*Review*

# Nicotinamide: A Multifaceted Molecule in Skin Health and Beyond

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**Abstract:** Nicotinamide (NAM), the amide form of vitamin B3, is a precursor to essential cofactors nicotinamide adenine dinucleotide (NAD$^+$) and NADPH. NAD$^+$ is integral to numerous cellular processes, including metabolism regulation, ATP production, mitochondrial respiration, reactive oxygen species (ROS) management, DNA repair, cellular senescence, and aging. NAM supplementation has demonstrated efficacy in restoring cellular energy, repairing DNA damage, and inhibiting inflammation by suppressing pro-inflammatory cytokines release. Due to its natural presence in a variety of foods and its excellent safety profile—even at high doses of up to 3 g/day—NAM is extensively used in the chemoprevention of non-melanoma skin cancers and the treatment of dermatological conditions such as blistering diseases, atopic dermatitis, rosacea, and acne vulgaris. Recently, its anti-aging properties have elevated NAM's prominence in skincare formulations. Beyond DNA repair and energy replenishment, NAM significantly impacts oxidative stress reduction, cell cycle regulation, and apoptosis modulation. Despite these multifaceted benefits, the comprehensive molecular mechanisms underlying NAM's actions remain not fully elucidated. This review consolidates recent research to shed light on these mechanisms, emphasizing the critical role of NAM in cellular health and its therapeutic potential. By enhancing our understanding, this work underscores the importance of continued exploration into NAM's applications, aiming to inform future clinical practices and skincare innovations.

**Keywords:** nicotinamide; chemoprevention; skin health; cellular oxidative stress; DNA damage; photoaging; ultraviolet radiation; inflammation; vitamin B3

## 1. Introduction

Nicotinamide (NAM)—also known as niacinamide—is the amid form of vitamin B3 and is a critical precursor for nicotinamide adenine dinucleotide (NAD$^+$) and NADPH. By participating in key oxidation–reduction reactions, NAD$^+$ supports cellular homeostasis, metabolism, ATP production, mitochondrial respiration, ROS management, DNA repair, and processes related to aging [1–5]. Studies show that NAM supplementation restores cellular energy, contributes to DNA damage repair, and suppresses inflammation by inhibiting the release of pro-inflammatory cytokines [6]. NAM is naturally present in a variety of foods, including meat, liver, fish, yeast, legumes, nuts, grain products, green leafy vegetables, cereals, coffee, and tea [7,8], making it an essential component of the daily diet. A deficiency of NAM is the primary cause of pellagra, an endemic disease characterized by the triad of dementia, diarrhea, and dermatitis [9].

Unlike other vitamin B3 derivatives (e.g., nicotinic acid, nicotinamide riboside, and nicotinamide mononucleotide), NAM generally shows excellent tolerability—even at doses

up to 3 g/day—with fewer adverse effects [10–12]. Unlike its derivates, such as nicotinic acid, nicotinamide riboside, and nicotinamide mononucleotide, which may cause side effects like flushing, itching, hypotension, and headaches, NAM is generally safe and well-tolerated, even at high doses (up 3 mg/die), with rare adverse effects observed over prolonged treatments [10–12].

Recent research underscores the pivotal role of the skin as the body's primary interface with external stressors, classifying it as a "stress organ" endowed with complex neuroendocrine capabilities. More than a passive barrier, the skin contains an elaborate network of local endocrine components—including a cutaneous hypothalamic-pituitary-adrenal (HPA)-like axis—enabling it to produce, metabolize, and respond to hormones and neuromediators. These systems collectively protect against various insults, such as pathogens, toxins, and ultraviolet radiation, by modulating inflammatory responses, immune surveillance, and barrier function. For instance, Slominski and colleagues [13] describe how the skin synthesizes and responds to corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, and other peptides, illustrating the complex local regulatory loops that can operate independently of systemic endocrine pathways. More recent findings [14] further highlight the skin's sophisticated neuroendocrine network and its ability to orchestrate local immune responses, cell proliferation, and differentiation under stressful conditions. These observations support the concept that the skin is not merely a passive barrier but a dynamic organ adept at sensing and responding to environmental and physiological stressors through interconnected neuroendocrine and immune mechanisms. Owing to its beneficial properties, NAM has found extensive use as a chemopreventive agent for non-melanoma skin cancer (NMSC) and as a treatment for various skin conditions, including blistering diseases, acne vulgaris, and other skin disorders [7]. More recently, NAM has gained popularity as an active ingredient in daily skincare formulations, particularly for its anti-aging effects [15]. Against this background, NAM's benefits extend beyond DNA repair and energy replenishment to include oxidative stress mitigation, regulation of the cell cycle, and modulation of apoptosis. This review summarizes the molecular mechanism underlying the effects of NAM, focusing on the latest research findings.

## 2. Nicotinamide

### 2.1. General Information and Metabolism

NAM is part of the vitamin B3 family, which includes nicotinic acid (NA), nicotinamide mononucleotide (NMN), and nicotinamide riboside (NR) [16]. NAM and NA were first identified in 1937 by Kohen and Elvehjem as the dietary factor able to prevent pellagra symptoms in dogs [17], while NR was discovered in 2004 by Bieganowski and Brenner [18]. All vitamin B3 components are key contributors to $NAD^+$ synthesis through distinct metabolic pathways, as illustrated in Figure 1.

The Preiss–Handler pathway converts NA into $NAD^+$ via three enzymatic steps: (1) NA is converted to nicotinic acid mononucleotide (NAMN) by nicotinic acid phosphoribosyltransferase (NAPT), (2) NAMN is converted to nicotinic acid adenine dinucleotide (NAAD) by nicotinamide mononucleotide adenylyltransferase (NMNAT), (3) NAAD is converted to $NAD^+$ by $NAD^+$ synthetase (NADS) [16,19]. The salvage pathway rapidly restores NAD levels by recycling NAM molecules released during enzymatic processes such as SIRT-mediated deacetylation, PARP-mediated ADP-ribosylation, and CD38 activities [20–22]. In this pathway, NAM is converted into nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyl transferase (NAMPT), the rate-limiting enzyme that uses 5′-phosphoribosyl-1-pyrophosphate (PRPP) as a substrate. NAMPT expression is often dysregulated in conditions like obesity, cancers, and metabolic disorders. Its activity is also

modulated by circadian rhythms, leading to oscillations in cellular NAD levels [16,23–25]. NMN is then converted into $NAD^+$ by NMNAT. Finally, NR indirectly supports the salvage pathway through its conversion into NMN by nicotinamide riboside kinase (NRK) or into NAM via uridine hydrolase (Urh1), purine nucleoside phosphorylase (Pnp1), and methylthioadenosine phosphorylase (Meu1) [26,27]. A small proportion of $NAD^+$ is synthesized via the de novo pathway which converts tryptophan to NAMN through multiple steps. However, this way is insufficient to maintain and restore $NAD^+$ levels (60 mg of tryptophan produces 1 mg of $NAD^+$) [16,28].
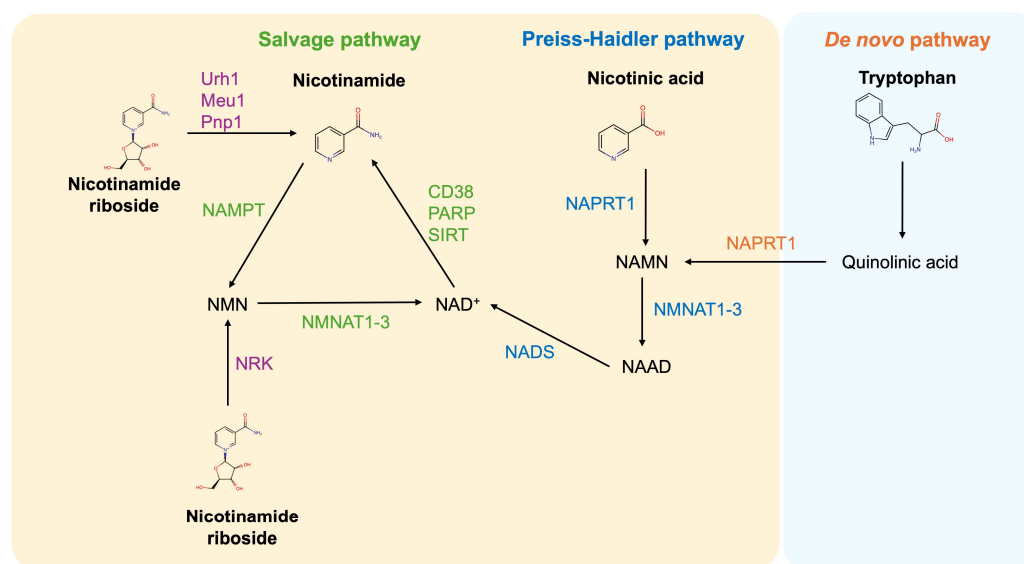


**Figure 1.** Pathways for $NAD^+$ synthesis in mammalian cells. In mammalian cells, $NAD^+$ can be synthesized from NA through the Preiss–Haidler pathway or de novo from tryptophan. However, most $NAD^+$ is recycled via the salvage pathway from NAM. NAD, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; NAMN, nicotinic acid mononucleotide; NAAD, nicotinic acid adenine dinucleotide; NADS, NAD synthetase; NMNAT, nicotinamide mononucleotide adenylyl transferase; NAMPT, nicotinamide phosphoribosyl transferase; NAPRT, nicotinic acid phosphoribosiltransferase; Urh1, uridine hydrolase; Meu1, methylthioadenosine phosphorylase; Pnp1, purine nucleoside phosphorylase; NRK, nicotinamide riboside kinase.

Beyond its conversion to $NAD^+$ through the de novo pathway, tryptophan can also be metabolized in the skin into serotonin and melatonin [29]. The latter, in particular, has garnered attention for its local photoprotective properties, including scavenging of reactive oxygen species and regulation of apoptosis under UV stress [30]. Such processes are highly relevant to skin pathology and photocarcinogenesis, suggesting that localized serotonin–melatonin pathways in the skin could offer both diagnostic and therapeutic insights. Future comparative analyses that integrate these metabolic routes may help clarify the complex interplay between oxidative stress, immune responses, and carcinogenesis in cutaneous tissues.

The primary circulating form of vitamin B3 is NAM. NA, predominantly found in plant-based foods, is converted into $NAD^+$ in the intestine and liver. $NAD^+$ is subsequently cleaved to release NAM into the bloodstream for uptake by extrahepatic tissues [31,32]. Dietary NAM, which is abundant in animal-based foods, is absorbed by the small intestine and transported into endothelial cells through passive diffusion—either simple or facilitated—depending on intracellular NAM concentrations (Figure 2) [33,34]. Excessive NAM is metabolized in hepatocytes by cytochrome P450 into nicotinamide-N-oxide (N-Ox) and N-methyl-nicotinamide (MNA), which is, in turn, converted into N1-methyl-2-pyridone-5-carboxamide (2-pyr) and N1- methyl-4-pyridone-3-carboxamide (4-pyr) [32,35].
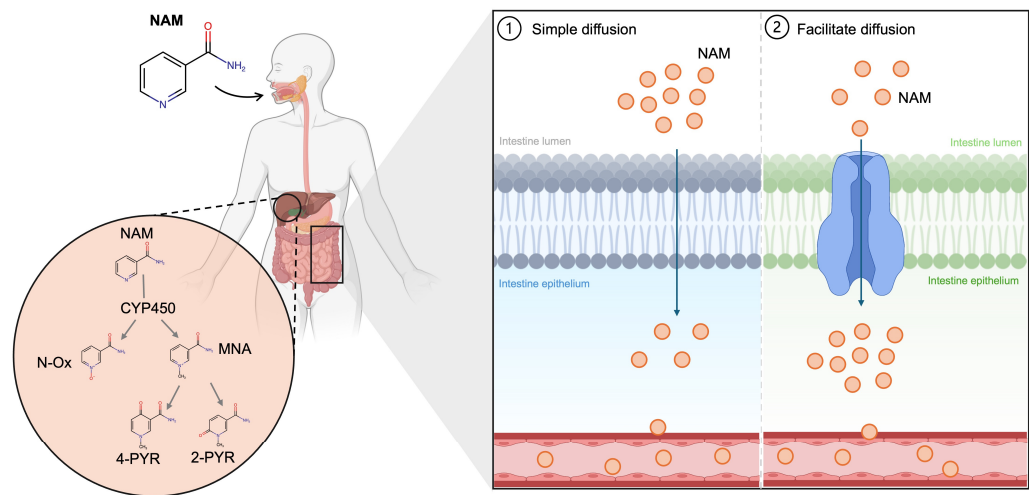
**Figure 2.** Schematic representation of NAM metabolism. Oral ingested NAM is absorbed in the small intestine through simple or facilitated diffusion, reaching the liver where excess NAM is metabolized by cytochrome P450 NAM into 4-PYR and 2-PYR, which are excreted. NAM, nicotinamide; CYP450, cytochrome P450; N-Ox, nicotinamide N-oxide; MNA, N-methyl-nicotinamide; 4-PYR, N1- methyl-4-pyridone-3-carboxamide; 2-PYR, N1-methyl-2-pyridone-5-carboxamide.

Despite their similar chemical structure, NA and NAM differ from a therapeutic point of view. NA is clinically used to manage dyslipidemia due to its ability to bind to the G-protein-coupled receptor 109a (GPCR109a). This binding reduces lipolysis in adipose tissue [36], but it also stimulates the secretion of prostaglandin D2 and E2 by Langerhans cells, leading to side effects such as vasodilation and flushing [37,38]. In contrast, NAM exhibits much greater tolerability, with minimal side effects reported only at high doses (up to 3 g daily) [10,39]. As a result, NAM is extensively utilized in the treatment of various skin disorders, including acne, rosacea, and aging, and as a chemopreventive agent for skin cancers, even in frail patients [32,40,41]. The differences in their side effect profiles may be attributed to NAM's lack of a carboxyl group in its chemical structure and the absence of specific receptors such as GPCR109A. In Table 1, the differences among vitamin B3 derivates are summarized.

**Table 1.** Overview of the differences among vitamin B3 derivates. ND, no detected.

| Vitamin B3 Derivate | Molecular Mechanism | Clinical Use | Side Effects |
|---|---|---|---|
| Nicotinamide (NAM) | - Restore NAD$^+$<br>- DNA damage repair<br>- Immunosuppression<br>- Reduction of ROS<br>- Inhibition of nitric oxide synthase [42,43] | - Pellagra<br>- Chemoprevention<br>- Antimicrobial<br>- Antipruritic<br>- Anti-inflammatory<br>- Treatment of acne, rosacea, melasma, atopic dermatitis [42,44,45] | Visible at high doses (up to 3 mg/die):<br>- Hepatic insufficiency<br>- Nausea<br>- Diarrhea<br>- Flushing [6,46] |
| Nicotinic acid (NA) | - Reduction of lipolysis in adipose tissue<br>- Stimulation secretion of prostaglandin D2 and E2<br>- Activation of GPCR109A receptor [47] | - Dyslipidemia<br>- Pellagra [48,49] | - Vasodilation and flushing<br>- Gastrointestinal disorders<br>- Rash<br>- Hyperglycemia<br>- Hyperuricemia [50] |
| Nicotinamide riboside (NR) | - Restore NAD$^+$ | Clinical trials [26,51] | ND |

NAM Administration and Possible Side Effects.

When prescribed *for the treatment of* human skin diseases, the usual oral dosage of NAM is 250–500 mg/*die*, with a good tolerability profile, with nausea and diarrhea only rarely being reported and counteracted by simply taking NAM with food [52]. Some studies have also evaluated its tolerability in special categories such as organ transplant recipients [53] and patients with HIV [54], thus showing the positive effects and safety of NAM. Despite the lack of conclusive data available on the possible genotoxic or carcinogenic effects of NAM [40], its administration at doses higher than 3.5 g daily has been found to be toxic and to potentially cause headache, dizziness, vomiting, and also increase in the liver enzymes and hepatotoxicity [52]. On the contrary, NAM was previously been shown to protect the liver from alcohol [55]. Moreover, high doses of NAM administered intravenously represent the specific therapy to counteract the Vacon poisoning. Vacon is a powder rodenticide able to acutely destroy the pancreatic beta islet cells, thus provoking diabetic ketoacidosis and mental status changes [56]. Luckily, Vacon is not currently available for general use.

The oral administration of NAM allows a transient but significant increase in $NAD^+$ blood level, as demonstrated by Ito and colleagues in their clinical trial [57]. Indeed, they have proved that oral supplementation with 500 mg of NAM boosted blood $NAD^+$ levels between 12 and 48 h after the administration, finding also blood lipidome change. Other preclinical studies conducted on animal models confirmed the beneficial effects of NAM administration, showing improved lifespan and increased $NAD^+$ levels [4,58,59]. Overall, these findings suggest a beneficial role of NAM administration against aging and other diseases due to its ability to restore cellular energy and the absence of side effects with the daily tolerable dose [60].

### 2.2. Mechanisms of Action

### 2.2.1. DNA Repair

All cells of the human body are continuously exposed to various agents that cause DNA lesions. If these lesions are not repaired or repaired incorrectly, they can eventually lead to mutations [61]. Some DNA damages occur accidentally during DNA replication or can be induced by reactive oxygen species (ROS), which are naturally produced during oxidative respiration [62]. These molecules often cause single-strand breaks (SSBs), characterized by the loss of a single nucleotide and damage at the site of the break [63]. Other DNA damages result from exposure to exogenous agents, such as ultraviolet radiation and chemical or physical factors [64]. To counteract these alterations, cells are equipped with efficient systems, collectively referred to as the DNA damage response (DDR), able to recognize and correct mutated nucleotides [64]. The DDR network comprises numerous proteins and genes that function as DNA lesion sensors and regulate the cell cycle via DNA-damage checkpoints [65]. For example, the nucleotide excision repair (NER) system, which involves PARP-1, addresses lesions typically induced by ultraviolet radiation, while the base excision repair (BER) pathway, including 8-oxoguanine glycosylase (OGG1), targets modifications induced by ROS [66]. To facilitate DNA repair, cells arrest the cell cycle through the activation of p53, which, in turn, inhibits the activity of cyclin-dependent kinases (CDK) until DNA repair is complete [65,67]. However, in case of severe DNA damage, cells may permanently arrest the cell cycle, undergoing apoptosis and senescence [68]. The DDR process requires significant amounts of ATP, leading to rapid consumption of $NAD^+$ and a drastic reduction in cellular energy levels. Nevertheless, NAM, as both $NAD^+$ precursor and inhibitor of some DDR proteins, can help restore ATP production and promote DNA repair. Indeed, NAM is a specific inhibitor of PARP1 and sirtuin-1 (SIRT1) both part of the DDR system [69]. PARP1 is one of the earliest nuclear proteins recruited to the sites of DNA damage and can repair single- and double-strand

DNA breaks by attaching a negatively charged polymer called poly(ADP-ribose) (PAR) to itself and other targets [70]. The ADP units needed for the polymerization of PAR are donated by $NAD^+$ [71,72]. Consequently, the prolonged activity of PARP1 induced by persistent stress or severe DNA damage leads to a rapid consumption of nuclear $NAD^+$ and causes ATP depletion, critical energy imbalance, and activation of apoptosis [73]. SIRT1 is a NAD-dependent class III histone deacetylase (HDAC III) that regulates cell senescence, apoptosis, cell metabolism, oxidative stress, and inflammation [74,75]. The regulation of SIRT1 expression is controlled at both transcriptional and post-transcriptional levels, including hypermethylation of its specific promoter, p53-induced downregulation, non-coding RNAs (NcRNAs), ubiquitination, glycosylation, and phosphorylation [75,76]. On the other hand, SIRT1 is regulated by additional factors that operate directly on the protein. One of these factors is the $NAD^+/NADH$ ratio, which correlates with protein activity. Indeed, when $NAD^+$ is depleted due to inflammation, oxidative stress, or PARP-1 activity, SIRT1 is downregulated, promoting a chain reaction of inflammation, senescence, and damage [75,77,78]. NAM supplementation transiently inhibits SIRT1, allowing sufficient replenishment of $NAD^+$ levels and recovery of the protein [79]. Interestingly, the SIRT1 inhibition mediated by NAM does not affect the deacetylation activity of the protein [40,80]. The ability of NAM to enhance DNA repair is particularly tangible on skin cells, especially after exposure to ultraviolet radiation, as described in Section 3.1.

### 2.2.2. DNA Damage-Induced Inflammation

Inflammation is an innate response to harmful stimuli and plays a critical role in promoting the healing process [81]. However, unresolved or chronic inflammation, particularly when induced by external factors such as ultraviolet radiation, contributes to the development of chronic diseases, accelerates aging, and plays a role in carcinogenesis [82,83]. In particular, the connection between inflammation and cancer development is complex. Indeed, chronic inflammation originates in a cancer-favoring environment, promoting cellular proliferation and viability, remodeling of extracellular matrix, and favoring cell migration [84]. In particular, the cornerstone of inflammation is the production of ROS designed to counteract pathogens, but it also leads to collateral damage to the host's DNA [84,85]. The presence of DNA damage induces the activation of the DNA-damage sensor system conducive to the consequences described in Section 2.2.1. On the other hand, the presence of DNA damage is an inducer of inflammation [86]. Indeed, DNA damages induce the expression of type I interferons and other inflammatory factors, which, in turn, contributes to ROS production and DNA mutations [86,87]. NAM supplementation contributes to the reduction of inflammation by enhancing DNA damage repair and indirectly inhibiting the nuclear factor-κB (NF-κB) activity, which is one of the principal factors involved in the inflammatory response [86,88]. Indeed, NF-κB is a family of transcription factors that can be activated through two different pathways: the canonical and non-canonical pathways. The canonical pathway is a rapid and transient activation of NF-κB mediated through Toll-like receptors (TLRs), interleukin-1 β (IL-1β), tumor necrosis factor α(TNFα), and lipopolysaccharides (LPS) [89–91]. On the other hand, the non-canonical pathway is a slow and persistent activation of NF-κB that is dependent on protein synthesis and triggered by a subset of TNFR signals [92]. This pathway is fundamental for immune system regulation, including B cell maturation and survival, lymphoid organ development, and autoimmune T cell detection [91,92]. Dysregulation of this pathway results in excessive pro-inflammatory cytokines release, leading to autoimmune diseases, chronic inflammation, and contributing to tumor microenvironment [89,93]. Therefore, mitigating inflammation could be an effective strategy to hinder or prevent cancer development [84]. As demonstrated by Torres-Méndez et al. [94] and by Hou et al. [95],

NAM supplementation reduced brain inflammation in diabetic mice and transgenic mice models for Alzheimer's disease, respectively. Also, data presented by Elhassan et al. [96] demonstrated that NR oral supplementation in aged men drastically reduced circulating inflammatory cytokines, together with improved skeletal muscle NAD$^+$ metabolome.

### 2.2.3. Oxidative Stress

The term ROS refers to a group of highly reactive molecules that contain oxygen radicals [97]. ROS are derived from endogenous and exogenous sources. Endogenous ROS are generated as bioproducts of cellular signaling, oxidative respiration, and inflammation processes [98,99]. Exogenous ROS are the consequence of exposure to external stimuli, like ionizing radiation, such as γ- or X-rays, UVA, or oxidizing chemicals [99]. Depending on their concentration and duration of exposure, ROS can have both beneficial and detrimental effects [100]. Nevertheless, in order to keep under control ROS levels, cells are equipped with defense mechanisms, including non-enzymatic ROS scavengers like glutathione (GSH) and vitamin C and E (α-tocopherol), and antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase [99,101]. However, when the balance tips in favor of ROS over antioxidants, oxidative stress occurs, leading to significant damage to DNA, protein, and lipid peroxidation [72,102]. Moreover, ROS can somehow activate the mitogen-activated protein kinases/extracellular signal-related kinases (MAPK/ERK) pathways that regulate cell proliferation, differentiation, inflammation, apoptosis, and cell survival [103–105]. NAM supplementation has been shown to prevent oxidative stress by reducing ROS levels, thereby protecting cells from their harmful effects [106]. Indeed, Tan et al. [107] have demonstrated that NAM can efficiently reduce oxidative stress induced by UVB radiation in both human primary keratinocytes and three-dimensional organotypic epidermal models, reducing cellular senescence and signs of aging. Similarly, in our recent study, we found that NAM decreases ROS production and oxidative stress in primary keratinocytes isolated from fields of cancerization [108]. Interestingly, NAM protective effects extend beyond the skin. In a mouse model of optical nerve injury, NAM supplementation reduced oxidative stress and neuroinflammation, leading to improved vision [109]. Furthermore, NAM protects natural killer cells from oxidative stress, enhancing their function and remission rates in patients with non-Hodgkin lymphoma [110]. While numerous studies support NAM's antioxidant role [111], it remains unclear whether its effects are strictly NAD-dependent or if NAM interacts with other pathways or antioxidant molecules. Further research is needed to elucidate these mechanisms.

### 2.2.4. Aging

Aging is a progressive degenerative state that involves all organs and tissues of the body [112]. It results from a complex interplay of different biological processes, including the accumulation of DNA damage, telomers shortening, NAD$^+$ depletion, chronic inflammation, and cellular senescence, all of which contribute to functional decline [112]. These processes are interconnected and can be triggered by both endogenous and exogenous stimuli, like UV, chemicals, and chemotherapy [113]. Among these factors, DNA damage plays a central role in driving aging [67]. Indeed, the activation of the DDR system in response to DNA damages triggers several pathways that ultimately converge on p53 activation, which, in turn, promotes the transcription of cyclin-dependent kinase inhibitors p16 and p21, leading to permanent cell cycle arrest—a state known as senescence [114,115]. Senescence primarily occurs in proliferating cells exposed to persistent stimuli. In addition to the cell cycle, senescent cells exhibit several detrimental characteristics. They overexpress anti-apoptotic enzymes, secrete senescence-associated secretory phenotypes (SASP) that include pro-inflammatory cytokines, growth factors, and proteases, and display increased oxidative

stress [116–118]. Collectively, these changes, along with the accumulation of senescent cells, compromise tissue integrity and actively contribute to the aging process [116–119]. Moreover, SASP-induced inflammation and DDR activation are highly energy-demanding processes, further depleting NAD$^+$ levels, which naturally decline during aging [5,120]. Compounding these issues, senescent cells appear to exhibit impaired NAMPT activity, although it is not clearly understood [5]. One potential strategy to mitigate aging is the supplementation of NAD$^+$ precursors, such as NMN, NR, or NAM, in order to restore NAD$^+$ levels and inhibit highly energy-consuming enzymes. As demonstrated by Kang et al. [121] and Mahajan et al. [122], NAM-treated human primary fibroblasts presented reduced aging markers expression, attenuated ROS production, decreased senescence, and restored cell cycle. Also, Oblong et al. [123] have proved that fibroblasts isolated from aged donors, when stimulated with NAM, present improved mitochondrial functions and bioenergetic availability.

## 3. Nicotinamide and Skin

### 3.1. NAM and UV-Induced Effects

Ultraviolet radiation (UVR) is the main threat to skin integrity. UVR encompasses three types of radiation: UVC (200–280 nm), UVB (280–315 nm), and UVA (315–400 nm) (Figure 3). The ozone layer effectively blocks UVC and the majority of UVB radiation (approximately 90–95%) emitted by the sun. As a result, the UV radiation that reaches the Earth's surface is predominantly composed of UVA with a small percentage of UVB (5–10%), depending on factors such as latitude, ozone layer thickness, and geographic location [124].
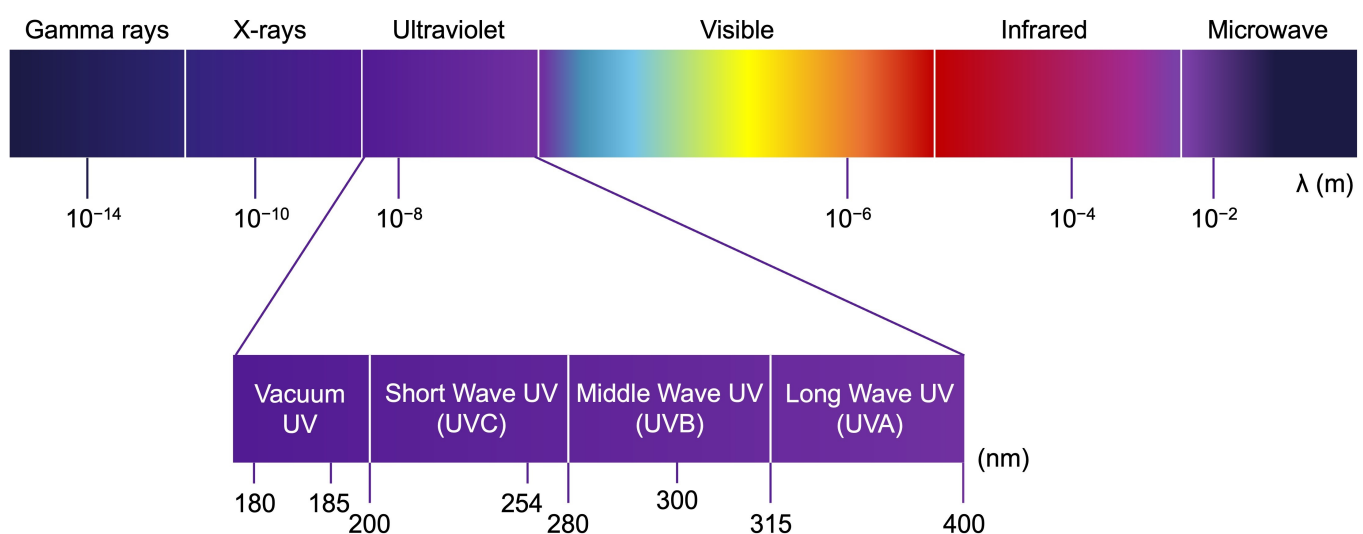


**Figure 3.** Representation of the electromagnetic spectrum emitted by the sun. UVC is known for its germicidal properties since it can seriously damage RNA and DNA of bacteria and fungi [125]. UVB catalyzes the reactions of vitamin D synthesis, in particular between 290 and 315 nm (280 nm wavelength is absorbed by the atmosphere), but is also responsible for acute and chronic effects, including skin carcinogenesis [126,127]. UVA is widely used in clinics for phototherapy but also accelerates skin aging and indirectly contributes to cancer development [128].

UVR exposure is fundamental for vitamin D production [129], but it also exerts a range of other beneficial effects. Emerging evidence reveals that UVR can induce both local and systemic responses, including modulation of immune function and regulation of neuroendocrine pathways, independent of its role in vitamin D production. [130].

However, both UVA and UVB are responsible for dreaded acute or chronic effects on the skin [131,132]. Acute effects encompass sunburn, tanning, local immunosuppression, and photodamage [133], while chronic effects include photocarcinogenesis and photoaging [132,134]. UV photodamages are caused by both direct and indirect actions on several cellular structures. Indeed, UVB photons are directly absorbed by the DNA, causing the formation of cyclobutane-pyrimidine dimers (CPDs) and pyrimidine-pyrimidone (6-4) photoproducts ((6-4)-PP), leading to mutations [135]. On the other hand, UVA triggers the production of ROS and reactive nitrogen species (RNS), which, in turn, contribute to DNA damage, lipid and protein peroxidation, and the activation of the inflammatory response [135–138]. However, even if these mechanisms are generally demarcated, some overlaps do exist [139].

So far, several photoprotective strategies have been adopted to mitigate or prevent these UV photodamages, which include the application of sunscreens, wearing photoprotective clothes, and the use of chemopreventive molecules like nicotinamide [140,141]. In humans, NAM has been shown to counteract UV-induced damage through its immune-protective properties and its involvement in energy-dependent cellular processes, including post-irradiation DNA repair. A 2009 study by Yiasemides et al. [142] investigated these effects in six healthy volunteers who received a single sub-erythemal dose of solar-simulated UV (ssUV) radiation on the lower back. Participants were then treated with either 5% nicotinamide lotion or a placebo. A microarray analysis of skin biopsies revealed that UV exposure caused downregulation of genes associated with energy metabolism, immune response, and anti-apoptotic pathways in placebo-treated skin. In contrast, these changes were not observed in skin treated with nicotinamide, highlighting its protective and restorative effects at the molecular level. Moreover, two independent studies [142,143] demonstrated that nicotinamide significantly mitigates solar-simulated UV (ssUV)-induced suppression of Mantoux reactions. This effect was observed in volunteers who received either oral nicotinamide at a dose of 500 mg daily or topical 5% nicotinamide, underscoring its ability to preserve immune function following UV exposure. To confirm these results, in vitro studies have been conducted on skin cells also to unravel the molecular mechanism behind NAM's photoprotective effects. Indeed, NAM can efficiently reduce aging markers, oxidative stress, and senescence, restore cell cycle arrest, enhance DNA repair, and modulate inflammation in UVB-irradiated human fibroblasts [144] and primary keratinocytes [107,108,145–148]. Similar effects have been found by Chhabra et al. [149] on UVA/UVB-irradiated normal melanocytes treated with NAM. The possible ways through which NAM can exert its protective effects are the restoration of $NAD^+$ levels within cells and the inhibition of NAD-dependent enzymes, facilitating replenishment of cellular energy necessary for the DNA-damage repair system and all cellular reactions. Nevertheless, so far, this hypothesis is still not totally confirmed due to the scarcity of data available in the literature. Therefore, further studies are fundamental to unveil all NAM's interactions within cells in order to reinforce the importance of this molecule for the treatment and prevention of several skin disorders, including cancers.

Currently, numerous studies are underway exploring the potential applications of nicotinamide in preventing and treating not only skin cancer but also a variety of other dermatological conditions. The most relevant studies are summarized in Table 2.

**Table 2.** List of the most relevant clinical trials on nicotinamide in dermatological diseases.

| Schedule/Duration | CT ID | Target | Clinical Phase |
|---|---|---|---|
| NICOTINAMIDE 500 mg/TD + corticosteroids; 12 weeks. | NCT03260166 | Cutaneous or systemic lupus erythematosus | Phase II |
| NICOTINAMIDE 2% or 4% topical; 12 weeks. | NCT05362188 | Cutaneous lupus erythematosus | Phase I |
| NICOTINAMIDE 500 mg/TD vs placebo; 4 weeks. | NCT04271735 | Psoriasis | NA |
| NICOTINAMIDE 4% topical + calcipotriol 0.005%; 12 weeks. | NCT01763424 | Psoriasis | Phase II/III |
| NICOTINAMIDE topical vs. calcipotriol vs. DPS-012 vs. placebo; 12 weeks. | NCT01368887 | Psoriasis (scalp) | Phase II |
| NICOTINAMIDE 4% topical vs. virgin coconut oil; 4 weeks. | NCT04218500 | Occupational hand dermatitis | NA |
| NICOTINAMIDE cosmetic product vs. placebo; 1 week. | NCT06331390 | Irritant contact dermatitis | NA |
| NICOTINAMIDE cosmetic product; 4 weeks. | NCT05454722 | Atopic dermatitis | NA |
| NICOTINAMIDE topical + adapalene; 6 weeks. | NCT03626298 | Acne vulgaris | Phase IV |
| NICOTINAMIDE 2% topical + 0.5% zync + ac. hyaluronic; 8 weeks. | NCT06120452 | Acne vulgaris and post-acne hyperpigmentation | NA |
| NICOTINAMIDE 4% topical vs. placebo; 4 weeks. | NCT01542138 | Axillary hyperpigmentation | Phase IV |
| NICOTINAMIDE 2% topical vs. metformin 30%; 9 weeks. | NCT05790577 | Melasma | Phase II |
| NICOTINAMIDE topical + arbutin + plant extracts; 20 weeks | NCT05986123 | Post-inflammatory Hyperpigmentation | NA |
| NICOTINAMIDE cosmetic product vs. others; 12 weeks. | NCT06770127 | Facial post-inflammatory Hyperpigmentation | Observational |
| NICOTINAMIDE 500 mg/TD vs placebo; 52 weeks | NCT03769285 | NMSC prevention (Transplanted patients) | Phase II |
| NICOTINAMIDE 500 mg/TD 52 weeks | NCT04843553 | AK prevention (Transplanted patients) | Phase I |

NA: Not applicable.

### 3.2. Photoaging

Unlike other organs, skin aging is accelerated by the action of external stimuli, such as ultraviolet exposure, leading to premature aging or photoaging [150]. The main consequences of photoaging are irregular pigmentation, roughness, telangiectasias, deep wrinkles, and precancerous lesions [151]. Therefore, photoaging treatment and prevention is essential to reduce the risk of developing these modifications [152]. Clinical studies have demonstrated that topical nicotinamide provides a wide range of benefits for improving the appearance of aging facial skin. However, questions regarding its long-term efficacy and safety remain, highlighting the need for further research. A study by Bisset et al. [153] supports these findings. In their 12-week, double-blind, placebo-controlled, split-face trial, 50 Caucasian women aged 40 to 60 years were randomly assigned to use a control moisturizer on one side of the face and the same moisturizer containing 5% nicotinamide on the other. Nicotinamide was well-tolerated and showed significant improvements compared to the control in multiple parameters, including fine lines and wrinkles, hyperpigmentation spots, skin texture, and red blotchiness. Notably, it also significantly reduced skin yellowing compared to the control.

Additionally, cosmetic formulations containing nicotinamide have been shown to enhance the stratum corneum's aqueous content and reduce transepidermal water loss, resulting in improved skin appearance, firmness, elasticity, and reduced wrinkles [154]. The

anti-aging effectiveness of nicotinamide was further confirmed in a study by Bogdanowicz et al. [155], which documented improvements in fine lines, wrinkles, luminosity, smoothness, homogeneity, and plumpness in 44 women treated with a topical product containing both nicotinamide and hyaluronic acid. These effects were accompanied by a decrease in the expression of several senescence-associated secretory phenotype (SASP) genes.

*3.3. Non-Melanoma Skin Cancer*

Recent clinical studies have provided compelling evidence supporting the role of nicotinamide in skin cancer prevention. In 2015, Kim et al. [12] presented the combined findings of two randomized, double-blind phase 2 trials involving 74 participants with photo-damaged skin and a history of skin cancer. These trials evaluated the effect of oral nicotinamide on actinic keratosis (AK) counts and demonstrated a significant reduction in the likelihood of developing at least one skin cancer among participants treated with nicotinamide compared to those receiving a placebo. Similarly, two Australian phase 2, double-blind, randomized, placebo-controlled trials reported that a daily dose of 500 mg oral nicotinamide led to a reduction in precancerous lesions and in situ skin carcinomas after just four months of treatment [8]. A landmark randomized trial published by Chen et al. in 2015 [39] further underscored these findings, showing that oral nicotinamide significantly reduced the incidence of new non-melanoma skin cancers and actinic keratoses in high-risk individuals, including kidney transplant recipients. Drago et al. [53] conducted a focused investigation into the effects of 500 mg daily nicotinamide on AKs in solid organ transplant recipients. Thirty-eight patients were randomized to receive either nicotinamide or placebo. Among those treated with nicotinamide, 88% experienced a reduction in AK size, 42% showed complete regression of AKs, and no new AKs developed during the study period. In contrast, 91% of the control group experienced an increase in the number or size of AKs, with seven lesions progressing to squamous cell carcinoma (SCC). Importantly, no skin cancers were reported in the nicotinamide group, highlighting its protective potential against both precancerous and malignant lesions. These findings collectively demonstrate nicotinamide's efficacy in reducing the burden of skin cancer and precancerous lesions, particularly in high-risk populations. However, another randomized controlled trial conducted in 2023 [156] that enrolled 154 solid organ transplant recipients with a previous diagnosis of skin cancer failed to find differences in the rates of subsequent cancer development between patients treated with nicotinamide and the placebo group. Regarding topical treatment, a randomized clinical trial by de Castro [157] evaluated the effectiveness of 5% nicotinamide cream in maintaining the clinical response achieved after cryosurgery for actinic keratoses (AKs). The study confirmed the safety and tolerability of the product; however, no significant differences in AK reduction or complete clearance were observed between the treatment and placebo groups.

In our experience [158], a topical formulation containing high-protection sunscreens, a DNA Repair Complex with antioxidant and reparative properties targeting UV-induced DNA damage, and nicotinamide demonstrated efficacy in managing AKs in both immunosuppressed and immunocompetent patients. The reduction in AKASI scores ranged from 22.76% to 31.73%, respectively, highlighting its potential as an adjunctive therapy.

## 4. Other Skin Disorders

*4.1. Acne*

The role of nicotinamide in the treatment of acne is well established and was already proposed in the mid-90s [159] and confirmed in subsequent randomized studies [160–162] as a potential alternative to topical antibiotics. The proposed mechanism involves the downregulation of matrix metalloproteinases, such as MMP-1, MMP-2, MMP-9, and MMP-

14, which play a role in acne pathogenesis, as well as the modulation of pro-inflammatory cytokines [163]. Additionally, nicotinamide has been shown to reduce sebaceous gland activity. While the exact mechanism has not yet been fully elucidated, it has been hypothesized that nicotinamide is converted into niacin, a B-group vitamin; this molecule, in turn, can interact with the HCA2 receptor, raise calcium levels and consequently reduce sebum production [15]. Nicotinamide has also been suggested as a part of topical combination therapies alongside other molecules with keratolytic, antiseptic, and antimicrobial activity [163–165]. A randomized study [166] demonstrated a synergic effect when nicotinamide was combined with benzoyl peroxide. In addition, the oral administration of nicotinamide as a part of dietary supplements has been proposed. Two open-label, prospective studies involving 198 and 235 patients, respectively, affected by inflammatory acne [159,167] reported a visible amelioration in most patients, with no significative differences compared to those receiving concomitant antibiotic treatments. More recently, nicotinamide, in the form of niacinamide, was also proposed as a concomitant topical treatment able to reduce the cutaneous side effects (i.e., redness, dryness, and itching) in patients treated with oral isotretinoin for severe acne [168].

### 4.2. Bullous Diseases

Several clinical cases published in the late 20th century [169–174] explored with conflicting results the use of nicotinamide in treating patients suffering from different autoimmune bullous diseases, including acquired epidermolysis bullosa. Among these, only the case reported by Honl [169] demonstrated a clinical response to nicotinamide as monotherapy. In all other cases, the anti-inflammatory effect of tetracyclines and the immunomodulatory action of nicotinamide was exploited synergistically. In 2000, an open trial involving 11 patients with bullous pemphigoid treated with tetracycline and nicotinamide (1.5–2 g/daily) showed promising results: six patients achieved an almost complete response, and two others demonstrated a partial response [175]. More recently, in 2019, Kalinska-Bienias [176] published data from a 3-year retrospective study that included 106 patients with bullous pemphigoid. This study compared the efficacy of a treatment regimen combining tetracycline, nicotinamide, and topical steroids with prednisone monotherapy. The combination therapy demonstrated comparable efficacy in disease control while offering improved 1-year and 3-year survival rates for patients treated with the nicotinamide combination. Several clinical cases published in the late 20th century [169–173] explored the use of nicotinamide in treating patients suffering from different autoimmune bullous diseases. Among these, only the case reported by Honl [169] demonstrated a clinical response to nicotinamide as monotherapy. In all other cases, the anti-inflammatory effect of tetracyclines and the immunomodulatory action of nicotinamide was exploited synergistically. In 2000, an open trial involving 11 patients with bullous pemphigoid treated with tetracycline and nicotinamide (1.5–2 g/daily) showed promising results: six patients achieved an almost complete response, and two others demonstrated a partial response [175]. More recently, in 2019, Kalinska-Bienias [176] published data from a 3-year retrospective study that included 106 patients with bullous pemphigoid. This study compared the efficacy of a treatment regimen combining tetracycline, nicotinamide, and topical steroids with prednisone monotherapy. The combination therapy demonstrated comparable efficacy in disease control while offering improved 1-year and 3-year survival rates for patients treated with the nicotinamide combination.

### 4.3. Atopic Dermatitis

The essential role of nicotinamide in managing atopic dermatitis is supported by numerous studies. Notably, El-Heis et al. in 2016 [177] observed that higher concentrations

of nicotinamide in maternal serum were associated with a reduced risk of developing atopic dermatitis at 12 months of age. Also, the antipruritic effect of nicotinamide and its role in restoring the skin barrier, likely mediated through its interaction with AQP3, which is overexpressed in atopic dermatitis, makes this molecule mainly effective in treating this pathological condition [42,178,179]. In 2005, Soma et al. [180] conducted a study on 28 atopic patients treated with 2% nicotinamide cream for 4–8 weeks. They observed a significant reduction in the transepidermal water loss (TEWL) and an increase in stratum corneum hydration compared to untreated areas or areas treated with white petrolatum in the same patient. More recently, Zhu et al. [181] demonstrated the efficacy of a nicotinamide-containing cleansing gel and body emollient in improving clinical symptoms and quality of life in patients affected by mild AD. Among 84 patients treated with nicotinamide-based topical products, significant reductions were observed in the SCORAD clinical score, as well as in POEMS and DLQI questionnaire results, compared to the control group. Additionally, substantial improvements in TEWL and stratum corneum water content measurement were documented, indicating skin barrier restoration.

Nicotinamide also shows a synergistic effect when combined with topical tacrolimus, allowing for a reduction in the required dose of tacrolimus for effective AD treatment [182].

*4.4. Others*

Nicotinamide has shown efficacy in managing other various dermatological conditions, including rosacea, psoriasis, and melasma. In rosacea, a common facial dermatosis characterized by flares triggered by exposome factors, topical application of 0.25% N-methylnicotinamide gel—a metabolite of nicotinamide—achieved improvement in 76% of treated patients [183]. Additional topical formulations containing nicotinamide have also demonstrated efficacy in alleviating symptoms in rosacea patients [184–186] also in randomized trials [187]. The NICOS (Nicomide Improvement in Clinical Outcomes) study evaluated oral nicotinamide combined with copper, zinc, and folic acid in patients with rosacea and acne vulgaris, reporting moderate to substantial improvement in 79% of participants after four weeks [167].

In psoriasis, a 2010 randomized, double-blind, placebo-controlled study by Levine et al. [188] assessed the efficacy of a combination of calcipotriene and nicotinamide. Although the results were not statistically significant, patients receiving nicotinamide showed a dose-dependent trend of clinical improvement. More recently, El-Khalawani et al. [189] demonstrated that a 4% topical nicotinamide formulation applied twice daily for 12 weeks yielded satisfactory short-term results in 60 patients with mild-to-moderate psoriasis. This benefit may be attributed to nicotinamide's capacity to suppress dendritic cell activation, as shown in vitro [190].

Topical formulations containing 2% to 5% nicotinamide have demonstrated efficacy in treating melasma and other forms of UV-induced hyperpigmentation. Melasma is characterized by the appearance of brownish or grayish patches on sun-exposed areas of the skin, driven by a combination of genetic, hormonal, and environmental factors. Ultraviolet (UV) radiation can also induce other hyperpigmentation conditions—such as freckles, solar lentigines, and post-inflammatory hyperpigmentation—by stimulating increased melanin production as a protective response to DNA damage. Beneficial effects have been observed both when nicotinamide is used alone and in combination with N-acetyl glucosamine or cysteamine, highlighting its potential as a therapeutic option for pigmentary disorders [153,191,192]. Moreover, a 2011 clinical trial published by Navarrete-Solis [193] compared 4% nicotinamide cream with hydroquinone, a well-known depigmenting agent. While both treatments led to an improvement, hydroquinone showed a slightly superior efficacy, whereas nicotinamide offered better tolerability. Histopathologic analysis revealed

reduced mast cell infiltration and improved solar elastosis in nicotinamide-treated areas. Also, DNA hypermethylation has been shown to be reduced in melasma skin areas after treatment with nicotinamide 4% [194].

Finally, a possible role of nicotinamide can also be hypothesized in the stimulation of re-epithelization after surgical or pathological wounds [195,196]. In fact, this molecule can support wound healing processes primarily by enhancing cellular energy metabolism, moderating inflammation, and promoting healthy skin cell function. Also, a possible role in preventing fibrotic scarring has been hypothesized [197].

These findings highlight the versatility of nicotinamide as a therapeutic agent in dermatology, offering anti-inflammatory, immunomodulatory, and skin barrier-enhancing benefits across a spectrum of skin conditions.

## 5. Conclusions

In conclusion, nicotinamide emerges as a versatile, well-tolerated, and clinically relevant molecule with broad applications in dermatology and beyond. As a $NAD^+$ precursor, it supports multiple cellular functions that are central to maintaining genomic stability and metabolic homeostasis. By facilitating DNA repair, modulating inflammatory pathways, and attenuating oxidative stress, nicotinamide not only assists in preventing cellular damage but also counters processes that drive aging and carcinogenesis. In the skin, its robust profile is evident: from photoaging and non-melanoma skin cancer prevention to the management of acne, atopic dermatitis, and other chronic inflammatory conditions, nicotinamide exhibits preventive, reparative, and protective properties that improve both clinical outcomes and patient quality of life. Although its safety profile is well-established even at high doses, questions remain regarding the precise mechanisms through which it exerts its beneficial effects—whether entirely through NAD-dependent pathways or via other yet-to-be-clarified molecular interactions. Further research is warranted to fully elucidate the long-term safety and efficacy of nicotinamide supplementation, to optimize dosing strategies, and to identify potential synergistic formulations. Besides, the identification of new biomarkers linked with the efficacy of NAM treatment will allow a better classification of patients that can take advantage of NAM administration and predict its positive response. As our understanding deepens, nicotinamide may become a key pillar in integrated therapeutic approaches for a range of skin conditions and systemic diseases, bridging the gap between nutritional supplementation, pharmacological intervention, and preventive healthcare strategies.

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