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Review Article

THE NAD+ ROLE IN CELLULAR REGENERATION AND AGEING SKIN

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ABSTRACT

The review primarily examines the effects of nicotinamide dinucleotide (NAD+) on mitochondrial balance, DNA repair, energy regulation, and signalling pathways associated with skin health. The prevalence of skin disorders worldwide demonstrates the necessity of cellular renewal as we age. Ageing is associated with a sharp decline in NAD+. Genomic instability, epigenetic modifications, mitochondrial issues, cell ageing, and stem cell depletion are some of the main indicators of skin ageing. NAD+ precursors, including nicotinamide, nicotinic acid, nicotinamide riboside, and NMR, have been shown in preclinical studies to enhance DNA repair, mitochondrial function, and other inflammatory processes. Niacin and nicotinamide clinical trials show advantages for skin conditions, metabolic health, and general resilience. Pharmacological therapies are in the pipeline for general therapeutic use, from CD38 and PARP inhibitors to NAD^+ precursors. NAD^+ modulation in skin disease has promise in photoprotection, healing, regeneration of tissues, treatment of hyperpigmentary disease, as well as in anti-ageing formulations. The limitations in oral supplement form are remedied by next-generation delivery tools like hydrogel patches, nanoliposomes, and microneedles that enhance delivery to the location of interest by boosting bioavailability. These findings thus indicate that NAD^+ is not only a biological indicator, but is also a potential therapeutic target to preserve youthful skin, as well as to forestall age-related disease. To guarantee optimal dose, delivery, as well as long-lasting safety, more translational studies.

Objective: *This review summarizes the biological role of NAD+ metabolism and evaluates the therapeutic potential of nicotinamide in maintaining skin health, delaying aging-related changes, and preventing dermatological disorders.*

Methods: *A narrative review approach was used. Relevant literature focusing on NAD+ metabolism, sirtuin signaling, nicotinamide biology, mitochondrial regulation, skin aging, and dermatological applications was evaluated.*

Keywords*: NAD+, DNA repair, Mitochondrial function, Microneedling, Anti-ageing dermatology.*

INTRODUCTION

World burden of skin disease:

For better comprehension of dermatological conditions of disease in low-resource countries, effective and sustainable global health programs need to consider the mitigation of the world's skin disease burden. Skin diseases are generally grave as the initial presentation of chronic systemic illnesses, such as HIV, and tropical diseases like elephantiasis and other conditions like lymphadenopathy. As one can observe, skin and subcutaneous diseases ranked as the 4th most important global causes of non-fatal burden of disease in 2010 and 2013, indicating the important role of dermatology in developing global health programs. [1]

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NAD+ EVOLUTION AND BIOCHEMISTRY:

Nicotinamide (NAM) is a derivative of vitamin B3 that's a crucial pillar for nicotinamide adenine dinucleotide (NAD^+) and NADPH. These molecules form the core of numerous life-preservation mechanisms—maintain cells in balance, produce ATP, support mitochondrial integrity, reduce oxidative damage, fix broken DNA, and even regulate ageing.NAM supplementation has been found to restore cellular energy, enhance DNA repair, and suppress inflammation by preventing pro-inflammatory cytokine release [6]. A blessing in disguise, NAM occurs naturally in a humongous array of everyday foodstuffs such as meat, liver, fish, yeast, pulses, nuts, cereals, leafy green veggies, coffee, and tea . But when the body cannot obtain access to sufficient amounts, deficiency leads to pellagra—an endemic disorder with the classical triad of dementia, diarrhoea, and dermatitis. [2]

Nicotinamide (NAM) is a term that refers to a family of vitamin B3 compounds, which are accompanied by other compounds like nicotinic acid (NA), Nicotinamide mononucleotide (NAM), and nicotinamide riboside (NR). The compounds' history goes back as early as 1937, when NAM and NA were found by Kohen and Elvehjem to be dietary factors that could be utilised as pellagra preventatives in dogs. All the vitamin B3 compounds are crucial in the synthesis of NAD+, a molecule of great importance in the process of energy metabolism and cellular function, and possess a different metabolic pathway.

NAD^+ Homeostasis

NAD^+ consists of three primary components: a pyridine ring, derived from tryptophan (Trp) or nicotinamide (NAM) precursors; a purine base (adenine, derived from ATP); and a phosphoribosyl group (PRPP). PRPP is synthesised from ribose-5-phosphate in the pentose phosphate pathway and is required for NAM- or NA-dependent processes. Adenine availability and purine metabolism regulation by purine nucleotide phosphorylase (PNP), recycling purine bases and metabolising precursor nicotinamide riboside (NR), also regulate NAD^+ biosynthesis.

Cells rely on several distinct NAD^+ biosynthetic pathways that differ by tissue and precursor in order to maintain homeostasis.

• **De novo (kynurenine pathway):** The tryptophan (Trp) is utilised in a series of reactions to synthesise quinolinic acid. Quinolinic acid is modified to form a new compound called as nicotinamide mononucleotide (NAM) through the enzymatic activity of the quinolinic phosphoribosyl transferase (QRPT). NAM is utilised in the NAD biosynthetic pathway, where it is converted to NAD+.

• **Preiss–Handler pathway:** This pathway involves nicotinic acid (NA), which will be converted to nicotinic acid mononucleotide (NAMN) through an enzymatic action of nicotinic acid phosphoribosyl transferase (NAPRT). NAMN is then converted into nicotinic acid adenine dinucleotide (NAAD) by NMNAT1, and NAAD is further converted to NAD^+ by NAD^+ synthase (NADS).

• **Salvage pathway:** It is the main biosynthetic route of NAD^+ in mammals. This pathway, nicotinamide (NAM) obtained following the NAD^+ consumption, is salvaged to nicotinamide mononucleotide (NMN) by the enzyme NAMPT, which is a rate-limiting step. NMN is converted to NAD^+ by NMNAT enzymes. Of these, NMNAT1 is widespread, NMNAT2 is found mostly in the brain, and NMNAT3 is found in the lung and spleen.

• **NRK-catalysed salvage:** Phosphorylation of nicotinamide riboside (NR) in this reaction is carried out by nicotinamide riboside kinases (NRK1/2) enzymes yield nicotinamide mononucleotide (NMN). NMN, in the process of its formation, enters the salvage pathway and is further metabolised to produce NAD^+.

Other NAD^+ precursors have since been found. NAD^+ can also be synthesised from reduced forms, such as dihydronicotinamide riboside (NRH) and dihydronicotinamide mononucleotide (NMNH). NRH is brought into the cell by equilibrating nucleoside transporters (ENTs), cycled to NMNH by adenosine kinase (AK), and then converted into reduced NADH, presumably by NMNAT. Nicotinic acid riboside (NAR), a deamidated NR derivative, is phosphorylated by NRK1 to NAMN or hydrolysed by uridine hydrolase (URH1) to NA. NAR, however, is a less efficient precursor since it requires further modification to be cell-permeable. [3]

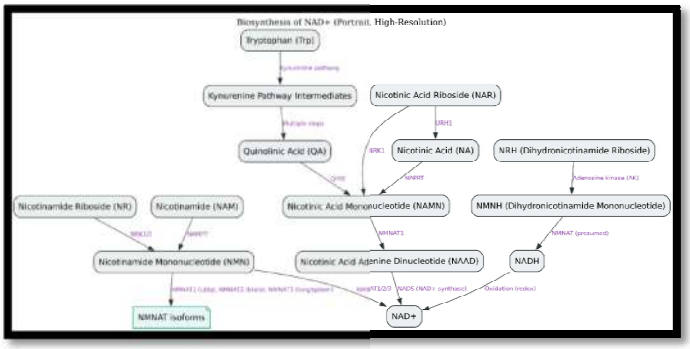

Fig 1: Schematic diagram of the different biochemical pathways of biosynthesis of NAD+. De novo biosynthesis of NAD+ from tryptophan (Trp) meets the Preiss–Handler pathway, which uses nicotinic acid (NA) for the transformation of the deamidated precursor.

HALLMARK OF SKIN AGING NAD+CONNECTION

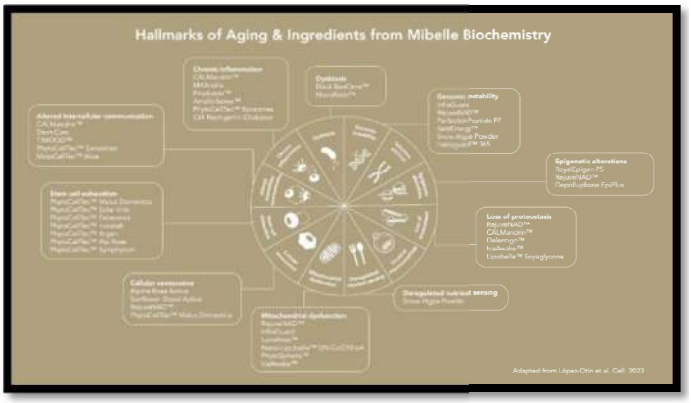

Fig 2: Hallmarks of aging and role of NAD+ in genomic stability, Epigenetic alteration, Mitochondrial dysfunction, cellular senescence, Stem cell exhaustion, Altered intracellular communication, Chronic inflammation

Hallmark of Aging	Role of NAD+
Genomic Instability	DNA damage originates both within the body, e.g., from regular body functions and errors during DNA copying, and from outside agents, e.g., the sun and chemicals. Damage can shatter DNA molecules, create missing bases, or join DNA fragments together. The body possesses repair processes, e.g., correction of single-base mistakes, elimination of damaged regions, and correction of mismatched fragments, which prevent the cell from dividing until the damage is eliminated. These repair processes consume energy and some proteins. When DNA repairs are unsuccessful, it results in alteration of DNA structure, reduced chromosomal ends, and increases risk of cancer. Damaged cells will lead to apoptosis or become non-dividing for life, a condition referred to as senescence. Senescent cells alter gene usage and send signals to assist the immune system in eliminating them, which can potentially prevent cancer.[4]
Epigenetic Alteration	Epigenetic changes are the most frequent reason for ageing skin, and they occur in two ways: **DNA Methylation:** With increasing age, some parts of the DNA will be converted into hypermethylated regions. This affects the control of the genes, leading to problems with cell function. **Histone Modification:** Histone modification means either the addition or removal of chemical compounds, keeping healthy skin stem cells regulated and guiding them to develop into other cells in the skin. When all of these changes become jumbled, such as when the Ash1l enzyme has problems, it disrupts the balance between creating new skin cells and transforming them into their ultimate shape. This causes excess skin cells to develop and slower maturation of mature skin cells. [5]
Mitochondrial Dysfunction	NAD+ is a class of molecule that helps the cells in order to performing vital functions, including generating ATP in the mitochondria. Robust and healthy mitochondria are vital for the survival of skin cells, the production of collagen, and protection against UV damage and other harmful chemicals. The level of NAD+ in the body declines, causing the mitochondria to work less efficiently and decreasing the production of energy [6].
Cellular Senescence	Cellular senescence is a leading cause of skin ageing and occurs due to stress factors such as DNA damage and the cell halting its cycle (with proteins such as p53 and p21). It is characterised by some signs that make it identifiable: **p16INK4a:** It is a marker that indicates how old cells are and is related to wrinkle formation and how old a person appears to be. SAβGAL: It is a general marker that can be used to identify senescent cells in tissue. Lamin B1: Loss of this protein level indicates cells have senesced, particularly following UVB light exposure. Newer Markers: They are RARD, a gene regulated by p53. Deletion of this gene exacerbates senescence. Another important fact regarding senescent cells is the Senescence-Associated Secretory Phenotype (SASP).

	SASP is a secreted mixture containing inflammation-inducing chemicals such as cytokines, chemokines, and growth factors (IL-6 and IL-8). SASP is typically induced by DNA damage and the NF-κB pathway. It may cause inflammation in surrounding cells, chronic inflammation, and issues with how those cells work. However, the relationship between senescence and SASP varies. It can vary depending on the cell type and what induced the senescence in the first place.
Stem Cell Exhaustion	The most significant stem cell population in the skin is the epidermal stem cells. When researchers explored keratinocyte stem cells in mouse hair follicles, they deduced that the stem cells bear a chronic DNA damage response, which results in a structural protein, collagen 17A1 (COL17A1), being broken down. The protein is necessary to maintain hair follicle stem cells (HFSCs) healthy and functional, and its breakdown is associated with aging of HFSCs. Recent research on epidermal stem cells and skin aging indicates that deficiencies in COL17A1 can result in a disorder referred to as junctional epidermolysis bullosa. It also makes the surrounding melanocytes and fibroblasts dwindle in number and function, thereby lowering the regenerating ability of epidermal stem cells, leading to skin thinning and aging. Abnormal epidermal stem cell behavior is usually a result of alterations in telomerase activity and shorter telomeres, defective DNA repair, and elevated oxidative stress. With further insight into the molecular mechanisms, the Jak-Sat signaling pathway is implicated and assists in forming a feedback loop in aging Krt-15-GFP-positive stem cells, which are one of the most well-characterized subpopulations of skin stem cells. This occurs when an environment with increased levels of inflammatory proteins such as BLC/CXCL13, GM-CSF, ICAM-1/CD54, and IL-1α is present, establishing that age-related inflammation can impair epidermal stem cell function. Also, the autophagic response of the body, which assists in the elimination of damaged cell parts, is implicated when epidermal stem cells have DNA mutations, and with decreased mitochondrial activity, increased reactive oxygen species (ROS), and increased cell death. Above all, since stem cells are so vital for healthy skin, there is increasing interest in employing the different types of stem cells to assist in repairing and enhancing the skin, particularly in the war against aging.[5]

NAD+ DEPENDENT ENZYME AND SIGNALING PATHWAY IN SKIN

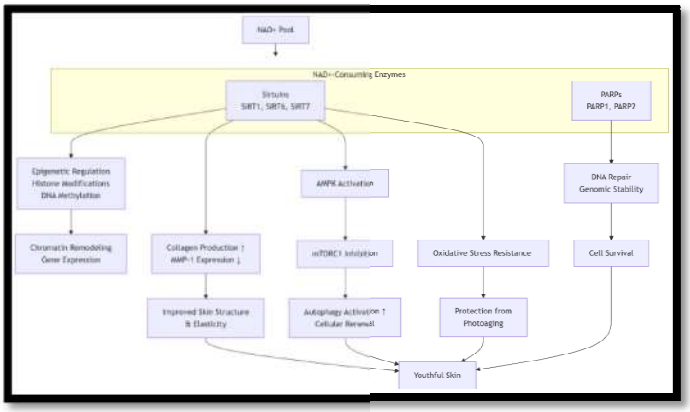

Fig 3: Demonstrates the NAD+ dependent enzyme and metabolic signalling pathways in Skin

NAD⁺ as a hub in cutaneous ageing

NAD⁺ is a ubiquitous coenzyme that also acts as a key substrate for signal enzymes that regulate genome maintenance, epigenetic status, and stress reactions in the skin.[7] . Multiple lines of evidence suggest that tissue NAD⁺ concentrations decrease during ageing and may decrease activity of downstream NAD⁺-depleting enzymes such as sirtuins and PARPs. [8] . Human skin demonstrates a critical age-dependent reduction in NAD⁺ concentrations, with quantitative projections predicting spectacular reductions from infancy to adulthood and subsequent reductions through middle life. [9]

Sirtuins (SIRT1, SIRT6, SIRT7): epigenetic regulation, matrix equilibrium, stress resilience

Sirtuins are NAD+-dependent deacetylases/deacylases derivatives that remodel will chromatin and process of controlling transcriptional programs necessary for repair, metabolism, and survival. [7] In dermis, SIRT1 is always involved in the intrinsic (chronological) and extrinsic (photo-) ageing process, wherein it regulates functions responsible for differentiation, oxidative stress, and tumorigenic risk. Sirtuins

(SIRT1, SIRT6, SIRT7): epigenetic regulation, matrix homeostasis, stress resistance. Sirtuins are NAD+-dependent deacetylases/deacylases that reorganise chromatin and modulate transcriptional programs necessary for repair, metabolism, and survival. [10]

SIRT1 signalling in dermal fibroblasts is combating loss of collagen by inhibiting matrix metalloproteinases like MMP-1 and facilitating de novo biosynthesis of collagen and thus maintaining dermal architecture and elasticity. [11]

Mechanistically, SIRT1 acts on AMPK to repress mTORC1, a switch directed towards autophagy instead of anabolic growth and maintenance of proteostasis in stressed skin cells. [12]

Through such axes, sirtuins cause resistance of fibroblasts and keratinocytes to UV-induced photoaging phenotypes and oxidative stress. [11]. At the tissue level, diminished expression/activity of sirtuins in aging dermal fibroblasts correlates with sirtuin loss with fibroblast aging and wound repair defect. [13]

AMPK–mTORC1–autophagy: Reactivating cutaneous cells

AMPK is a master energy sensor; upon activation, it inhibits mTORC1 and triggers autophagy by ULK1 and other nodes, a network that slows cellular senescence.[14] In skin models, AMPK-activated autophagy protects against anti-aging phenotypes and UVB damage in fibroblasts, placing autophagy as a potential therapeutic target in photoaging. [15],[16]. Often, crosstalk between autophagy and MAPK signalling in fibroblasts, keratinocytes, and melanocytes estimates the aging pathways and describes the combined-pathway interventions. [17]

PARPs (PARP1, PARP2): DNA repair, inflammation, and survival

PARP1/2 are in the proximity to DNA strand breaks and use NAD^+ to generate a compound called poly(ADP-ribose) polymers that recruit repair proteins, thereby maintaining genomic integrity after environmental stress like UV exposure. [18]. PARP1 will interact with DNA damage signalling (e.g., ATM) and controls mitochondrial responses in UVB-irradiated keratinocytes, positioning it at the interface of genome maintenance and metabolism. [19] .PARP1 activity also intersects with cutaneous inflammatory processes following UVB exposure, and mechanisms to approach them experimentally modify the extent of UVB-induced skin inflammation. [20] NAD^+ availability via NAMPT may potentially lead to hyperactivation of PARP1 in inflammatory skin conditions, and pharmacologic regulation of the pathway differentially controls DNA damage and cell death with context-dependent activities. [21]

Applying the network in the figure

NAD^+ reduction with ageing suppresses sirtuin and PARP functions, prioritised on epigenetic drift, DNA repair deficiency, matrix degradation, and compromised stress tolerance, culminating in compromised elasticity and photoaging[22], AMPK activation via sirtuin-mediated and concomitant mTORC1 inhibition increases autophagy, promoting turnover of injured proteins/organelles and initiating cellular rejuvenation that maintains youthful skin architecture. [12] Through their inhibition of MMP-catalysed degradation and stimulation of collagen synthesis, sirtuins directly result in enhanced dermal ECM strength and biomechanical properties. [11], [23]. PARP-mediated repair ensures genome stability and survival from oxidative and UV stress, but depletes NAD^+ on overactivation and requires tight regulation with metabolic state. [18],[19]

PRECLINICAL STUDIES ON NAD + :

The earliest finding of overexpressing NAD+ biosynthesis through genetics was found to extend the stress response and lifespan of yeast cells and Drosophila in turn led to the study of NAD+ enhancers in rodents, either healthy or disease models, frequently with associated dramatic results.

Table: 1 Preclinical Studies On NAD +:

Tissue	NAD+ Boosters	Primary Pathways Activated	Physiological Outcomes
Brain	PARP inhibitors	Sirtuins SIRT1 and SIRT3, Mitochondrial NAD+	Cognition, neuroprotection
Eye	—	Retinal energy homeostasis Sensory	Sensory and retinal function
Liver	Niacin / NA	Sirtuins, Urea cycle, NAD+ salvage	Glucose homeostasis
Adipose	—	SIRT1, PGC1a	Browning balance, lipogenesis
Pancreas	—	Beta cell NAD+, SIRT1	Insulin secretion
Muscle	—	Mitochondrial biogenesis, SIRT3	Insulin sensitivity, endurance
Vasculature	NR / NMN	Endothelial NO, SIRT1	Endothelial health, lower cardiovascular risk
Immune	CD38	CD38, PARPs	Lower inflammation,

	inhibitors		immune modulation
Kidney	—	Tubular NAD+, SIRT3	Protection from acute injury
Gonads	—	Sirtuin signaling	Fertility support

Human Trials :

NAD+ boosters have been successful in a range of mouse models of human disease, and therefore, most clinical trials of NAD+ boosters in humans have been performed. The most extensively tested of the NAD+ precursors in humans is NA (niacin). At high doses, more than a gram, NA is an effective treatment for hypercholesterolemia because it lowers LDL and is one of only a few drugs that increase HDL significantly. It is available over the counter either as compressed NA (Niacor) or extended-release to avoid the flushing due to the release of prostaglandins. Niaspan was originally approved for several indications by the FDA in 1997 and subsequently used in combination with statins for the treatment of primary hyperlipidemia and mixed dyslipidemia. NA and NAM have been or are being investigated for many other health effects on health, such as therapy for acne, kidney disease, lupus, AD, schizophrenia, diabetes mellitus, non-small-cell lung carcinoma, obesity, HIV-induced dyslipidemia, NAFLD, sickle cell disease, and others. While NA has been shown to increase NAD+ levels in rodents, the idea that NA increases cholesterol profiles in humans, at least in part because of the increase in the level of NAD+, is not typically an issue in the literature.

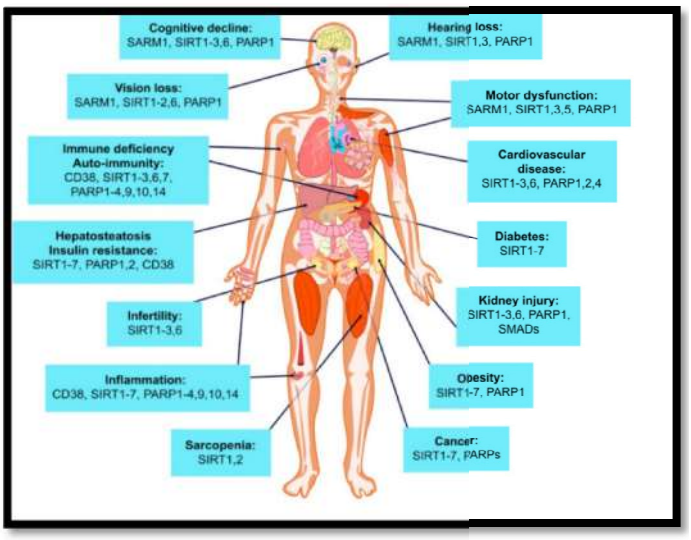

Fig 4 :. Potential Impact of NAD+ Boosters on Human Health via NAD+ Signalling Pathways decline in NAD+ during ageing is believed to be a major cause of disease and disability, such as hearing and vision loss, as well as cognitive and motor dysfunction, immune deficiencies, autoimmunity, and dysregulation of the inflammatory response leading to arthritis, metabolic dysfunction, and cardiovascular disease. In mouse models, NAD+ boosters prevent or treat a variety of different diseases, prompting a search for NAD+ boosters that are safe and effective as drugs to treat both rare and common diseases and, potentially, aging itself.

Pharmacological Modulation of NAD Pathways: Mechanisms and Health Outcomes

The NAD has a huge impact on cellular metabolism, mitochondrial functions, DNA repair, and homeostasis. Pharmacological modulation of NAD pathways has a major effect on therapeutic benefits in various physiological functions, like metabolic, cardiovascular, neurodegenerative, oncological, and psychiatric disorders. These NAD precursors, such as niacin (NA), nicotinamide riboside (NR), and nicotinamide (NAM), have been found to improve lipid profiles, improve kidney recovery, decrease cardiovascular risks, and restore neuronal function. In such pathways, CD38 inhibitors. PARP inhibitors and other pharmacological classes, such as SARM inhibitors and NAMPT activators, have been investigated for future use in NAD modulation, though evidence is limited. The following table elaborates on the existing evidence on mechanisms of action, pharmacological agents, and noted health outcomes in such therapeutic classes.

Table 2: Classes of NAD+-Boosting Molecules and Known Effects in Humans

Mechanism of Action	Pharmacological Agent	Health Outcomes Observed
NAD+ precursors	Niacin (NA)	↓ TC and LDL in dyslipidemia
		↓ Serum phosphate after kidney injury
		↑ GFR after kidney injury
		↓ Risk of myocardial infarct
		↓ Risk of stroke
		↓ Risk of CVD mortality
		↑ Recovery from schizophrenia
		↓ Rate of cognitive decline in AD
		↓ Rate of metastases/relapse in breast cancer

		↑ HDL-C in sickle cell disease
	NR	↑ NAD+ in blood (dose-dependent)
		No adverse effects
	NAM	↑ NAD+ levels in blood and evidence of improved mitochondrial function in MELAS
	NaR	
	NaMN	
	NAAD	
	NMN	
	IHN	
CD38 inhibitors	Quercetin	↓ LDL in CVD
		↓ Blood pressure
		↓ BMI
		↓ Waist circumference
		↓ Triglycerides
	Luteolin	↓ Serum levels of IL-6 and TNF
		↑ Adaptive functioning in autism
	Apigenin	
	78c	
	Luteolinidin	
	Kuromanin	
PARP inhibitors	BGB-290, olaparib, rucaparib, veliparib, CEP-9722, E7016, talazoparib, iniparib	↓ Tumor size, metastases, and relapse in breast and ovarian cancer
	PJ34	
	DPQ	
	3-aminobenzamide	

NAD+ AUGMENTATION STRATEGIES FOR SKIN HEALTH

NUTRITIONAL SUPPLEMENTATION OF NAD+ AND NADH:

It has been shown that nicotinamide adenine dinucleotide (NADH), the coenzyme form of active vitamin B3, effectively reverses the harmful effects of jet lag on mental performance and sleep-wakefulness. 51 In addition, it is also shown to increase energy production by enhancing the formation of ATP. A small clinical trial of NADH showed a favourable response and improved quality of life in patients with CFS. This particular trial used the stabilised oral absorbable form in a randomised, double-blind, placebo-controlled crossover trial involving 26 subjects. The patients were randomly divided and given either 10 mg of NADH or a placebo for 1 month. After a 1-month washout period without supplementation, the patients were then crossed over to the other treatment regimen for an additional 1-month duration. In this group of 26 patients, 8 of 26 (31%) responded to NADH, while 2 of 26 (8%) responded to the placebo. No severe adverse reactions were noted in relation to NADH, 52 nor have animal studies shown any toxic properties, even when given in very high doses. 53 An additional clinical study must be conducted to establish fully the potential beneficial effects of NADH in the diagnosis of CFS patients.[25]

MICRONEEDLES IN NAD+

Microneedles: A Smart Approach to NAD+

MNs are getting to be a keen approach with time from the ordinary transdermal approach. These are preferred over hypodermal needles due to the ease of MNs. It is additionally beneficial since they can pass stratum corneum with minimal pain. MNs, moreover, show higher bioavailability compared to that of transdermal/topical preparations.MN patches can be self-administered with persistent compliance and safety. The faster drug of activity is additionally accomplished with MNs due to coordinated discharge for retention within the systemic circulation. Moreover, stimuli-responsive MNs offer a shrewd approach for the on-demand discharge of drugs. Yu et al. Created MNs stacked with affront as hypoxia-sensitive vesicles that dismantled within the nearness of neighborhood hypoxia, actuated by high glucose levels. [26]

Drug delivery mechanism of Microneedling in NAD+:

NAD^+ is a substantial, water-attracting compound that struggles to penetrate the skin barrier. The absorption through the mouth is also restricted because of its instability and the way it is broken down.

1. MNs present a hopeful option because:

2. They avoid the digestive system and initial metabolic processing

3. They can send NAD^+ straight to the dermis, allowing it to spread into the bloodstream.

4. The type of MN can determine the control of the release:

5. Dissolving MNs → Fast release of NAD^+.

6. Diffusion-based MNs → Ongoing release.

Microneedle Innovation for NAD:

Planned as a negligibly obtrusive elective to pills or infusions. Employment of minor microneedles (hundreds of microns long) that easily enter the skin.

How the Microneedle Procedure Works for NAD

1. Drug Loading

NMN (nicotinamide mononucleotide) is consolidated into microneedles either by Coating: NMN is coated on the surface of strong microneedles. Dissolving/Fabricated: NMN blended into biodegradable polymers (PVA, PVP, CMC) and moulded into dissolving microneedles.

2. Application to Skin: The microneedle fix is squeezed onto the skin. Microneedles effortlessly enter the external layer, making micro-channels.

3. Drug Release (Medication Discharge) Coated microneedles: NMN breaks down off the surface into the skin.

Dissolving microneedles: The complete needle breaks down, discharging NMN slowly.

4. Absorption: NMN diffuses into more profound skin layers and enters nearby tissue and circulation. This bypasses the stomach-related framework and liver digestion system, which ordinarily diminishes oral NMN retention.

Prove from Inquire Research

3D-printed microneedles coated with NMN appeared to cause dose-dependent increments in the NAD-related digestion system in skin cells (measured with multiphoton microscopy).

Dissolving microneedles (PVA + CMC) discharged up to ~92% of NMN inside 18 hours, with effective ex vivo skin entrance.

Saturation ponders appeared ~189 ¼g of NMN might cross skin, whereas a few remained put away in more profound layers for supported impact. [26,27].

What are Nanoliposomes?

Nanoliposomes are tiny vesicles made of phospholipid layers, similar to small cell membranes. They can hold water-soluble molecules and Fat-soluble molecules. They shield fragile medications from being broken down by enzymes and enhance their absorption.

Why Use Nanoliposomes for NAD^+?

Issue with NAD^+: It is large, water-loving, and easily breaks down in the bloodstream. It has low oral bioavailability, as it quickly degrades in the digestive system and liver. Nanoliposomes as a remedy. Encapsulation keeps NAD^+ safe from degradation. It helps cells take it up through membrane fusion or endocytosis. They can be designed for targeted delivery. They offer potential for slow release

● Enclosing NAD^+ within nanoliposomes solves its drawbacks:

● Safeguarding: Guards NAD^+ against a swift breakdown in the gut and blood

● **Better intake:** Liposomal layers merge with gut or cell membranes, aiding absorption. Enhanced availability: Improves the transport of whole NAD^+ or its building blocks directly into cells

● **Focused delivery:** Nanoliposomes can be designed to target NAD^+ to particular organs (for example, brain, muscle, or mitochondria).

● **Controlled release:** Permits steady distribution, preventing fluctuations in NAD^+ levels.

● Strategies for Delivering Nanoliposome-NAD^+

● Intravenous (IV) nanoliposomes → Provides immediate systemic delivery, avoiding gastrointestinal metabolism.

● Oral nanoliposomes → Some research indicates better stability and absorption of water-soluble biomolecules.

● Transdermal (using MNs and nanoliposomes) → MNs penetrate the skin, allowing nanoliposomes to release NAD^+ into the dermis for systemic absorption.

● Targeted nanoliposomes → Their surface is modified with specific ligands (like peptides) to guide NAD^+ towards particular tissues (such as neurons or muscle).[28]

Delivery Method

● **Encapsulation:** NAD^+ particles are contained within the watery centre of liposomes

● **Transport:** After being taken orally or through injection, nanoliposomes move through the blood

● **Fusion/Endocytosis:** Liposomes connect with cell membranes, either fusing or undergoing endocytosis.

● **Release:** NAD^+ is freed into the cytoplasm for use in metabolic processes. [29]

Uses

1. Research on ageing and longevity – Keeping NAD^+ levels stable aids in reducing age-related deterioration.

2. Protection of nerves – Aids in the healing of nerve cells and enhances mitochondrial operations

3. Health of metabolism – Boosts insulin sensitivity, enhances energy metabolism, and improves muscle performance.

4. Medical treatments – Possible applications for diseases such as Alzheimer's, Parkinson's, heart disease, and chronic fatigue syndrome.

5. IV or dietary supplements – Liposomal NAD^+ products are currently sold as health supplements. [30]

TRANSLATION DERMATOLOGY APLLICATION COSMETICAL:

ANTIAGING FORMULATION WITH NAM AND NR:

Nicotinamide adenine dinucleotide (NAD+) is an essential cofactor of all living systems, which is involved in fundamental biological processes, i.e., metabolism, cell signalling, gene expression, DNA repair, etc.. In the following years, NAD+ was identified as a nucleoside sugar phosphate, which is associated with redox processes. Nevertheless, discoveries of recent studies proved multiple roles of NAD+ metabolism in ageing and longevity. Especially, age-related decrease in levels of NAD+ has been documented in numerous studies, which may be attributed to the imbalance in NAD+ production and utilisation. Decreased levels of NAD+ are correlated with the characteristics of ageing and age-associated diseases, i.e., metabolic disorders, cancer, and neurodegenerative disorders. NAD+ is again utilised by the NAD+-dependent sirtuins and the DNA damage sensors poly (ADP-ribose) polymerases (PARPs) in protein deacetylation and poly-ADP-ribosylation (PARylation) reactions, respectively. In addition, NAD+ glycohydrolases (CD38 and CD157) also utilise NAD+ by donating NAD+ to ADP-ribose (ADPR) or cyclic-ADPR. Thus, the role of NAD+ widened from a central molecule in intermediary metabolism to a central regulator of various cell signalling processes, and now a key factor for ageing and age-related diseases.

NR AND AGING:

NR is a natural precursor of NAD+. It can be directly converted to NMN by the action of NRKs, and thus bypasses the requirement of NAMPT in the salvage pathway, and offers an alternative method of increasing the levels of NAD+. Similar to NMN, NR also exhibited positive effects in anti-ageing and age-related disease protection. It was found to enhance longevity as well as health span in several laboratory models of animals.

NAM AND AGING:

NAM is also a precursor to NAD+ and a key molecule of energy metabolism. Reduced levels of NAM have also been reported to increase lifespan in yeast and C. elegans, but elevated levels have been associated with reduced lifespan via inhibition of Sir2 activity. In high-fat-diet-induced ageing and obesity models, NAM increased health span but could not increase lifespan, as indicated by equivalent mean and maximum lifespan. In the obesity model, it has been capable of restoring glucagon storage to age-matched levels of control-diet mice and also of increasing diet-induced hepatosteatosis, oxidative stress, and inflammation. [31]

PHOTOAGING AND HYPERPIGMENTATION:

NAD+ is a naturally occurring substance found in living organisms, and the side effects of NAD+ are hardly known. NAD+ controls numerous biological processes such as glycolysis, the respiratory chain, DNA repair, and antioxidant defence. Various precursors participate in the synthesis of NAD+, such as nicotinamide mononucleotide (NMN), nicotinic acid (NA), nicotinamide, tryptophan, and NR. The use of NAD+ induction to stimulate pigmentation disorders is underway, with nicotinamide being a precursor well known for its skin-whitening activity. In the present analysis, we have investigated the skin-whitening activity of other NAD+ precursors.

Nicotinamide and niacin, among other NAD+ precursors, are vital components of biological systems and are universally present in natural foods like eggs, vegetables, fruits, and fish. They are stated to be effective in whitening the skin and maintaining cellular homeostasis.

In conclusion, NR is a potent therapeutic drug that inhibits melanin formation at certain concentrations and exerts protective functions on skin through restoration of viability for keratinocytes and inhibition of expression of matrix metalloproteinases. Therefore, NR is a potent skin-whitening medication and of very significant significance as a safe therapeutic medication for severe diseases caused by photo-stimulation. [32]

WOUND HEALING AND TISSUE REGENERATION:

Wound healing is rapid re-epithelialization with an aesthetically pleasing appearance. Progresses in cellular and molecular biology over recent years have improved our awareness of the mechanism of wound healing and tissue regeneration, with notable enhancement of the management of wounds. Nicotinamide (NA) or niacinamide or nicotinic acid amide is an aqueous-soluble biologically active derivative of vitamin B3. It has been increasingly investigated for varied uses, particularly in dermatology. NA was found to have anti-inflammatory, antioxidative effects and regulatory activity on the expression of immunomodulatory proteins. It was shown in a study by Myczkowski that the use of NA infusion, with removal of split

skin, reduced the wound healing time from 15 - 17 to 7 - 10 days. [33]

FUTURE PERSPECTIVE:

ADVANCED DELIVERY SYSTEM IN HYDROGEL PATCHES

Hydrogels, in their three-dimensional network of hydrophilic polymers, have emerged as a foundation in the establishment of biomaterial science, revolutionising applications across a broad spectrum of biomedical fields. These networks, with the ability to absorb and hold large quantities of water, are noted by their high swelling capacity without dissolution, and structural strength by chemical or physical cross-linking reactions .

Classification of Hydrogels:

Hydrogels are classified based on various criteria like origin, cross-linking techniques, composition, degradability, stimulus response, and ionic charge. For this purpose, we categorise them into physical and chemical hydrogels according to cross-linking formation mechanisms. [34]

COMBINATION THERAPIES NAD+ BOOTERS WITH STEM CELL THERAPY:

Positive Impact of NAD+ boosting:

Elevated levels of NAD+ reverse mitochondrial disease and restore mitochondrial function and the age-related disease observed in various mouse models of human disease. Scientific reports suggest that elevated levels of NAD+ impact a variety of disparate conditions and diseases, including metabolic syndrome, type 2 diabetes, and/or insulin sensitivity, cancer, cardiovascular disease, neurodegeneration, renal function, and Alzheimer's disease.

NAMPT and/or NAD decrease the pool and suppress the proliferation of neural progenitor stem cells.80 In several lineages, NAD and NAMPT can be required not only for proliferation but also for cell fate choice. NAMPT is required by neural stem progenitor cells for cell cycle progression. Nevertheless, during oligodendrocyte lineage, downregulation of NAMPT decreased oligodendrogenesis.

NAMPT inhibition significantly reduces OCT4 and other pluripotency factors, including Sox2, Klf4, or NaGOG, and EMT factors, including Twist, Snai1, Slug, or FoxC2.7,82. Downregulation of NAMPT also enhances the expression of pluripotent differentiating factors. It has been demonstrated that, in human stem cells, a 50% decrease in NAD+ concentration leads to spontaneous differentiation and apoptosis.IPs contain elevated levels of NAD synthesis salvage pathway enzymes and rely on them for survival. Additionally, nicotinamide, the NAD precursor, enhances the survival of hSCs.83 Supraphysiological levels of NA augment the degree of IP reprogramming. In mouse models in vivo, an increase in intracellular NAD+ levels by NA riboside treatment regenerated intestinal, neural, and muscle stem cells and prolonged lifespan.84,85 Dietary supplementation with NAD precursors also enhances mitochondrial activity. Thus, boosting NAD levels in the cell promotes stemness and pluripotency, both of which appear to require effective mitochondrial function. Thus, NAD+ increase resulted in enhanced stem cell proliferation and pluripotency, as indicated by SC marker expression.

This indicates that NAD itself cannot induce a complete stem transcriptional network94 but can induce an intermediate SC state that may be favourably influenced by other reprogramming signals. These NAD-primed SCs metabolise the majority of glucose to lactate, allowing the recycling of NAD from the cytosol and ensuring its usage in other cellular pathways of synthesis. NAD+ also promotes mitochondrial inhibition of oxygen and ATP production. Naive embryonic stem cells, like the NAD-primed ones, also use glutamine as a critical nutrient and generate a-ketoglutarate for H3K27me3 demethylation, thus maintaining the embryonic stem cell hypomethylated state.[34]

CONCLUSION:

Two decades of investigation have entrenched the position of NAD^+ as the central regulator of cellular metabolism, DNA repair, and stress responses, all with integral relevance to skin ageing and regeneration. Low NAD^+ levels are inevitably observed with advancing age and are causal contributors to mitochondrial dysfunction, genomic instability, and impaired tissue repair. NAD^+ replenishment with precursors such as nicotinamide, NR, and NMN has encouraging data in experimental models, with improved restoration of oxidative balance, restoration of epidermal barrier function, and improved healing of wounds. Small clinical studies also document the therapeutic promise of these therapies, though details specific to dermatologic endpoints remain lacking. From the dermatologic perspective, the NAD^+ enhancement capability provides promise not only in the retardation of obvious signs of ageing but also in maintaining skin resilience to ultraviolet damage, inflammation, and environmental stress. Progress in the field of delivery systems, transdermally in the form of microneedles, in the form of nanoliposomes, as well as hydrogel formulations, may address the issues of bioavailability that are relevant to systemic supplementation and impart targeted benefit to skin tissue. Notably, important gaps still exist. Preliminary clinical proof still lingers, while prolonged safety, the best dose, and comparative efficacy among all NAD^+ precursors remain unknown. For the future, biochemical understanding accompanied by judiciously controlled human studies will become important. Overall, NAD^+ modulation is an encouraging therapeutic strategy in dermatology that can potentially link basic ageing biology to clinically relevant interventions for skin health.

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