



UTHEVER[®]

Youth Forever, To Be World's Best NMN

Clinical-Backed NMN

NMN White Paper



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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

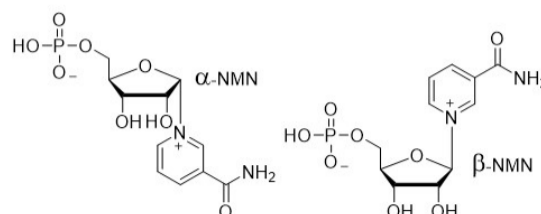
Nicotinamide Mononucleotide (NMN), is a derivative of vitamin B₃, which has important physiological functions on human cells. It can be naturally synthesized in cells or obtained from a variety of plant and animal food sources^[1], as listed in Table 1.

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.

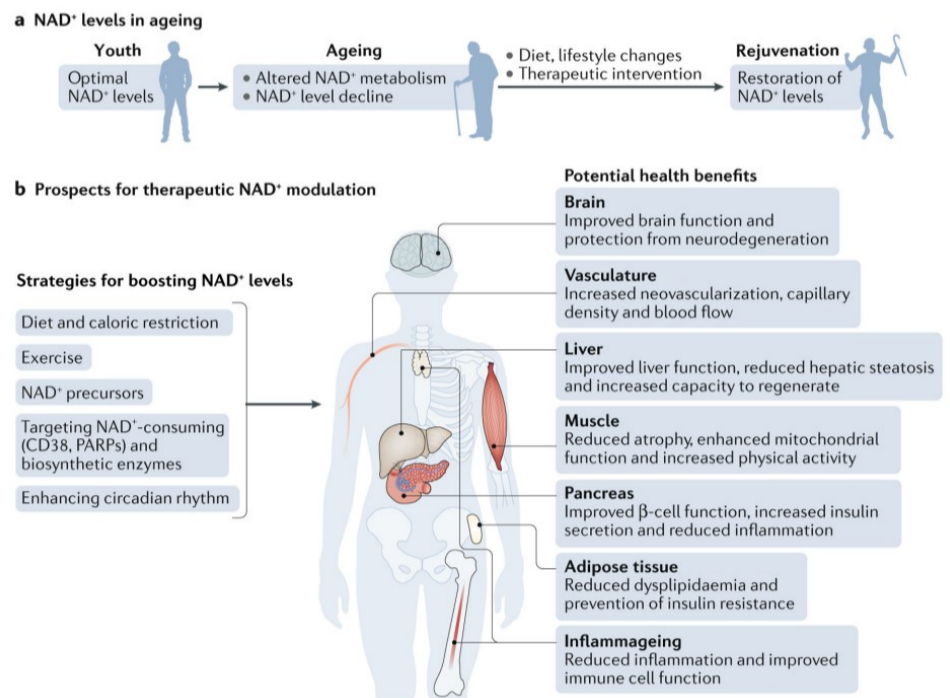


Figure 1. NAD⁺ levels and their impact on health



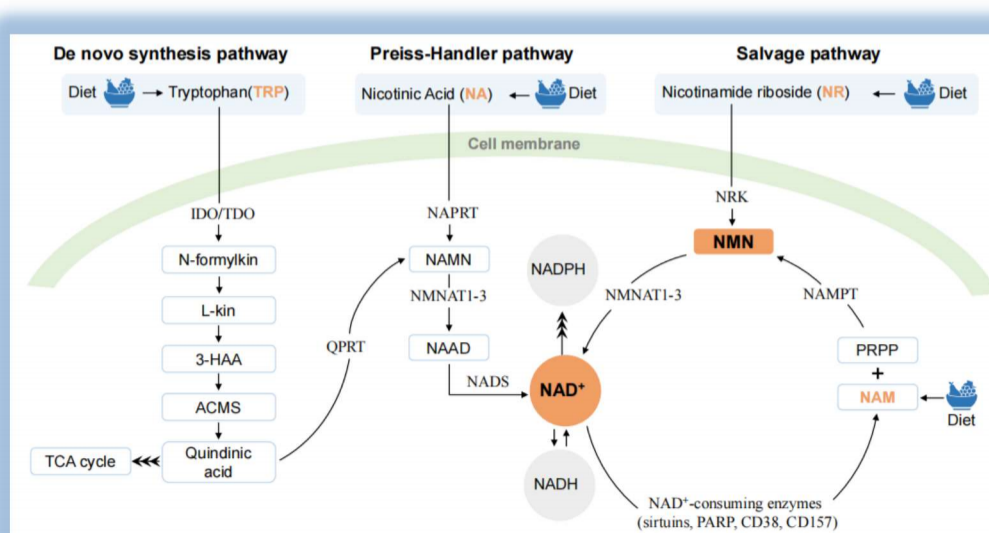
Relationship and difference between NMN and other NAD⁺ precursors

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 ^{lox/lox} and NG2-Cre ^{ERT34} Mice	Intraperitoneal injection: 10 mg/kg body weight	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 $\alpha 2$ and glutamic acid decarboxylase 65/67 expression; Enhanced immune system by boosting nitric oxide secretion and IL-1 β 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 ^[35]
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 ^[36]
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 AI-induced bone injuries by decreasing bone loss, suppressed oxidative stress as well as inhibited thioredoxin-interacting 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]



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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 C57BL/6J 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 ^[55]
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)¹

¹ This table only collects experimental results after 2015.



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.

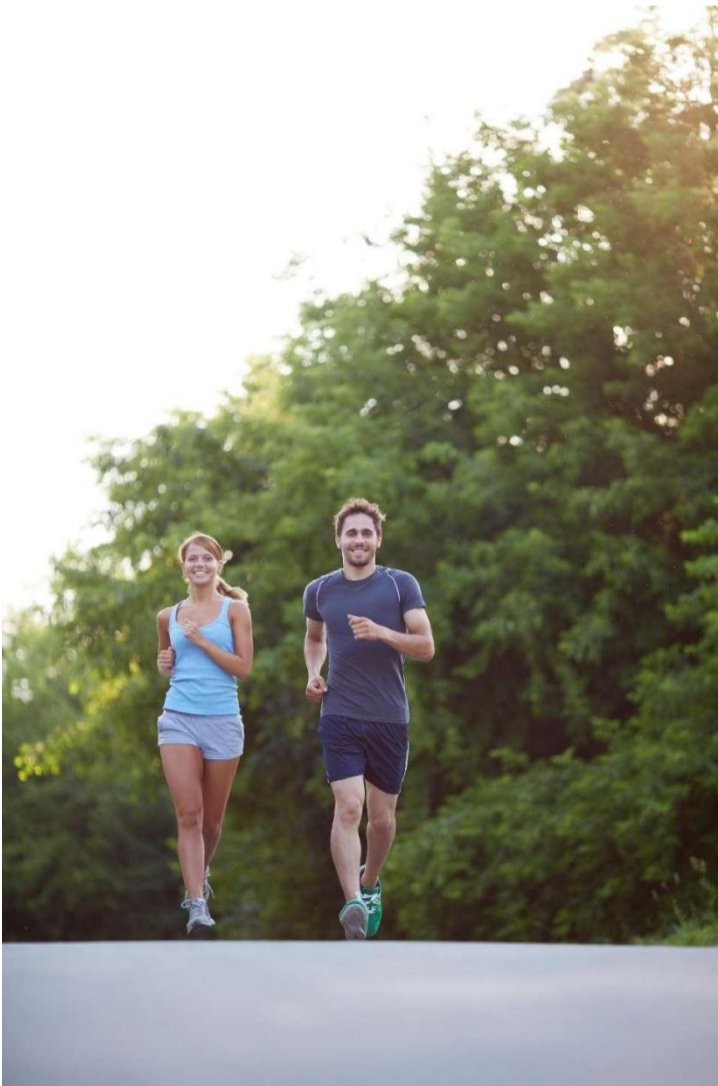


Table 3. The safety and antiaging effects of NMN in human clinical trials

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 for 5 h	Clinical parameters, ophthalmic parameters, sleep quality score, serum parameters, NMN metabolites levels in plasma	↑NMN metabolites (2Py and 4Py) 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, SF036 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]



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.

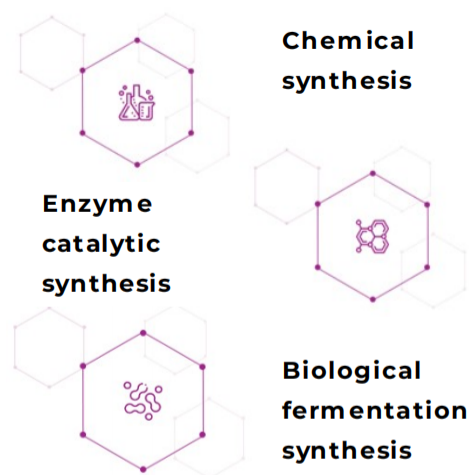
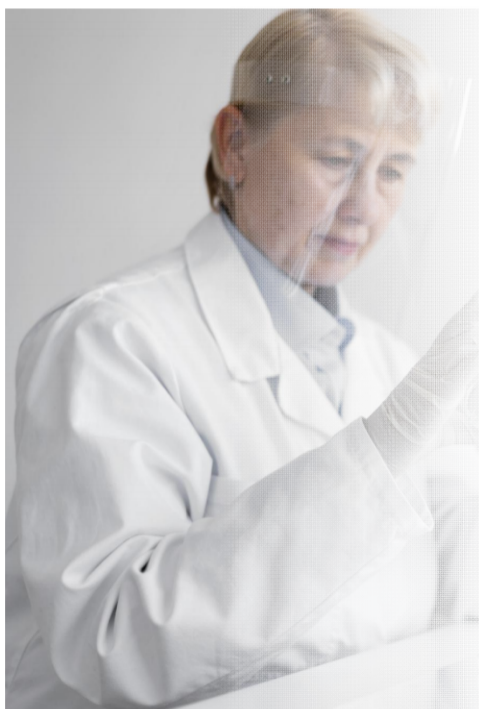


Table 4: Comparison of three processes

	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%	/
Residual organic solvent	Yes	No	No
R&D cycle	Short	Longer	Longest
Technical barrier	Low	Higher	Highest



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.

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-2021-0601, NF-2022-12050 and NF-2023-17850.



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 10%.



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For more info, please visit: www.uthever.com

Contact Us

Email: info@effepharm.com

Tel: +86 (021) 5770 9202

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References available upon request.



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



Grounded in scientific research

Uthever[®] NMN supports multiple scientific research projects to explore the potential benefits of NMN*

- NMN has protective and reparative effects on skin damage caused by UVB.^[1]
- NMN alleviates radiation-induced disturbances in the intestinal microbiota and intestinal damage.^[2]
- NMN reduces the mortality rate of mice after infection with the novel coronavirus.^[3]



Commitment to innovation

Uthever[®] adheres to continuous technological breakthroughs to deliver more cost-effective NMN.



Chemical Synthesis



Enzyme Catalysis



Cell Factory Synthesis

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Youth Forever, To Be World's Best NMN

Advantages



Actively undertake compliance filings

EU NOVEL FOOD pending



Trusted by global brands

The Uthever[®] trademark is licensed and used by more than 40 brands worldwide.



Versatile applications

Uthever[®] provides NMN with multiple density specifications, suitable for powder, tablets, capsules, and other dosage forms.

