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The therapeutic perspective of NAD^+ precursors in age-related diseases

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ABSTRACT

Nicotinamide adenine dinucleotide (NAD^+) is the fundamental molecule that performs numerous biological reactions and is crucial for maintaining cellular homeostasis. Studies have found that NAD^+ decreases with age in certain tissues, and age-related NAD^+ depletion affects physiological functions and contributes to various aging-related diseases. Supplementation of NAD^+ precursor significantly elevates NAD^+ levels in murine tissues, effectively mitigates metabolic syndrome, enhances cardiovascular health, protects against neurodegeneration, and boosts muscular strength. Despite the versatile therapeutic functions of NAD^+ in animal studies, the efficacy of NAD^+ precursors in clinical studies have been limited compared with that in the pre-clinical study. Clinical studies have demonstrated that NAD^+ precursor treatment efficiently increases NAD^+ levels in various tissues, though their clinical proficiency is insufficient to ameliorate the diseases. However, the latest studies regarding NAD^+ precursors and their metabolism highlight the significant role of gut microbiota. The studies found that orally administered NAD^+ intermediates interact with the gut microbiome. These findings provide compelling evidence for future trials to further explore the involvement of gut microbiota in NAD^+ metabolism. Also, the reduced form of NAD^+ precursor shows their potential to raise NAD^+, though preclinical studies have yet to discover their efficacy. This review sheds light on NAD^+ therapeutic efficiency in preclinical and clinical studies and the effect of the gut microbiota on NAD^+ metabolism.

1. Introduction

Over a century ago, Arthur Harden and William John Young discovered NAD^+ as a heat-stable cofactor crucial in yeast fermentation [1]. Later studies found that NAD^+ is involved in redox reactions by transferring electrons between an oxidized form of NAD^+ and a reduced form of NADH. Thus, NAD^+ mediates various cellular processes through redox reactions [2,3]. NADPH, a phosphorylated form of NADH, serves as a reductant to convert an oxidized glutathione (GSSG) into a reduced glutathione (GSH) and is involved in the antioxidant system [4,5]. NAD^+ also acts as a co-substrate for various NAD^+-consuming enzymes, including sirtuins, poly-ADP-ribose polymerase (PARP), NAD^+ glycohydrolase (CD38), and sterile alpha and toll/interleukin-1 receptor motif-containing protein 1 (SARM1). These enzymes play a crucial role in signaling pathways. Thus, NAD^+ is involved in several biological functions, including cellular bioenergetics, DNA repairing, metabolic homeostasis, genomic stability, mitochondrial biogenesis, and cell survival [6]. Overall, participating in numerous functions, NAD^+ is a crucial molecule for cellular processing, as summarized in Fig. 1.

In the early days of research on NAD^+, Conrad Elvehjem made a groundbreaking discovery that the precursor of NAD^+, nicotinic acid (NA), can be used to treat Pellagra - a severe nutritional deficiency disease resulting from the inadequacy of vitamin B3 (niacin) in the body [7]. Further, recent studies demonstrated that the association of NAD^+ with aging makes it significant as its levels decrease with age in certain tissues [8]. Aging is a functional debility of the cellular process observed in most of biological species. This decline in cellular functions results in vulnerability to induce age-associated diseases, i.e., diabetes, fatty liver, cardiovascular diseases, neurodegeneration, and muscular diseases [9]. The discrepancy between NAD^+ production and degradation leads to age-induced changes in numerous biological processes [2].

Supplementation of NAD^+ precursors have been extensively used in preclinical models. Boosting NAD^+ levels via NAD^+ precursors has proven advantageous effects in animal models of aging-associated diseases [10,11]. Following successful rodent studies, worldwide clinical investigations have effectively translated NAD^+ precursors into human

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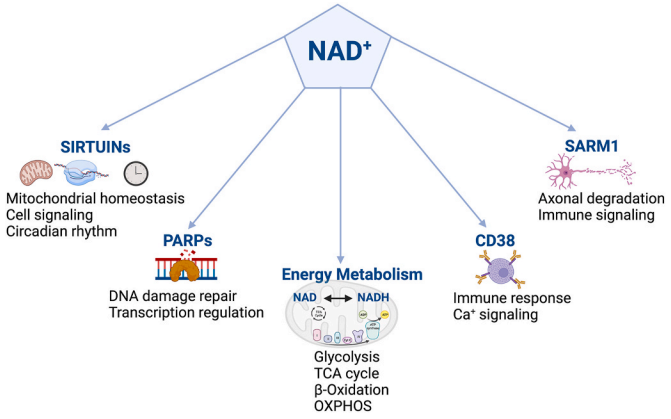

Fig. 1. Physiological functions of NAD^+.
NAD^+ is a beneficial coenzyme that plays a vital role in many biological processes. It facilitates the transfer of electron and effectively converts NAD^+ into reduced NADH in redox reactions, i.e., β-oxidation, glycolysis, tricarboxylic acid cycle (TCA), and oxidative phosphorylation (OXPHOS). Moreover, NAD^+ also functions as a co-substrate for signaling molecules that are essential for various cellular functions. Enzymes such as sirtuins, poly-ADP-ribose polymerase (PARP), NAD^+ glycohydrolase (CD38), and sterile alpha and toll/interleukin-1 receptor motif-containing protein 1 (SARM1) depend on NAD^+ to carry out their respective cellular functions. Therefore, NAD^+ is a critical element in maintaining optimal cellular health and function.

subjects. Currently, numerous clinical trials are underway to examine the efficacy of NAD^+ precursor. Although several studies have completed, the efficacy of NAD^+ precursors in humans was much less than that in animal studies [12–14]. Therefore, it is an urgent issue to reveal the reason for the gap between rodent and human results. Recent discoveries related to NAD^+ metabolism have shed light on the role of the gut microbiome in the absorption of NAD^+ precursors, providing new insight for discovering their significance in clinical translation [15–17]. Moreover, identifying reduced forms of NAD^+ precursors makes it an exciting area for further research [18,19]. This review aims to highlight the potential of NAD^+ in addressing age-related pathologies, the clinical translation of its precursors, and the recent advancements in NAD^+ metabolism.

2. NAD^+ metabolism inside the cell

2.1. NAD^+ biosynthesis

NAD^+ homeostasis is essential for proper cellular processing and functioning [20]. NAD^+ is synthesized from dietary NAD^+ precursors like nicotinic acid NA, nicotinamide (NAM), nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), and an amino acid known as tryptophan. There are three main pathways through which synthesized NAD^+ intracellularly: the *de novo*, Preiss-Handler, and salvage pathways (Fig. 2).

The *de novo* pathway consumes tryptophan to generate NAD^+. This pathway undergoes five enzymatic reactions and one nonenzymatic reaction, leading to intermediate quinolinic acid (QA) formation. An enzyme, quinolinate phosphoribosyltransferase (Qaprt), changes QA into the nicotinic acid mononucleotide (NAMN) [21,22]. On the other hand, the Preiss-Handler pathway consumes NA to generate NAD^+. NA is transformed into NAMN via the nicotinic acid phosphoribosyltransferase (Naprt) enzyme [23]. Further, nicotinamide mononucleotide adenylyltransferases (Nmnats) converts NAMN into nicotinic acid adenine dinucleotide (NAAD) by transferring adenine nucleotide moiety from ATP [24]. The final step in the process involves the enzymatic activity of NAD synthetase (NADS), which converts NAAD into NAD^+ by coupling the conversion from glutamine to glutamate [25]. The Salvage pathway consumes nutritional NAM, NR, and NMN to form NAD^+. NAM is recycled from NAD^+ consumption and transformed into NMN via the enzymatic activity of nicotinamide phosphoribosyl transferase (Nampt) [26]. Moreover, the NMN can also be made from NR via the action of the nicotinamide riboside kinase (Nrk) enzyme [27]. Further, NMN is converted to NAD^+ through the Nmnats [24]. This recycling pathway of NAM by salvage pathway is critical for maintaining the cellular NAD^+ pool from the large and rapid degradation of NAD^+ by NAD^+-consuming enzymes, such as PARPs and CD38.

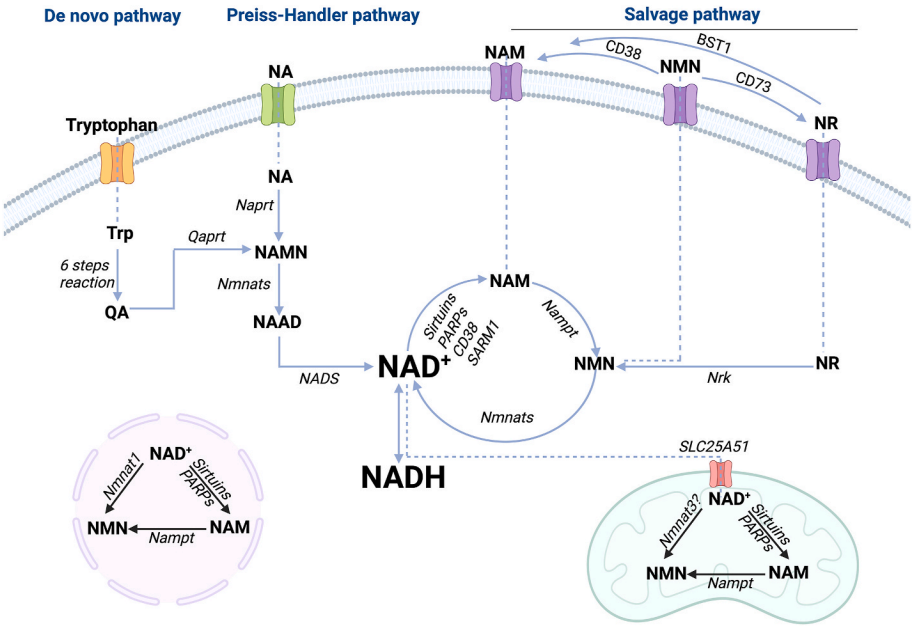

Fig. 2. Intracellular biosynthesis of NAD^+.
NAD^+ is synthesized from NAD^+ precursors and amino acids tryptophan via three main pathways: *De novo*, Preiss-Handler, and salvage. The levels of NAD^+ are regulated by various enzymes that are synthesized in the compartments of the cells. NAM, nicotinamide; NR, nicotinamide riboside; NMN, nicotinamide mononucleotide; NAD^+, nicotinamide adenine dinucleotide, NA, nicotinic acid; NAMN, nicotinic acid mononucleotide; NAAD, nicotinic acid adenine dinucleotide.

2.2. NAD $^{+}$ consumption

The role of NAD^+ is additionally extended by its substrate roles for various cellular enzymes, such as sirtuins, PARPs, CD38, and SARM1 [11,20]. Sirtuins are the proteins that remove acetyl groups from proteins accompanied by their transfer to ADP ribose. Moreover, some sirtuins, such as SIRT5 and SIRT6, mediate non-acetyl lysine acylations, including succinylation, malonylation, and fatty acid acylation. Seven different sirtuins are inside the cells and regulate various cellular processes [6,28]. Sirtuins are crucial network regulators that control energy homeostasis, enhance metabolic efficiency and upregulate mitochondrial oxidative metabolism, increasing resistance to oxidative stress [6] Moreover, sirtuins also play a crucial role in regulating the circadian clock and gene expression, and studies have shown that sirtuins promote longevity and can mitigate many age-related diseases [29,30]. The decline of sirtuins with aging impaired circadian function, metabolic homeostasis, and genomic integrity, contributing to the age-related phenotype [31,32].

Another protein, PARPs, consumes NAD^+ to ADP-ribosylate target proteins by transferring ADP ribose (ADPR) from NAD^+ molecules to itself or the target proteins; this process is known as poly ADP-ribosylation or mono-ADP-ribosylation. NAD^+ regulates PARP-mediated multiple cellular processes, such as DNA damage repair, transcriptional regulation, and cell death signaling [33]. The PARP family comprises 17 distinct types of PARPs, each in different cell parts. PARP1 is a crucial nuclear protein that identifies and repairs DNA damage during cellular stress. During DNA damage, PARP1 consumes a significant amount of cellular NAD^+, leading to a substantial decrease in NAD^+ concentration [34]. The inhibition of PARP1 has emerged as a promising therapeutic approach in the management of obesity-induced metabolic disorders like NAFLD, diabetes, atherosclerosis, and cancer [35,36].

CD38 is an ectoenzyme hydrolysing NAD^+ into nicotinamide (NAM) and producing ADPR. CD38 also exerts cyclase activity to produce cyclic ADPR (cADPR) from NAD^+. cADPR is a Ca^+ mobilizer regulating calcium signaling and immune responses [37]. CD38 is the main consumer of NAD^+ and is associated with age-related NAD^+ decline [38]. The CD38 is upregulated with age in various tissues and cells, including the inflammatory macrophage, and contributes to NAD^+ depletion [39]. This finding is confirmed when CD38 deficient mice show a high-fold increase in intracellular NAD^+ levels [40,41] and have an impact on age-related pathologies. In contrast, the mice with CD38 overexpression have shown signs of mitochondrial defects [42]. This finding suggests that CD38 inhibition can be used to boost NAD^+. A recent study also reported that CD38 is expressed in the ovarian extrafollicular space, primarily in immune cells, and its levels increase with reproductive age. Reproductively young mice lacking CD38 exhibit elevated ovarian NAD^+ levels, larger primordial follicle pools, and increased fertility relative to wild-type controls [43]. Conclusively, CD38 inhibition treatment has the potential to raise NAD^+ levels and ameliorates the pathologies associated with NAD^+ decline.

Further, NAD^+ degradation has also been linked to SARM1. SARM1 was originally discovered as a negative regulator of Toll-like receptor signaling pathways and a controlling player in liver lipid metabolism and inflammation. Later, it was demonstrated that the activation of SARM1 was linked to axonal degeneration. Further, SAMR1 was shown to degrade NAD^+ into ADPR, NAM and marginal cADPR by its glycohydrolase activity [44,45]. SARM1 in neurons also plays a significant role in facilitating neuronal inflammation, which can lead to brain damage [46]. Therefore, SARM1 could be a promising target for preventing or mitigating axonal degeneration [47]. These results suggest that the inadequate activation of NAD^+-consuming enzymes also decreases NAD^+ levels and contributes to the aging process.

2.3. Subcellular compartmentalization of NAD^+

NAD^+ synthesis is tightly regulated in subcellular compartments, including the nucleus, mitochondria, and cytoplasm, while a large volume of intracellular NAD^+ is present in the mitochondria [48]. The subcellular synthesis of NAD^+ is supposed to be regulated by Nmnats that transform NMN into NAD^+. There are three Nmnats isozymes in various cell compartments: Nmnat1 in the nucleus, Nmnat2 in the cytoplasm, and Nmnat3 in the mitochondria and the cytosol [49]. Nmnat1 has the most robust enzymatic activities among these three. The global absence of Nmnat1 results in the embryonic death of mice, suggesting its importance for NAD^+ synthesis during the developmental stage [50]. However, recent studies demonstrated the less importance of Nmnat1 in certain tissues or redundancy between other Nmnats isozymes. Adipocyte-specific Nmnat1 knockout mice showed decreased nuclear NAD^+ levels in brown adipose tissues but exhibited no obvious changes in their physiological functions [51]. The deletion of Nmnat1 in the liver or skeletal muscle showed no obvious abnormalities in physiological and pathological conditions [52,53]. Nmnat3 has been proposed as the mitochondrial NAD^+ synthesis enzyme, though Nmnat3 knockout mice purportedly have similar levels of mitochondrial NAD^+ to control mice [54]. Recently, Slc25a51 was discovered as a mitochondrial NAD^+ transporter by several investigations [55,56]. In cultured cells, Slc25a51 knockdown markedly reduced mitochondrial NAD^+ levels and inhibited mitochondrial respiration [55]. NAD^+ is, therefore, thought to be produced in the cytoplasm and subsequently transferred into the mitochondria, suggesting that three Nmnats isozymes cooperatively generate each subcellular NAD^+.

The metabolic function of NAD^+ varies among cellular compartments; nuclear NAD^+ is mainly consumed for DNA damage transcriptional regulation, cytoplasmic NAD^+ is necessary for glycolysis, and the mitochondrial pool generates electron carriers [57]. Similarly, the distribution of NAD^+-consuming enzymes is also localized in the subcellular compartment. Nuclear SIRT1, SIRT6, and SIRT7 are important for gene transcription, DNA repair, and genome stability. Mitochondrial SIRT3, SIRT4, and SIRT5, along with nuclear SIRT1, regulate mitochondrial homeostasis and metabolism [58]. Besides sirtuins, PARP is also localized in different parts of the cells, while PARP1 is the most abundant PARP and is expressed in all cell compartments. This nuclear PARP1 is strongly activated by DNA damage, leading to the consumption of a large amount of cellular NAD^+, while the mitochondrial PARP1 is involved in mitochondrial homeostasis [36]. NAD^+ plays different roles in various cellular compartments. However, how NAD^+ precursors synthesize and transport NAD^+ between different compartments is not yet fully understood. It is essential to investigate how these precursors synthesize NAD^+ within the cell and whether they can enter all compartments or if they mainly produce cytosolic NAD^+, which is later transported to the mitochondria and nucleus. A comprehensive understanding of the mechanisms by which these precursors contribute to the synthesis of NAD^+ in different cell compartments is crucial.

3. Association between NAD $^{+}$ levels and aging

In the past, innumerable analyses have reported the association between NAD^+ levels and aging in rodents and humans (Table 1) [59,60]. The studies using rodents have revealed that NAD^+ levels decline in multiple tissues, including the liver, skeletal muscle, adipose tissue, heart, brain, kidney, pancreas, lungs, spleen, and skin [2,38,61–74], albeit the discrepant results have also been reported. These reports have demonstrated that NAD^+ levels were not changed between young and aged mice of tissues, such as liver and skeletal muscle [65,70,75–77]. Further, human studies also have reported the decline of NAD^+ levels with age in blood, plasma, and cerebrospinal fluid [74,78,79]. A cross-sectional study demonstrated that NAD^+ levels in skeletal muscle decline with age and positively correlated muscle function during aging [80]. However, some studies reported no change in NAD^+ levels with

Table 1
Changes in NAD $^{+}$ levels with aging in human and rodent studies.

Species	Tissue	Age	Gender	NAD^+ levels with age	Reference
Human	Blood, plasma	29–81 years	Both sexes	Decline with age	[74]
	Red Blood cells	29–81 years	Both sexes	No change	[74]
	Plasma	20–87 years	Both sexes	Decline with age	[79]
		24–91 years	Both sexes	No change	[78]
	CSF	24–91 years	Both sexes	Decline with age	[78]
	Brain	21–68 years	Both sexes	Decline with age	[66]
		26–78 years	Both sexes	Decline with age	[81]
		21–69 years	Both sexes	No change	[91]
	Muscle	20–80 years	Both sexes	Decline with age	[80]
		21–69 years	Both sexes	No change	[91]
	Skin	0–77 years	Both sexes	Decline with age	[63]
Rodents	Liver	3–25 months	Male	Decline with age	[70]
		3–24 months	Female	Decline with age	[73]
		4–20 months	Male	Decline with age	[61]
		6–24 months	Male	Decline with age	[64]
		5–32 months	Male	Decline with age	[38]
		8–110 weeks	Female	No change	[76]
		6–55 weeks	Male	No change	[77]
		3–31months	Both sexes	No change	[65]
	Skeletal muscle	3–31months	Both sexes	Decline with age	[65]
		3–25 months	Male	Decline with age	[70]
		4–24 months	Male	Decline with age	[67]
		6–24 months	Male	Decline with age	[64]
		6–30 months	Not specified	Decline with age	[72]
		5–32 months	male	Decline with age	[38]
	Adipose tissue	3–31months	Both sexes	Decline with age	[65]
		3–25 months	Male	Decline with age	[70]
		5–32 months	Male	Decline with age	[38]
	Heart	3–24 months	Female	Decline with age	[73]
		3–25 months	Male	No change	[70]
	Brain	3–24 months	Female	Decline with age	[68]
		3–25 months	Male	No change	[70]
	Hippocampus	6–12 months	Not specified	Decline with age	[69]
		2–19 months	Both sexes	Decline with age	[71]
		10–30 weeks	Male	Decline with age	[62]
	Cerebellum	4–16 months	Male	No change	[75]
	Kidney	3–24 months	Female	Decline with age	[73]
		3–25 months	Male	Decline with age	[70]
	Pancreas	3–31months	Both sexes	Decline with age	[65]
		3–25 months	Male	No change	[70]
	Lungs	3–24 months	Female	Decline with age	[73]
		3–25 months	Male	No change	[70]
	Spleen	5–32 months	Male	Decline with age	[38]
		3–25 months	Male	No change	[70]

age in plasma and red blood cells [78,81]. Using magnetic resonance spectroscopy, NAD^+ levels in the brains of healthy subjects were shown to decrease with age [81,82]. Although the exact reason for these discrepancies is unknown, the difference in the quantification method is speculated as the cause. Additionally, it is known that NAD^+ levels are different in each subcellular compartment, and the sample preparation may cause the difference. In human studies, most study size is less than one hundred. Thus, it is relatively small to make a clear conclusion.

So far, many studies have indicated that NAD^+ levels in certain tissues decrease with age. However, it is also a fact that the decline of NAD^+ levels in cells and tissues is not a universal phenomenon. Thus, further studies are necessary to make a consensus regarding the age-dependent decline of NAD^+.

4. Therapeutical efficacy of NAD $^{+}$ precursors

Reduced NAD^+ levels impair NAD^+-dependent cellular processes and accelerate numerous age-related diseases [64,72]. NAD^+ repletion is drawing attention as an anti-aging intervention. Supplementation of NAD^+ precursors can be advantageous in maintaining normal cellular metabolism regulated by NAD^+ and NAD^+-dependent enzymes. NAD^+ precursors, such as NA, NAM, NR, and NMN, provide beneficial effects in various preclinical disease models of age-induced deficits, including metabolic disorders, cardiovascular, neurodegenerative diseases, and musculoskeletal diseases (Fig. 3).

Besides animal studies, several clinical studies of NAD^+ precursors have been reported. The therapeutic benefits of NA have been widely recognised for a long time in clinical settings. Due to its lipid-lowering effect, NA is a well-known treatment option for dyslipidemia [64]. It acts as a ligand for the G–protein-coupled receptor GPR109a [83,84], which has been shown to inhibit hepatosteatosis and the progression of atherosclerosis and other inflammatory conditions [85]. The discovery of Gpr109a as a receptor for NA demonstrates that niacin-mediated effects are not only due to NAD^+ generation but also downstream signaling activation following niacin binding to the cell surface receptor [86]. However, rapid increases in circulating NA levels that result from GPR109a activation may induce niacin flush, causing discomfort to the patient [87,88].

Researchers have explored alternative precursors such as NAM, NR, and NMN after experiencing side effects of NA. Clinical trials have been conducted to evaluate the safety of NR and NMN when taken orally. Studies have unequivocally reported no serious adverse effects following treatment with NR and NMN [12,13]. Based on these investigations, the highest safe dose of NR is 2000 mg per day [89], while NMN has been confirmed to be safe at a maximum recorded dose of 1250 mg per day [14]. These findings indicate that NAD^+ precursors are safe to use. Determining how these precursors affect the NAD^+ metabolome is also

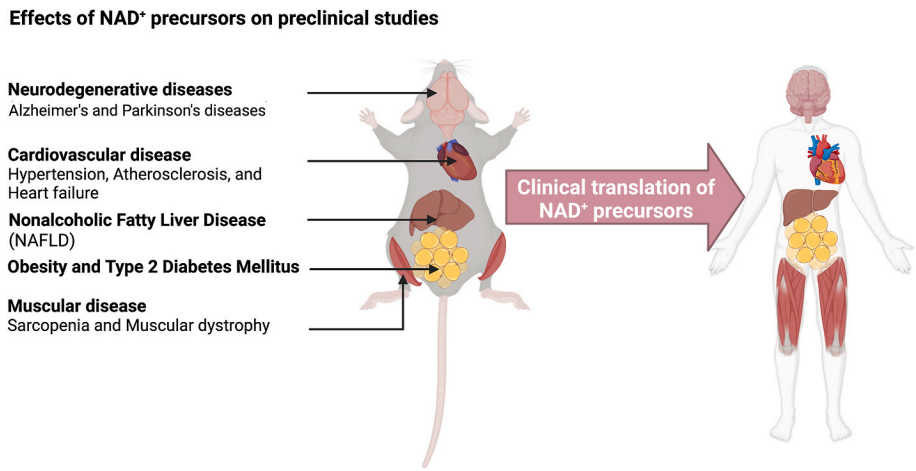

Fig. 3. Replenishment of NAD $^{+}$ precursors ameliorate age-related pathologies in preclinical and clinical studies.
Supplementation of NAD^+ has been proven to provide therapeutic benefits for several diseases including metabolic, cardiovascular, musculoskeletal, and neurodegenerative diseases. Multiple preclinical studies have provided scientific evidence that NAD^+ precursors effectively halted the progression of diseases. Moreover, ongoing clinical trials suggest that supplementing NAD^+ intermediates may have the potential to combat these diseases.

the main goal of the research. NR supplementation raised the NAD^+ concentration in the blood [90,91]. Like NR, NMN also has an impact on NAD^+ metabolism. According to various studies, NMN raises NAD^+ dose-dependently in the blood and peripheral blood mononuclear cells [92–94]. Several clinical trials of NAD^+ precursors showed beneficial effects in pathological conditions (Table 2). Here, we review the

Table 2
Therapeutic potential of NAD $^{+}$ precursors in clinical trials of age-associated diseases.

Age-related disease	NAD^+ Precursor and Dosage	Participants	Physiological effects of precursors treatment	Reference
Obesity	NR (1–2 g/day, for 6 and 12 weeks)	Overweight/obese pre-diabetic patients	No effect on body weight	[12,89, 104]
Insulin resistance/ Type 2-DM	NAM (500 mg/three times/day) for 6 months with insulin or sulphonylureas	Type 2 Diabetes Mellitus with secondary failure to sulphonylureas	Nicotinamide improves C-peptide(insulin) release in type 2 diabetic patients with secondary failure to sulphonylureas while blood glucose and HbAIC levels remain unchanged to NAM.	[107]
	NR (1–2 g/day, for 6 and 12 weeks)	Overweight/obese pre-diabetic patients	NR failed to improve insulin sensitivity or effect glucose metabolism.	[12,115]
	NMN (250 mg/day for 10 weeks)	Obese pre-diabetic postmenopausal women	NMN improved insulin sensitivity in overweight/obese pre-diabetic postmenopausal women.	[93]
NAFLD	NR (2000 mg/day for 12 weeks)	Overweight/obese pre-diabetic patients	Borderline decrease in hepatic triglyceride levels	[12]
	NR (1000 mg/day 6weeks)	Overweight or obese men and women	No change was observed in hepatic lipid content	[115]
	NAM 1000mg/daily for 12 weeks with diabetic therapy	Diabetic NAFLD	NAM improved low density lipoprotein, cholesterol, and insulin resistance marker, while no effect on liver steatosis and fibrosis. NAM also improved quality of life (QOL) of diabetic NAFLD patients.	[117]
Cardiovascular Diseases	NR (500 mg twice a day for 6 weeks)	Healthy/middle and older adults	NR reduces blood pressure and arterial stiffness	[125]
	NR (500–1000mg/twice a day for 9days)	Stage D heart failure patient	Increased NAD^+ levels, enhanced oxygen consumption, reduced inflammatory cytokines in PMBCs	[127]
	NMN (125–250 for 12 weeks)	Healthy/middle aged	NMN reduces arterial stiffness	[126]
Neurodegenerative Diseases	NAM (1500 mg of twice a day for 24 weeks)	Alzheimer's disease	NAM failed to improve cognitive function	[139]
	NAM (2-4 gm/day for 24 months).	Friedrich ataxia	The NICOFA study is to assess the clinical efficacy of NAM in patient with Friedrich ataxia.	[142]
	NA (100–250 mg/day for 12 months)	Parkinson's patients	NA improved a composite quality of life score and slow disease progression	[140]
	NR (1000 mg for 30days)	Parkinson's patients	NR increase NAD^+ levels in brain tissue and decreased levels of inflammatory cytokines in serum and cerebrospinal fluid	[141]
Skeletal Muscle Diseases	NR (1000 mg/day for 21 days)	Aged group	Increase in muscle NAD^+-derived metabolites	[91]
	NR (1000 mg/day 6weeks)	Overweight/obese men and women	NR increased skeletal muscle levels of NAD^+ associated metabolites, altered acylcarnitine concentrations and caused minor changes to body composition	[115]
	NR Acute (2 h or short-term 7 days)	Aged	Acute NR intake (2 h prior to exercise) increased performance in aged individuals	[146]
	NA (750 mg/day up to 1 g/day)	Mitochondrial myopathy patients	NA increased NAD^+ levels in muscle tissues, improved muscle strength in patients with mitochondrial myopathy	[154]
	NMN (250 mg ante or post meridian)	Older adults >65 years	NMN reduced drowsiness and improved lower limb function after post-meridian treatment	[153]
	NMN (250 mg of for 12 weeks)	65-year-old men	NMN improved walking speed and grip strength	[94]
	NMN (250 mg/day for 24 weeks)	Older diabetic patients >65 years	NMN did not alter muscular strength, gripping power and walking speed	[13]

effectiveness of NAD^+ precursors in animal studies in different age-related pathologies and the outcomes of NAD^+ precursors in their clinical translation.

4.1. NAD^+ and metabolic diseases

4.1.1. NAD^+ and obesity

Obesity affects approximately 30 % of the global population and poses a hazard to various metabolic and cardiovascular diseases. The accumulation of fat in adipose tissue, liver, and skeletal muscle due to obesity leads to low-grade systemic inflammation and accelerates the aging process [95,96]. Reportedly, the NAD^+ levels inside the cell have been found to decrease with obesity in rodents [65,97]. While administering NAD^+ intermediates, they inhibit the decline in NAD^+ levels in obese mouse models [98,99]. Oral supplementation of NR suppresses diet-induced weight gain and enhances calorie expenditure [65,98]. Long-term administration of another NAD^+ precursor, NMN, showed enhanced physical activity with higher energy expenditure that reduces weight gain in aged mice [98]. Another precursor, NAM also showed improvement in diet-induced weight gain, NAM treatment induced the beiging, brown adipose tissue-like phenotype change of white adipose tissue, resulting in increased energy expenditure and reduction in weight loss [100]. Taken together, administering NAD^+ precursors can reduce age and diet-related weight gain, and oral intervention with NMN and NR may successfully combat obesity. It is important to note that certain studies have presented conflicting evidence regarding the relationship between obesity and NAD^+ levels; these studies have shown that NAD^+ levels remain unchanged in individuals with obesity [101–103]. Moreover, when translating the NAD^+ intermediate NR for the anti-obesity regimen, these precursors do not affect body composition in clinical trials in the obese state [12,89,104]. Therefore, more research is required to determine the effectiveness of NAD^+ molecules for obesity. The relationship between the gut microbiome and obesity is a subject of increasing interest in the scientific community, with research suggesting a potential correlation between the alteration of microbiome composition during obesity [105]. Moreover, recent findings propose a possible link between the gut microbiome and NAD^+ levels in the body, underscoring the significance of maintaining a healthy gut microbiome against obesity. Thus, the effect to gut microbiota is one of possible reason to explain the discrepancy of the efficacy of NR supplementation to obesity between pre-clinical and clinical study. However, a more in-depth investigation is necessary to elucidate the underlying mechanisms of these associations.

4.1.2. NAD^+ and type 2 diabetes mellitus

Both aging and obesity can impair insulin sensitivity, increasing the risk of type 2 diabetes mellitus [9]. Several groups reported NAD^+ precursors NR or NMN raise NAD^+ levels and demonstrated their ability to reduce obesity-induced insulin resistance in mice [65,99]. NR supplementation protects them from gaining diet-induced weight and prevents them from developing glucose intolerance by raising fatty acid oxidation and enhancing insulin sensitivity [99]. Another study using NA and NAM also verified the effects on glucose metabolism and fatty liver; this study compares the different doses of NA and NAM, 10 mg/kg and 100 mg/kg in drinking water for four weeks and found that NAM is more effective than NA on regulating glucose metabolism and mitochondria biogenesis [106]. Moreover, NMN has also been studied to treat insulin resistance, administering NMN intraperitoneally at 500 mg/kg/day improved insulin tolerance in mice. Hepatic triglyceride and cholesterol content also decreased, suggesting NMN improves metabolic syndrome traits [65]. Another study using NMN also supports the effects of NMN in aging; long-term NMN therapy reduces age-related insulin resistance and stops aging-related alterations in gene expression, and older animals retain skeletal muscle mitochondrial respiratory capacity, which may help enhance glucose tolerance [98]. These studies demonstrate that NAD^+ metabolism is a suitable target for insulin resistance.

The clinical translation of NAD^+ precursor, NAM, for diabetes treatment was conducted long ago by Polo et al. in patients with type 2 diabetic having a history of secondary failure of sulphonylureas. In this study, they administered the NAM with insulin and sulphonylureas. The finding of this study shows that NAM administration increases the release of C-peptide(insulin) in both groups. This increase in C-peptide release in sulphonylureas treatment leads to the same metabolic profile as in patients treated with insulin [107]. Later, NR has also been translated into clinical studies; however, NR did not show anticipated results. NR did not significantly improve human insulin sensitivity, as reported in clinical trials [90,104]. In another clinical trial using NMN, oral administration (250 mg/day) increased NAD^+ turnover and muscle insulin sensitivity in obese women with prediabetes [93]. Treatment with NMN improved insulin signaling and increased expression of muscle remodeling genes. According to these findings, administering NMN to high-risk individuals may decrease the likelihood of developing diabetes. Additional research is necessary to examine the impact of alternative NAD^+ precursors and their comparative analysis on insulin resistance.

4.1.3. NAD^+ and non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is a metabolic state that is prevalent with obesity worldwide [108]. NAFLD is characterized by lipid accumulation, which leads to the start of inflammation and causes chronic end-stage liver diseases [109,110]. Aging and fatty liver, along with obesity, both affect the hepatic NAD^+. Aging tends to decline the hepatic NAD^+ levels in both mice and humans [61]. Hepatic NAD^+ is also affected by fatty liver caused by diet-induced obesity in mice [111]. Contrarily, NAD^+ supplement therapy has been shown to ameliorate hepatic steatosis in obesity and metabolic disorders. NR administration was demonstrated to have comparable effects on hepatic triglycerides in mice [99]. NR treatment for three months decreased hepatic steatosis in aged mice [112]. These findings suggest that targeting NAD^+ metabolism could be a viable therapeutic strategy for treating NAFLD [61,65,90]. On the contrary, some studies demonstrated discrepant results that hepatic NAD^+ does not decrease in obesity, nor does NR treatment improve the phenotype in NAFLD mice [76,113]. This contraindicated result related to NR suggests the need to study other NAD^+ precursors that may be more effective than NR. Additionally, one study found that intraperitoneal injection of NMN resulted in hepatic triglyceride accumulation [114].

NR has effectively treated metabolic disorders in preclinical studies, but clinical trials have shown limited benefits in treating hepatic steatosis. NR supplementation reduces hepatic steatosis but does not affect body weight and energy metabolism in obese patients [12]. In another clinical trial, 1000 mg NR for six weeks slightly diminish body fat-free mass but failed to improve insulin sensitivity, mitochondrial function, and hepatic lipid content in healthy overweight patients [115]. NR did not show a desirable result in clinical studies; however, NMN single dose intravenously considerably lessens blood triglycerides in healthy people [116]. Similarly, another trial mentioned NAM at a dose of (1000 mg/day) decreases the low-density lipoprotein, cholesterol, and liver enzyme alanine transaminase, improved quality of life in diabetic NAFLD patients while no significant effects have seen in liver fibrosis or steatosis [117]. The effect of each NAD^+ precursor is variable, and further studies with different NAD^+ precursors are required to analyze their efficacy against NAFLD.

4.2. NAD^+ and cardiovascular diseases

Cardiac health is significantly affected by age and obesity, leading to impaired function and a range of pathological conditions like hypertension, atherosclerosis, and heart failure [118]. As with age, the heart also possesses a decline in NAD^+. This reduction can greatly vary between species and studies, with reports of a decrease ranging approximately up to 65 % in aged rodents [73]. The potential therapeutic target

for many cardiovascular pathologies has been linked to NAD^+. A study reported that NMN treatment improves the gene expressions of the aorta, protects it from vascular aging and prevents atherosclerotic vascular conditions in aged mice [119]. Similarly, supplementation of NAM improves atherosclerotic lesions and protects against lipoprotein oxidation and aortic inflammation in mice lacking apolipoprotein E [120]. A recent study reported that NAM increased NAD^+ biosynthesis and lowered systolic blood pressure in mice and rats [121]. Aging also increases the vulnerability of heart failure due to cardiac functional changes. In the pre-clinical study, the Zhang group examined the impact of NAD^+ on heart failure. This study showed the effects of NMN in cardiac-specific Kruppel-like factor-4 (Klf4) deficient mice. Klf4 is crucial in maintaining cardiac health by regulating mitochondrial homeostasis and facilitating mitochondrial biogenesis and autophagy [122]. In the absence of Klf4, mitochondrial functions are impaired, which can result in cardiac dysfunction. In Klf4 deficient mice, intraperitoneal injection of NMN at a dosage of 500 mg/kg increased NAD^+ levels in cardiac tissue, conserving mitochondria against stress-induced damage and reducing myocardial inflammation [123]. These studies highlight the efficacy of NAD^+ supplementation in various cardiovascular conditions, including hypertension, atherosclerotic vascular disease and heart failure.

Clinically, NA has been used as a targeted therapy for hyperlipidemia that potentially lowers serum triglycerides [87]. NA treatment lessens the risk of cardiovascular incidents, such as acute coronary syndrome, though its usage has been limited due to side effects like hot flushes [124]. In substitute for NA, different NAD^+ precursors were studied clinically. A recent study reported that healthy middle-aged and older persons who supplement with the NR for six weeks experience a decrease in blood pressure and rigorousness of the aorta [125]. The other clinical study also reported that using other NAD^+ metabolite NMN (125–250 mg) for 12 weeks improved arterial stiffness [126], consistent with the mouse study [119]. Another clinical study reported that oral NR administration escalates NAD^+, mends mitochondrial functions, and lessens proinflammatory cytokine in PMBCs of advanced heart failure patients [127]. Overall, from the above-mentioned studies, NAD^+ supplementation therapy shows beneficial effects in age-related cardiac issues; furthermore, detailed research is essential.

4.3. NAD^+ and neurodegenerative diseases

Alzheimer's and Parkinson's disease are neurodegenerative disorders that can be caused by age-related neuronal degeneration [128]. NAD^+ metabolism is also affiliated with the age-related progression of neuronal loss. As with age, the levels of NAD^+ in the brain tend to decrease in humans and animals. The rodent study showed that the hippocampus of 12-month-old mice has reduced NAD^+ levels due to decreased NAD^+ synthesis [69]. Similarly, healthy individuals experience a decline in NAD^+ content in their brains as they age [82]. Preclinical studies have investigated the effects of NAD^+ precursors in neurodegenerative diseases [129]. Studies have demonstrated that administering NAD^+ precursors has enriched cognitive function in rodent models, indicating that NAD^+ intermediates possess a neuroprotective effect [130–132]. Growing evidence indicates NAD^+-dependent pathways play a critical role in the development of Alzheimer's disease (AD). Studies on early-onset AD in rodents have found that NAD^+ depletion is associated with metabolic dysfunction [133,134]. However, treating rodents with NAM or NR to increase NAD^+ levels has prevented AD-related pathology and improved cognitive functions [133,134]. Moreover, emerging evidence also suggests that dopaminergic neurons affected by Parkinson's disease (PD) have reduced NAD^+ levels [135] and supplementing with NAD^+ therapies enhances mitochondrial biogenesis and improves mitochondrial functions [136,137]. As several studies reported positive results, NAD^+ supplementation in PD could be the key to unlocking new treatments. Besides AD and PD, a recent study revealed that NAM supplementation can reduce brain inflammation. In this study, dietary NAM prevented brain inflammation via NAD^+-dependent deacetylation mechanisms with increased sirtuin signaling activity [138].

The clinical translation of NAD^+ intermediates in neurodegenerative diseases has also been reported. During a study conducted on humans, it was found that administering 3 g of NAM (1500 mg twice per day) for a period of 24 weeks did not improve the cognitive function of patients with Alzheimer's disease [139]. Therefore, further analysis of different precursors is required to determine the effectiveness of NAD^+ in treating Alzheimer's disease. Several clinical studies have investigated the effectiveness of NAD^+ precursors for treating Parkinson's disease. Studies have shown that taking 100–250 mg of nicotinic acid (NA) can positively impact the quality of life of Parkinson's patients [140]. Additionally, administering 1 gm of NR to PD patients orally for 30 days has significantly increased NAD^+ levels, as confirmed by ^{31}P-Magnetic resonance spectroscopy. Furthermore, NR has been found to decrease pro-inflammatory cytokines in the blood and cerebrospinal fluid, indicating that it significantly lowers inflammation in PD patients [141]. A clinical trial is currently being conducted to assess the efficacy of administering NAM at a dosage range of 2-4 gm per day for a duration of 2 years in treating Fredrich ataxia, a rare genetic disorder that affects the nervous system and causes movement difficulties [142]. In conclusion, NAD^+ intermediates can help rescue neurodegeneration; however, further detailed studies are necessary to determine the desirable outcomes of these precursors.

4.4. NAD^+ and skeletal muscle diseases

Muscular mass and strength often decline with age, leading to a condition known as sarcopenia. This condition can significantly affect mobility and quality of life for older adults. Several studies have mentioned the potential association between NAD^+ and sarcopenia and reported that mammals' NAD^+ levels decrease in skeletal muscle with age [72,143]. Inhibition of NAD^+ synthesis via Nampt deletion in the skeletal muscle of mice leads to a decline in NAD^+ by 85 %. This reduction in NAD^+ levels affects muscular functions and perturbs physiological changes via NAD^+-mediated glycolysis and fatty acid oxidation, resulting decreased energy production [67]. The replenishment of NAD^+ by its precursors improves muscular function. In preclinical studies, NMN supplements for 12 months had improved oxidative metabolism and physical activity [98]. Similarly, 5 weeks of NAM supplementation positively affects SIRT1 activity in the skeletal muscle of young and aged rats [144]. Moreover, an interesting finding reported the muscle and brain axis. They found that the Slc12a8, the NMN transporter, is present in lateral hypothalamus LH and is crucial in regulating the LH-mediated whole-body metabolism and skeletal muscle functions. This study showed that LH-specific Slc12a8 knockdown in young mice decreases muscle functions, while overexpression in aged mice ameliorates age-related decline. These results provide insights into the development of frailty and sarcopenia during aging, emphasizing the role of Slc12a8 in maintaining optimal physiological function [145].

In older people, acute supplementation of 500 mg NR before exercise boosted blood NADH and NADPH, but not NAD^+ levels in muscle tissues. Further, NR supplementation in older people showed improvements in physical performance, which may indicate a link between age and NR treatment effectiveness [146]. Furthermore, not only muscular weakness, NAD^+ has also been associated with muscular dystrophies and myopathy. Increasing NAD^+ bioavailability can have beneficial effects on myopathy by promoting mitochondrial biogenesis [147,148]. NR supplementation slows the progression of mitochondrial myopathy [149]. Additionally, NR therapy has been demonstrated to enhance the stem cells and accelerate muscle regeneration following cardiotoxin-induced damage [147]. Several preclinical studies have demonstrated the effectiveness of NAD^+ precursors in treating muscle diseases. However, some clinical trial demonstrated that NR supplementation does not improve muscular functions, though NAD^+

metabolome increased in muscles [89,91,150]. The study to explore the relationship between NAD^+ and Duchenne muscular dystrophy (DMD) demonstrated the contradicting result [151]. The research findings suggest that NAD^+ depletion occurs in DMD due to persistent muscle injuries. Further, they increase NAD^+ levels through treatment with CD38 inhibitor or NR, but the expected outcome of rescuing muscular functions or providing protection from injury was not achieved. Therefore, the study concludes that NAD^+ augmentation is not a viable therapy for DMD [151]. Another precursor, NMN, also showed beneficial results in exercise training. One study reported that NMN enhanced oxygen consumption in healthy runners [152]. A study has shown that administering 250 mg of NMN can lessen drowsiness, enhance physical performance, and increase grip strength and gait speed in older men during exercise [94,153]. However, another group reported a negative result, stating that treating 250 mg of NMN for 12 or 24 weeks did not affect muscle strength [13]. In clinical studies, other NAD^+ precursors are also beneficial for myopathies; recently, a group reported that in patients with mitochondrial myopathy, clinical research found that 1 gm of NA per day raised NAD^+ levels in muscle tissues and enhanced muscle strength [154]. These results suggest that NAD^+ precursors enhance muscle performance in some physiological conditions, but the contradicted results are also reported. Thus, further studies are necessary to understand the mechanism that increases muscular NAD^+ and to identify the most suitable precursor to mitigate muscular diseases.

5. Recent advancements in NAD $^+$ metabolism

The latest findings in NAD^+ metabolism signify the role of the gut interaction with orally administered NAD^+ precursors (Fig. 4) [15–17,155–157]. In a study conducted by Liu et al., they examined the *in vivo* fate of NR by using the double-labelled NR via isotope-tracer method. The results revealed that the intact form of NR (fully labelled NR) is reached to peripheral tissues when it is injected intravenously. However, when NR is administered orally, it does not remain in its intact form. It was observed that oral administration of NR was cleaved to NAM and

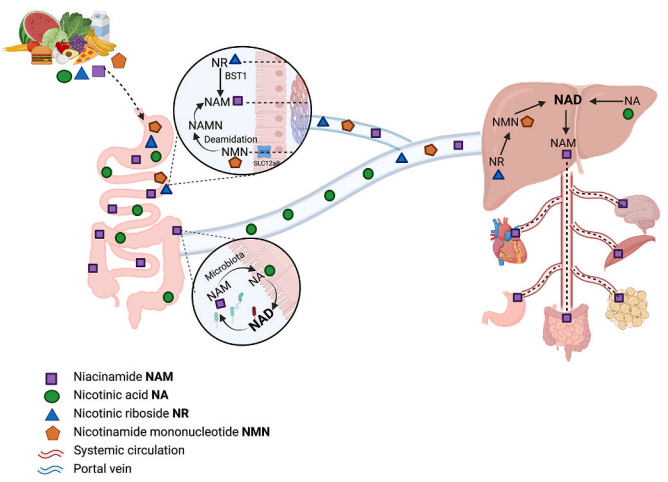

Fig. 4. The fate of orally administered NAD $^+$ precursors and involvement of gut microbiome in NAD $^+$ metabolism.
NAD^+ precursors that are orally administered can enter the gut in two distinct phases. The first route is the direct absorption of NAM, NR, and NMN from the small intestine. These precursors then enter the systemic circulation, providing a direct route to contribute to the synthesis of NAD^+. The second route involves the conversion of NR and NMN into NAM in the small intestine's lumen before proceeding towards the large intestine. In the large intestine, gut microbiota converts NAM into NA, which is then transported to the liver via portal circulation and synthesized into NAD^+. Further, the liver synthesizes NAM from NAD^+ and distributes it to other organs, including the gut, to maintain the continual supply of NAM required for the salvage pathway in each distal tissue for their optimal physiological function.

leads to an increase in NAM concentration in the blood. This suggests that orally administered NR is not directly metabolized into NAD^+ in peripheral tissues [156].

The role of microbiota in the intestine has been clarified by the Shats et al. They have found that dietary NAM and NR are converted into NA through gut microbiota [16]. Furthermore, the research conducted by Yaku et al. has revealed that the BST1 (Bone marrow stromal cell antigen 1) hydrolyzes orally administered NR into NAM in the small intestine, which is further converted to NA by gut microbe [17]. The oral pathway of another precursor, NMN, has been studied. NMN has a specific transporter called Slc12a8 located in the small intestine, which helps to regulate NAD^+ levels [157]. Further research by Kim et al. has shown that oral consumption of NMN is converted into NAMN through interaction with the gut microbiome [155]. A study conducted by Chellapa et al. has shed new light on NAD^+ precursors. The study suggests that the dietary NAM were directly absorbed into the circulation at upper gut and did not reach at the lower gut. After the absorption, circulating NAM again entered to gut lumen and was converted to NA by gut microbiota in the lower gut lumen [15]. The results of investigations on oral supplementation of NAD^+ intermediates have shown a significant link with gut microbes. It has been established that the NAD^+ intermediates require conversion into NA to effectively elevate NAD^+ levels. In addition, these studies also showed that deamidated metabolites, including NAR, NAMN, and NAAD were also elevated.

The impact of human NAD^+ metabolism has been studied, and it has been found that supplementing with oral NR leads to an increase in deamidated NAD^+ metabolites in the blood, indicating the involvement of the gut, as shown in preclinical studies [90,141]. Similarly, NMN treatment also shows a similar result, an increase in NAMN levels, suggesting that the gut microbiome plays a crucial role in the oral intake of these compounds [92]. These findings suggest a correlation between the NAD^+ metabolism of the host and gut microbiome. Further research is needed to determine how the gut microbiota affects human clinical outcomes and NAD^+ metabolism.

Another exciting feature is reported regarding NAD^+ metabolism; the reduced form of NR (NRH) has drawn interest as a potential replacement method for raising NAD^+ levels [19,158,159]. NRH has potently raised plasma NAD^+ and remains intact in plasma after 2 h of administration. The high stability of NRH is one of its most notable features. NRH did not deteriorate after being incubated with plasma for 2 h; however, NR disintegrated rapidly. Conversely, NRH increases liver and muscle NAD^+ more than NR [19,158]. The reduced form of NMN (NMNH) has also been investigated *in vitro* studies, and results showed that NMNH significantly increases NAD^+ levels [18,160]. Moreover, the reduced form of nicotinic acid riboside (NARH) is also investigated by Ciarlo, and the findings suggest that combined supplementation of NARH with NR significantly increases NAD^+ levels, the reason for an increase in NAD^+ is due to the generation of NRH. This result suggests that it can be used as a novel NAD^+ precursor [161]. Reduced forms of NAD^+ precursors have a significant effect on the increase of NAD^+ levels. It is necessary to conduct further research to comprehend the influence of reduced NAD^+ precursors on pathological conditions.

6. Conclusion

NAD^+ has a versatile role in physiological processes in the body, and numerous rodent studies have proved the therapeutic potential of NAD^+ precursor replenishment therapy against age-related pathologies. However, these precursors have shown a minimal effect in clinical studies compared to pre-clinical studies. To rule out this issue, this review focuses on different approaches in NAD^+ metabolism; if we consider these points in clinical trials, we might get desirable results. In addition, many studies have demonstrated that NAD^+ levels decline with age [8]. However, it is also shown that several tissues have no changes in NAD^+ levels with age [60]. Thus, it is important to clarify which tissues/cells are the suitable target of NAD^+ supplementation

therapy against aging.

NR and NMN treatment shows beneficial results in preclinical studies; despite these intermediates, there are more available NAD^+ precursors; recently, NR reduced form, the NRH, dramatically raises the NAD^+ levels in plasma after oral administration and is stable in blood circulation more than NR, suggesting that the NRH is more potent than NR [19,158,159]. Animal disease models should investigate the impact of reduced forms of NR and NMN in different pathological conditions. Moreover, comparative analysis of these precursors simultaneously might be beneficial to comprehend the efficacy of NAD^+ intermediates.

Further, the current progress in NAD^+ metabolism provides discernment to the NAD^+ metabolism; the gut microbiome breaks down NAM into NA, emphasizing the role of the microbiome in the oral metabolism of NAD^+ precursors [15–17]. It is fundamental to consider how the gut microbiome affects NAD^+ metabolism, and changes in microbiome composition may affect the availability of NAD^+ precursors. Future studies also require the comparative analysis of different precursors, and the role of gut microbiomes related to various intermediaries needs to be investigated. Assessment of how NAD^+ precursors affect microbiota and how their interaction with NAD^+ metabolism benefits the physiological condition is essential for future preclinical and clinical studies.

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