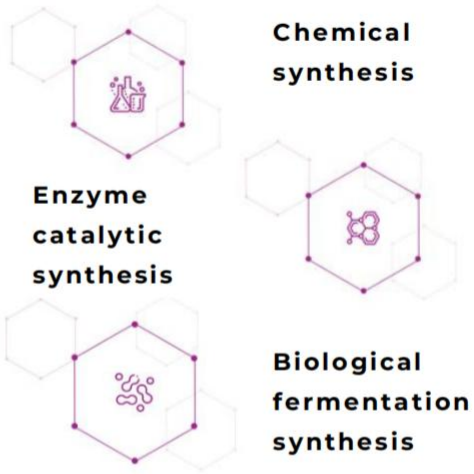
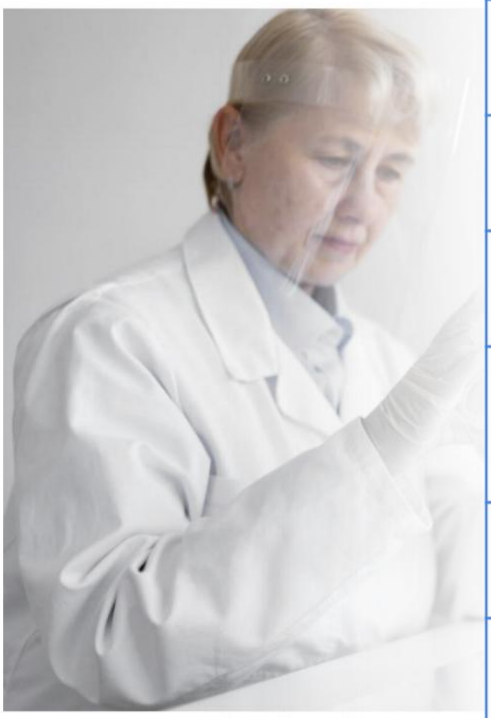


Table 4: Comparison of three processes

	Chemical synthesis	Enzyme catalytic synthesis	Biological fermentation synthesis
Initiator	NR	NR	Glucose and Niacinamide
Strain	/	E. coli/Yeast	E. coli/Yeast
Enzyme	/	Two	/
Enzyme substrate conversion efficiency	/	≥85%	/
R&D cycle	Short	Longer	Longest
Technical barrier	Low	Higher	Highest



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Authoritative authorizations and safety evaluations on NMN Food/ Dietary Supplement

NMN dietary supplements have been marketed in many countries.

In the United States, several companies' NMN products have passed the Self-GRAS certification. As of September 2025, the FDA has re-evaluated the regulatory status of NMN and no longer excludes it from the definition of a dietary supplement ingredient. NMN is now considered a New Dietary Ingredient (NDI), and several companies, including EffePharm, have received NDI acknowledgment from the FDA (NDI 1444 and NDI 1267).

In Japan, the Japanese Ministry of Health, Labour and Welfare added NMN to the ingredient list of "Health Food Raw Materials - not considered to be medicines".

In Canada, NMN is classified as a Natural Health Product under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations (Health Canada, 2023).

In Australia, the Therapeutic Goods Administration(TGA) classified NMN as supplement medicine.

In the European Union, currently NMN is under review as a novel food ingredient under NF-2024-27111 and NF-2025-33820. UTHEVER® NMN has received a positive scientific opinion from the European Food Safety Authority (EFSA) NDA Panel under the Novel Food Regulation(NF-2023-17850). The ingredient is currently progressing through the final authorization procedure by the European Commission prior to inclusion in the Union list of authorized Novel Foods.

In Brazil, UTHEVER® NMN has progressed through a distributor-led regulatory submission pathway with ANVISA. Commercialization has been enabled under defined intake conditions based on safety evaluation within the local regulatory framework.

Cosmetic

In China, Japan, South Korea, and other countries, there are cosmetics containing NMN in the market.

In China, NMN raw materials of many companies, including EffePharm, have filed their dossiers about NMN to the National Medical Products Administration, and their NMN material can be used in cosmetics as skin moisturizer, skin protective agent, antioxidant agent, anti-wrinkle agent, and the amount of use is less than or equal to 3%.

For more info, please visit:
www.uthever.com
Contact Us
Email: deal@effepharm.com

References available upon request.

UTHEVER® NMN

Novel Food

Positive EFSA Assessment Secured

- Product Name: β-Nicotinamide Mononucleotide (NMN)
- CAS No. :1094-61-7

World's First **Clinical -Proven** Branded NMN

Global Regulatory Leadership

- Positive EFSA assessment secured, final EU Novel Food authorization underway
- US FDA NDI compliant

Novel Food Application in Final Review

FDA NDI New Dietary Ingredient

What is NMN?

β-Nicotinamide Mononucleotide (NMN) is a derivative of vitamin B3, which plays a crucial role in human cell functions. NMN can be naturally produced in cells or obtained through fruits, vegetables, and poultry.[1] Research shows that NMN is a bioactive compound that can boost cellular NAD+ levels.[2] As we age, NAD+ levels in the body decline. Supplementing NAD+ can effectively slow down aging and improve the prevention and management of age-related diseases.[3]

Mechanisms of NMN

- Increase NAD+ levels
- Activate "longevity protein" sirtuins
- Repair DNA damage
- Promote energy production

Health Benefits of NMN

NMN has demonstrated efficacy in cardiovascular protection, alleviating depression, boosting cognitive function, aiding weight management, and showcasing anti-aging properties.

UTHEVER® NMN

Youth Forever, To Be World's Best NMN

EFFEPHARM

From Clinical Breakthrough to Market Leadership

Pioneering Human Clinical Research

World's First Clinically-Proven NMN Brand

38%
Increment in NAD+ levels

6.5%
Enhancement of walking endurance

6.5%
Improvement in quality of life

Uthever® Phase II Clinical Trials

Committed to evidence-based science, Uthever® is advancing Phase II clinical trials focused on three key areas:

- Sleep improvement
- Memory enhancement
- Weight management

Uthever® Global Regulatory Landscape

- Approved: U.S. FDA NDI, Brazil "New Ingredient"
- Compliant Supply: Japan, Hong Kong, Canada, Malaysia, and more
- Registration Ongoing: EU, UK, Australia, South Korea, Thailand, etc.

Trusted by 100+ Brands Worldwide

- Uthever® - No.1 Trademarked, Clinically Proven NMN*
- Uthever® is recognized and used by over 100 brands globally.

UTHEVER®

Youth Forever, To Be World's Best NMN

Advantages

Versatile Applications

Available in three density grades (G1/G2/G3) to support various dosage forms, including powders, tablets, and hard capsules.

7 Patents, Global Protection

Uthever® holds 7 core patents globally, leveraging R&D innovation to drive product leadership.

4 Quality Certifications

Manufactured under stringent global standards, with production systems certified by cGMP and other internationally recognized quality certifications, ensuring consistent quality and safety.

*Source: Euromonitor International Limited. Based on B2B sales volume of trademarked NMN ingredient brands in the USA in 2024. Trademarked NMN ingredient brand refers to a brand officially registered with a government trademark office, and destined to NMN (Nicotinamide Mononucleotide) ingredient, a bioactive compound that supports healthy aging by serving as a precursor to NAD+. Research completed in Dec 2025.

Reference available upon request.

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

For more info, please visit: www.uthever.com
Contact us
Email: deal@effepharm.com
Tel: +86 (21) 57709202

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SCIENTIFIC OPINION

Safety of beta-nicotinamide mononucleotide (β-NMN) pursuant the regulation (EU) 2015/2283 and the bioavailability of nicotinamide from this source in the context of Directive 2002/46/EC

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) | Dominique Turck | Torsten Bohn | Montaña Cámara | Jacqueline Castenmiller | Stefaan De Henauw | Ángeles Jos | Alexandre Maciuk | Inge Mangelsdorf | Breige McNulty | Androniki Naska | Kristina Pentieva | Alfonso Siani | Frank Thies | Margarita Aguilera-Gómez | Francesco Cubadda | Thomas Frenzel | Ursula Gundert-Remy | Francesca Marcon | Harry J. McArdle | Monika Neuhäuser-Berthold | Miguel Prieto Maradona | Alexandros Siskos | Matthew Wright | Elisa Beneventi | Annamaria Rossi | Maura Magani | Karen Ildico Hirsch-Ernst

Correspondence: Ask a Question

The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts.

Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on beta-nicotinamide mononucleotide (β-NMN) as a novel food (NF) pursuant to Regulation (EU) 2015/2283, including an evaluation of the safety of its use in food supplements as a source of niacin, and the bioavailability of nicotinamide from this source, in the context of Directive 2002/46/EC. The NF consists of chemically synthesised β-NMN and is intended for use in food supplements as a source of niacin up to 300 mg/day. The target population is adults, excluding pregnant and lactating women. The identity, production process, composition and specifications of the NF do not raise safety concerns. A human intervention study comparing the relative bioavailability of β-NMN and nicotinamide in equimolar amounts supported the use of a conversion factor (CF) of 1. On this basis, the proposed maximum intake corresponds to 109.7 mg/day of nicotinamide. This amount is approximately five times the population reference intake (PRI) of niacin for adults but remains below the upper level (UL) of 900 mg/day for nicotinamide. No concerns were identified regarding genotoxicity. In a 90-day repeated dose oral toxicity study in rats, effect on reproductive organs were observed and the no observed adverse effect level (NOAEL) of 400 mg/kg bw per day identified, resulting in a margin of exposure (MoE) of 93. The available human study did not raise safety concerns. Based on the nature and the metabolic fate of the NF, the proposed use levels and the available human data, the calculated MoE was considered sufficient. The Panel concludes that the NF is safe under the proposed conditions of use for the adult population, excluding pregnant and lactating women and that the NF constitutes a bioavailable source of nicotinamide, a form of niacin.

KEYWORDS

beta-nicotinamide mononucleotide, chemical synthesis, food supplement, niacin, novel foods, nutrient source

FDA NDI Clearance

U.S. FOOD & DRUG ADMINISTRATION

January 28, 2026

(b)(4)

Dear (b)(4):

This letter responds to the notification that you submitted, pursuant to 21 United States Code (U.S.C.) § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)), to the Food and Drug Administration (FDA or we) on behalf of Effepharm, Ltd (China). FDA received and filed the notification on November 17, 2025. Additional information was received on December 25, 2025, which did not alter the filing date of November 17, 2025. Your notification concerns the new dietary ingredient, "β-nicotinamide mononucleotide (β-NMN) or NMN" tradename "Uthever", that you intend to market as a bulk dietary ingredient.

This letter is also in further response to the notification (NDIN 1267) that was submitted for the same dietary ingredient (NMN); we recognize that NDIN 1444 is a resubmission to this original notification. As you know, on January 18, 2023, we responded to NDIN 1267 with a letter stating that NMN is excluded from the dietary supplement definition under 21 U.S.C. § 321(ff)(3)(B)(ii), which was FDA's position at the time. On March 6, 2023, FDA received a citizen petition from the Natural Products Association and the Alliance for Natural Health USA asking us to reconsider this position. On September 29, 2025, FDA responded to the petition and explained that the agency has reconsidered and changed its interpretation of one aspect of 21 U.S.C. § 321(ff)(3)(B) and, consequently, we have determined that NMN is not excluded from the dietary supplement definition.[1] Because NMN is not excluded from the dietary supplement definition, we are setting aside our January 18, 2023 letter to NDIN 1267.

According to the amended 1444 notification, the conditions of use are: "β-NMN is intended for use in adults at a daily intake of up to 600 mg/person/day for a limited duration of up to 60 days, or up to 300 mg/person/day for chronic use. The intended use excludes pregnant and lactating women, infants, and children."

Under 21 U.S.C. § 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary

[1] See FDA Response to "Amended Citizen Petition Regarding Regulatory Status of β-Nicotinamide Mononucleotide" from Natural Products Association and Alliance for Natural Health USA, September 29, 2025, available at https://www.regulations.gov/document/FDA-2023-P-0872-2754.

Certificate

The best-selling NMN ingredient brand in the United States"