

Nicotinamide adenine dinucleotide and the sirtuins caution: Pro-cancer functions

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Abstract

This scoping review aims to perform a brief but comprehensive assessment of existing peer-reviewed literature and determine whether raising nicotinamide adenine dinucleotide can prevent or promote tumorigenesis. The examination of extensive peer-reviewed data regarding the synthesis of nicotinamide adenine dinucleotide has been performed with a focus on nuclear dynamics and the deoxyribose nucleic acid repair pathway. Various enzymatic protective functions have been identified from nicotinamide adenine dinucleotide levels, as well as the threat role that is also explored. Nicotinamide adenine dinucleotide precursors and sirtuin-activating compounds are becoming ubiquitous in the commercial market. Further research into whether elevating levels of nicotinamide adenine dinucleotide or overexpression of sirtuins can increase the potential for neoplasm or other age-related pathophysiology is warranted due to the high energy requirements of certain diseases such as cancer.

KEY WORD

cancer, disease, NAD, overexpression, sirtuin, upregulation,

1 | INTRODUCTION

Nicotinamide adenine dinucleotide (NAD) precursors and sirtuin-activating compounds (STACs) are becoming popular among longevity-minded individuals. The misguided conception that raising NAD or sirtuin activity can only have positive effects on human physiology should be considered erroneous and even deleterious. Hype exists around molecules that appear to extend life or slow down the aging process; however, little regard is given to the aberrant side effects or diseases that the upregulation of some molecules or overexpression of some proteins can cause, such as cancer.

Cancer can be caused by various mechanisms, such as DNA damage from environmental factors or the activation of proto-oncogenes such as loss of tumor suppressor genes or even translocations of the

c-MYC proto-oncogene.^{1–3} Point mutations also deliver a wide variety of possible cancer causes as shown by Koeffler et al.³ Genes coding for guanosine triphosphate-binding proteins such as H-, K-, N-ras, or G proteins may be oncogenic and have already been identified in a sizable assortment of neoplasms. Many drivers of tumorigenesis exist; therefore, interference with cellular or genetic machinery with novel compounds such as NAD precursors or STACs should be approached cautiously.

Extensive energy is required for the rapid proliferation of cancer cells and NAD has been associated in increasing cellular energy production.⁴ Alternatively, NAD has also been implicated in the deoxyribose nucleic acid (DNA) repair pathway.^{5,6} This paradox is explored using a methodology of examining the multitude of NAD pathways in the reduced or oxidized form and how the interplay from these pathways may influence tumorigenesis.

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Nicotinamide adenine dinucleotide synthesis may be performed via numerous pathways such as the salvage pathway, Preiss-Handler pathway, de novo biosynthesis pathway, or the kynurenine pathway^{7–9}; however, the primary pathway for cellular NAD synthesis is the salvage pathway, according to Verdin (2015).⁷ Several methods have been proposed to raise and/or maintain NAD levels, such as inhibiting pathways that consume NAD such as cluster of differentiation 38 (CD38), α -amino- β -carboxymuconate- ϵ -semialdehyde decarboxylase (ACMSD), sterile α , TIR motif-containing protein 1 (SARM1), and poly(adenosine diphosphate-ribose)-1 (PARP1). In particular, CD38 is a glycohydrolase that is a major guzzler of NAD⁺. The flavonoid apigenin is a well-established CD38 inhibitor,¹⁰ and when apigenin was given to mice, the mice were shown to have approximately 50% higher NAD⁺ levels. Inhibiting enzymes that consume the NAD pool appears to make great therapeutic targets in maintaining NAD levels across cellular compartments, but does interfering with cellular machinery such as CD38 hinder the cell's ability to mitigate cancer?

Upregulation of NAD with well-known precursors is only half the battle; however, preventing pools of NAD from waning in the first place is also becoming a prime target. Impeding genes, enzymes, and proteins from being able to use NAD may induce unwanted effects many years downstream.

At 32 months, wild-type mice have approximately half the NAD levels of their more youthful counterparts, but when CD38 is knocked out, the mice maintain their NAD levels and are more resistant to age-related decline, including resistance to high fat diets (HFD), liver steatosis, and glucose intolerance.¹¹ The opposite was true when mice were overexpressing CD38, the mice had lower pools of NAD, dysfunctional mitochondria, decreased oxygen consumption, and an increase in lactate production was found.^{10–12} If this was carried over to the human population, then it may appear that CD38 can be reduced to increase NAD levels. However, the CD38 story is much more complex, as CD38 may intentionally reduce NAD to prevent the more frequent incidence of cancer progression found in older people.¹³

CD38 (a glycoprotein located on numerous white blood cells and serves in cell adhesion, calcium signalling, and signal transduction) catalyses cyclic ADP-ribose from NAD⁺ to ADP-ribose as well as converting nicotinamide adenine dinucleotide phosphate (NADP⁺) to nicotinic acid-adenine dinucleotide phosphate.¹² These reactions, whilst paramount for the control of intracellular calcium ions (Ca²⁺),^{14–16} feed on the existing NAD reserves residing in the cell. Losing control of Ca²⁺ holds cytotoxic potential across proliferation, metabolism, and gene transcription.¹⁷ Furthermore, dysregulation of Ca²⁺ causes the handling and transport of proteins along extracellular, endoplasmic reticulum, cytosolic, and mitochondrial environments to become erroneous, which impacts Ca²⁺ signalling corridors that may lead to increased cancer proliferation and invasion.¹⁸ Therefore, CD38 interference may lead to higher NAD levels that enhance existing cancer progression but may also lead to new early-stage cancer hallmarks.

Another NAD-depleting protein is poly(adenosine diphosphate-ribose)-1 or poly(ADP-ribose)1, which is known across the literature as PARP1, a nuclear enzyme that is now well established as a DNA damage sensor that can quickly recognize when damage has taken place and assists in the organization and structure of chromatin, including the DNA repair pathways.⁶ PARP1 also requires NAD⁺ to form (ADP-ribose) polymers on specific target proteins, and when there is widespread PARP1 initiation, PARP1 can reduce nuclear NAD levels considerably, leaving the nuclear machinery open to instability.¹⁹ In this instance, NAD clearly has anti-cancer properties and is a primary reason why NAD levels should be maintained at healthy levels.

A transcription factor known as nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B) is established as being able to deliver pro-inflammatory and specialist survival reactions in cells. NF- κ B activity is partly controlled by acetylation of its p65 sub-unit.¹⁹ Kauppinen et al. (2013) also demonstrated that PARP1 was able to influence NF- κ B transcriptional processes through influences on p65 acetylation via induced NAD⁺ changes.¹⁹ These data clearly demonstrate that low NAD levels can inhibit genomic repair pathways that may lead to cancer or additional proteomic or transcriptomic pathophysiologies derived from DNA coding errors. Furthermore, this information also demonstrates that ensuring NAD levels are maintained throughout age could offer a heightened ability to fend off cancers via the PARP1 repair machinery before cancer cell proliferation ensues. NAD is also highly active in preventing DNA damage from accumulating as we age. A surprising result found in a recent study is that the oxidized form of NAD appears to be a control mechanism in some of the effects in aging and disease susceptibility. Li et al.²⁰ discuss the protein DBC1 that uses a domain to bind with NAD⁺, which impedes the interaction of DBC1 with PARP1, allowing PARP1 to continue its DNA repair work unhindered. This evidence may indicate why NAD⁺ has been suggested as a molecule with rejuvenation properties.

Other pathways such as raising nicotinamide phosphoribosyltransferase (NAMPT) are also contenders in the NAD precursor realm.²¹ However, unexplored territory in humans is reached if we are to raise the level of enzymes such as NAMPT with the view to raise another coenzyme such as NAD. NAD and NAMPT have already been implicated in various cancers, as cancer requires vast energy to proliferate. Refractory diseases frequently depend on the enzymatic machinery located inside the NAD pathway.²² The same study by Lucena-Cacace et al. shows that high levels of NAD bestow therapy resistance to cancers. This directly infers those higher levels of NAD may cause tumors to be more potent. In this event, starving cancer of NAD and from the enzymes found in the myriad of NAD pathways may also hold merit in the fight against slowing further cancer progression. The inhibition of NAMPT was also shown to reduce oxidative stress, inflammation, DNA damage to keratinocytes, and hyperproliferation in zebrafish models with chronic skin inflammation.²³

A prominent pathway in NAD production is a de novo process; as a result, numerous steps are required along the NAD production

pathways by numerous precursor molecules for biosynthesis. Nicotinamide being an amide of nicotinic acid must undergo multiple reactions along this pathway in order for the NAD molecule to be synthesized,²⁴ which opens up numerous possibilities and discussions for the deactivation of NAD synthesis when cancer is present. Of note, the existence of several pathways leading to NAD production raises questions on the relative importance of each pathway and which of them has the highest potential to increase NAD levels among tumors. NAD levels wane as humans age, and the importance on genomic integrity must also be considered.

It is noted that there is clearly overlap across the NAD literature that indicates benign, beneficial, and harmful effects from NAD and the enzymes found in the various NAD synthesis pathways. This gap in the research certainly gives rise for the need for further discussion.

2 | NAD PRECURSORS

The main precursor for NAD biosynthesis is nicotinamide (NAM),²⁵ and this occurs through the salvage pathway.²⁶ On human erythrocytes NAM doubles the rate of NAD synthesis as opposed to nicotinic acid and is more efficient as a NAD precursor under physiological conditions.²⁷ Nicotinamide appears to protect neurons from injury, stroke, and also ischemia.²⁸ This latter study also discusses when low concentrations of NAM are present that neurological deficits such as Alzheimer's, Parkinson's, and Huntington's disease may take hold. NAM is responsible for the maintenance of NAD coenzymes in lipid catabolism and oxidative deamination. NAM is a version of vitamin B3 and is a primary facet of the pathway that synthesizes NAD.²⁸ Mouse models show that oral delivery of NAM attenuated both retinal ganglion cell soma loss and thinning of the fiber layer inside the retinal nerve. NAM is also paramount for the development and maintenance of the central nervous system by expediting the conversion of embryonic stem cells into neural progenitors and neuronal differentiation, which points to a key role in neural development.²⁸ Evidence suggests that NAM can also cross the blood-brain barrier both ways,²⁹ which makes NAM a great candidate for neuronal NAD synthesis and health. NAM can bolster DNA security and assists with membrane integrity, arrest cellular injury, phagocytosis, apoptosis, and clot formation within the vascular system.³⁰ These data clearly indicate the importance of NAM to prevent the onset of multimorbidity.

Nicotinic acid (NA) (also known as niacin or vitamin B3) is extremely important for neuronal defence and neuronal death,²⁸ demonstrating the importance of NA in healthy central nervous system function and neural and neuronal developmental pathways. Interestingly, NA was able to elevate tissue NAD levels more than NAM could and also was able to raise cellular NAD levels above what NAM could achieve. Hara et al. (2007)³¹ demonstrated that the enzyme NA phosphoribosyltransferase (NAPRT) was closely linked to cellular NAD levels in humans. NAPRT was found to be highly expressed in murine organs such as the small intestine, liver,

and kidneys. NAPRT was also found to assist NA in the synthesis of NAD in human cells. The same study showed that when cells expressed endogenous NAPRT, NA had the ability to synthesize almost twice the amount of NAD over what NAM could achieve. Worth noting that cytotoxicity of H2O2 was decreased through the NAPRT/NA pathway, making NA a promising candidate as an NAD precursor. Moreover, when NAPRT was knocked down, the opposite was found, leading the researchers to conclude that the enzymatic NAPRT/NA reaction for NAD synthesis is also a paramount pathway in the prevention of oxidative stress on cells.

According to Pieper (2003), NA may cause unwanted side effects such as hepatotoxicity and cutaneous flushing³²; NA is available by endogenous and exogenous sources, and only 2% of tryptophan (TRP) obtained through diet is converted into NA, with the conversion happening primarily in the liver.⁵ Furthermore, NA holds prominent antiinflammatory, antioxidant, and antiapoptotic properties across a myriad of cell lines and tissues,^{5,33,34} which also leads into positive health outcomes for conditions such as diabetes,³⁵ atherosclerosis,³⁶ and kidney and lung trauma.³⁷⁻³⁹ In this scenario, TRP may also be considered as a NAD precursor via the TRP metabolism found in the kidneys and liver. NA obtained from dietary intake promotes NAD levels.²⁸ TRP is metabolized into nicotinic acid mononucleotide that is then converted into NAD; however, Fricker et al. (2018) shows that 60 mg of TRP would be required whereas only 1 mg of NA would be required to garnish the same effect.²⁸ The higher rate of TRP that is required for NAD synthesis puts TRP at a disadvantage when compared to other NAD precursors. In this regard, many studies refer to either murine models or human studies; murine species are able to live on TRP only and thus retain their NAD supply, whereas humans do not share this same ability. This presents a required appreciation in interpreting the data sets from different research models; thus, conclusions between murine and human models cannot be taken as literal, but only as anecdotal indications as to the effects various NAD precursors may have on health and cancer.

Additionally, understanding how different NAD precursor molecules, their unique independent pathways, including their waste metabolites, is paramount in understanding the complex nature of disease progression, as a decline in NAD⁺ levels is clearly implicated in various metabolic and neurological diseases.⁴⁰

Other popular precursors are nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), including the reduced forms of these as dihydronicotinamide riboside (DNR) and reduced nicotinamide mononucleotide (NMNH) appear to be even more potent.⁴¹⁻⁴⁵ As shown by these studies, the reduced forms DNR and NMNH presently deliver the highest NAD levels of all the known precursors, though the seemingly simple difference of being in reduced form has also shown that these molecules adhere to completely different pathways, and in the case of DNR, the NAD synthesis was achieved through the NRK-1-independant pathway.⁴⁶ DNR did appear to show metabolic dysregulation that altered mitochondrial respiration.⁴⁷ NMNH also demonstrated differences over its oxidized form, including raising NAD levels more rapidly and doubling the levels of NAD available.⁴⁸ Although

heightened levels of NMNH did appear to deliver many health benefits such as renal tubular epithelial healing in mice. What the effect is of such high NAD levels in causing overexpression of other cellular machinery such as the deacetylases known as sirtuins is unknown and further investigation is justified.

3 | NAD AND SIRTUINS

Popular belief exists that raising NAD can also raise the activity of the sirtuin proteins.⁴⁹ Sirtuin proteins are a rigorous focus in longevity research and there is an abundance of scientific literature that supports the concept that NAD is essential in some, possibly all sirtuin upregulation.^{21,50–53} Seven sirtuins are shown to exist in mammals and use compartmentalized forms of NAD (2). Sirtuins (SIRT) 1, 6, and 7 use nuclear NAD, SIRT2 uses cytoplasmic NAD, and SIRT3, 4, and 5 all use mitochondrial NAD.⁷

The function of each sirtuin gene is vast and existing data does appear to implicate these genes across longevity. SIRT1 being found inside the nucleus and cytosol is responsible for histone deacetylation and the modulation of multiple transcription factors such as p53, nuclear factor k-light-chain-enhancer of activated B cells (NFkB), forkhead box (FOXO's), and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1α). SIRT2 is also cytosolic and performs multiple functions across conditions such as inducing checkpoint kinase BubR1 that is known to increase lifespan.⁵⁴ SIRT3, 4, and 5 reside inside the mitochondria and function to regulate factors such as oxidative stress and lipid metabolism. SIRT6 and 7 are nuclear and control genetic machinery such gene expression and DNA repair.^{21,49}

However, evidence also exists that sirtuin activity may be implicated in tumorigenesis. SIRT2 and SIRT6 appear to function as tumour suppressors, whereas SIRT1 may be bidirectional and operate as a tumor suppressor and oncogenic factor.⁵⁵ Moreover, SIRT1 is associated with facultative and constitutive heterochromatin status, and overexpression may induce unwanted replication by maintaining a prolonged euchromatin state. Alternatively, SIRT1 does contribute to telomeric preservation and enhances homologous recombination.⁵⁶ This contradictory data points to further research being required on finding the most protective and effective level for SIRT1 expression. SIRT1 is also implicated in deacetylating other proteins including FOXO3a, E2F1, KU70, RB1 that enables cell growth.^{57–60} Furthermore, SIRT1 promotes tumorigenesis via exhibiting antiapoptotic properties that may directly drive cancer proliferation.⁶¹

Other sirtuin genes may also deliver pro-cancer activity. Downregulating levels of SIRT2 have been shown to impede hepatocellular carcinoma by reducing the energy metabolism that neoplasm demands.⁶² SIRT2 is also involved in the migration of gastric cancer.⁶³

SIRT5 enriches glutaminolysis that is shown to raise the potential for colorectal carcinogenesis, which is then compounded by high levels of SIRT1 that are also associated with poor colorectal carcinoma outcomes.^{64,65}

4 | SIRTUINS IN VITRO AND IN VIVO FUNCTIONS

Recent research has indicated that modifications in sirtuin proteins points to uncertain and unforeseeable behaviour in many tumor varieties. However, Costa-Machado & Fernandez-Marcos⁶⁶ also found that sirtuin activation can possess strong cancer suppressive properties. The same study not only investigated in vitro evidence but drew on existing research to evidence that specific dangers of elevated sirtuin activity were synonymous with human disease. SIRT1 was found to be higher in breast, gastric, colon, acute myeloid leukemia, thyroid, lung, and prostate tumours. Elevated SIRT2 was found to increase c-MYC stability, deacetylated and repressed KRAs in lung and pancreatic cancer, inhibited JMJD2A in lung cancer and deacetylated K305 resulting in reduced breast tumour development. SIRT3 caused disruption to c-MYC and p53 stability, though contrarily restricted expression of TWIST in ovarian carcinoma along with the Wnt/β-catenin corridor in prostate tumours. SIRT3 was also found to disrupt HIF1a and reduce breast tumor progression, along with activation of superoxide dismutase 2 and isocitrate dehydrogenase 2 that reduced B-cell malignancies. Moreover, SIRT3 inhibited Notch1 expression that showed a decrease in gastric cancer. Furthermore, SIRT3 was implicated in poorer outcomes of diffuse large B-cell lymphoma, promoted colorectal carcinogenesis, though suppressed mammalian target of rapamycin complex 1 (mTORC1) when overexpressed which reduced tumor development. SIRT4 was able to exhibit suppression of glutamate dehydrogenase resulting in prevention of liver, lung, and Burkitt B-cell lymphoma along with decreased expression of mammalian target of rapamycin (mTOR) signalling with decreased liver tumour progression. SIRT5 was implicated in breast tumour growth, decreased lung tumour growth, promotion of colorectal tumours, and serine hydroxymethyltransferase-2 desuccinylation driving cancer proliferation. SIRT6 was shown to suppress pancreatic cancer, controlled c-MYC transcription in colon cancer, inhibited TWIST1 expression resulting in suppressed proliferation in non-small cell lung cancer, suppressed oncogenic functions, resulted in increased pancreatic tumours when downregulated, though inhibited ovarian cancer progression and oral squamous cell carcinomas. SIRT7 showed inhibition of p53, is shown to be downregulated in breast lung metastases in both humans and mice, stimulated epithelial-to-mesenchymal transition in prostate cancer cells, and restricted expression of miR34a advancing stomach tumor development.

5 | INDIRECT NAD MANIPULATION

Other novel methods to increase NAD levels exist, such as inhibiting the enzyme aminocarboxymuconate-semialdehyde decarboxylase (ACMSD). Attenuation of ACMSD has been shown to promote NAD⁺ synthesis (via *de novo*) and also increase SIRT1 function.⁶⁷ Of note, ACMSD is involved in several other biological processes; thus, suppressing ACMSD for increased NAD synthesis may appear as an

interesting target to raise NAD. However, low levels of ACMSD may hold detrimental effects, such as Parkinson's Disease (PD) development, as ACMSD is well depicted inside the kynurenine pathway where it works to regulate and limit the creation of quinolinic acid (QA).⁶⁸ QA is an N-Methyl-D-aspartic acid (NMDA) receptor agonist, presenting excitotoxicity properties that can damage nerve cells. It is noted that ACMSD is not the only driver or possible cause for PD and maintaining ACMSD may not treat or manage PD.

The type of precursors used for NAD synthesis make up only a small part of the science of increasing NAD levels. As shown earlier in this discussion many pathways exist such as de novo NAD synthesis from dietary intake of tryptophan or via the salvage pathways from NAM, NR, NMN, DNR and NMNH, and NA,⁶⁹ and different biological systems use different NAD pathways such as the heart that gets >99% of NAD via the salvage pathway.²¹ Combining these data with the variants from each NAD precursor such as NMN, which may improve cardiac function, opposed to NR, which may improve mitochondrial function in muscle, liver, and brown adipose tissue,^{11,70} it becomes evident that different precursors and their pathways may lean toward different benefits and health risks.

If it becomes common for users of NAD supplementation to use a combination of NAD precursors, then this may complicate the mechanisms at play, the benefits and risks. However, these data must be weighed against the fact that the literature used for this discussion used mono-analytical pathways and not diverse mixed methods; therefore, the results of every paper can be questioned as to how a precursor may perform under different conditions or how the sample processing influenced the outcome. The majority of published literature clearly leans toward increasing NAD levels for overall health and cellular metabolism; however, we note that there is also research that shows contradictory evidence with heightened NAD levels. Of note, nicotinamide supplementation induces metabolic effects that were detrimental to rats.^{71,72} However, this effect has not been replicated in humans and demonstrates that not all animal models relate to human physiology. NA in high consumption can expand methyl group consumption and hydrogen peroxide levels. This methyl depletion can increase ROS and insulin resistance.⁷¹ Though we note that this study was again in rats and was performed at levels of consumption that are rarely if ever recommended or used by humans. Consumption was at levels of 0.5, 2, and 4 g/kg of weight. Therefore, these studies in Sprague Dawley wild-type rats may not likely translate to cause for concern in humans. Even though we found numerous papers showing that NAD levels were easily raised with NR, NMN, NA, and NAM, we also found a trend that NR could hold mild detrimental effects in animal models such as substandard exercise ability that may or may not translate over to humans.⁷³ However, this is not to suggest that NR has a different effect on biology, but that different research methods and model organisms combined with contrasting sample processing techniques throughout the literature may suggest that the different effects seen from NR may simply be attributable to the lack of diverse scientific techniques used to synthesize and observe NAD. Attempts of increasing NAD by using precursors mixed with other compounds also

form part of the current research in this field. One such combination is NR combined with pterostilbene. It has been demonstrated during a randomized double-blind placebo-controlled study that when subjects took a combination of NR and pterostilbene their NAD levels increase.⁷⁴ Pterostilbene is a polyphenol found in blueberries and it is not shown how this polyphenol actually induced NAD synthesis.⁷⁴ From the literature it is more probable that the rise in NAD levels among subjects was solely the result of the effects of NR. However, the same paper does discuss that pterostilbene is an analogue of resveratrol, which is known to be a strong SIRT1 activator,⁵³ and with evidence mounting that sirtuin overexpression could be harmful, these type of combinations may hold further risk.

6 | SUMMARY

Clearly NAD is used in all cells, including cancer cells to produce energy. The findings of this paper suggest that NAD supplementation should be discussed with a healthcare practitioner if you have a strong family history of cancer, have cancer, or have had cancer. Any given subject should first speak to their healthcare provider when considering NAD and possibly perform screening tests. However, NAD may fend off many other age-related diseases and prevent cancer from developing, so developing strategies to purge senescent cells from the body prior to NAD supplementation should also be considered.

The pursuit to blindly raise sirtuin activity in the quest for longevity may also produce counterproductive results and may be misguided. However, cancer cells like normal cells require the same cellular machinery to function, and this review does not find that NAD nor sirtuins cause cancer but may simply assist fuelling cancer where present. Where it is shown that sirtuin or NAD inhibition shows beneficial effects against cancer progression, it does not infer those elevated levels of sirtuins or NAD assist in cancer progression but are simply part of the cancer progression. Raising sirtuin or NAD activity may increase disease penetrance, and further research is required to understand the complex mechanisms at play.

As shown with the risks of interfering with machinery such as ACMSD, NAD precursor products that are vague in their methodology or ingredients should be avoided, as products currently appearing on the market that interfere with NAD-consuming enzymes may come with increased disease risk. This may demonstrate some precursors hold higher risk than others, indicating that not all precursors are equal at upregulating cellular or nuclear machinery in the quest for healthy NAD levels. Unique approaches should be developed to ensure that not only NAD is maximized throughout the entire range of organelles, but that stringent confines exist for associated biological machinery so that overexpression and other risk factors are mitigated. How that can be achieved should become a major focus for NAD research.

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CONFLICT OF INTEREST

R.D.P. is Chief Scientific Officer of Helium-3 Biotech. M.M.E. and M.V. have no conflict of interest to declare.

AUTHOR CONTRIBUTION

R.D.P.: idealization, assembly, and review of the literature and writing; MV: draft revision and supervision.

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