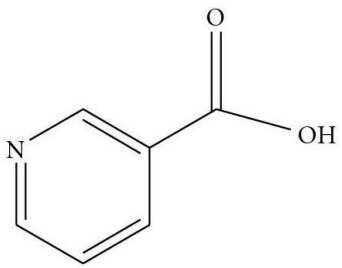
SYNERGIE SKIN
CLEAN SCIENCE

CLINICAL DATA – NIACINAMIDE

Specifications

Chemical Name: Pyridine-3-carboxamide

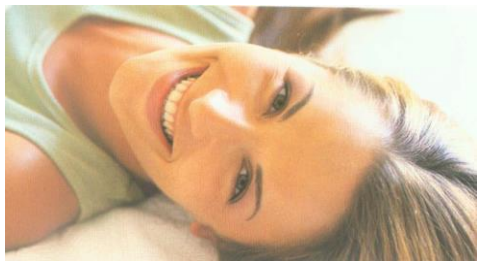
Chemical structure:



Empirical formula: $C_6H_6N_2O$

General functions

Niacinamide, which is also called nicotinamide, is the physiologically active form of niacin or vitamin B3. It is a member of the B-vitamin family. Another name for this water-soluble vitamin is Anti-Pellagra-Vitamin or PP (Pellagra-Preventive)-Factor. Pellagra, Italian for pelle agra meaning rough or burning skin, is a deficiency symptom where the skin becomes extremely rough and skin areas exposed to the sun develop a severe, scaly dermatitis. Niacinamide forms the essential part of the coenzyme nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) that are used to generate energy inside the cells. More than 40 biochemical reactions have been identified and are of paramount importance for normal tissue integrity, particularly for the skin, the gastrointestinal tract and the nervous system.



Another form of vitamin B3 is nicotinic acid. Since both are effective as vitamins the term niacin is often used as group name despite some authors using niacin synonymously only with nicotinic acid.

Applicant in cosmetics

Niacinamide is an active ingredient with an extraordinary breadth of cutaneous benefits. The multiplicity of effects and formulation benefits of niacinamide make it an ideal choice for a variety of cosmetic products targeting young and old skin alike.

***In-vitro* studies:**

Niacinamide coenzymes, the energy "currency" units driving the cell metabolism in the skin are depleted with age. A localized supply of niacinamide or nicotinic acid can help normalize this imbalance.

Aged fibroblasts secrete less collagen than young cells; niacinamide can stimulate new collagen synthesis. Niacinamide has a positive impact on connective tissue and gel

matrix components of the skin, which is of particular significance in aged and photoaged skin.

Niacinamide up-regulates epidermal ceramide synthesis with concurrent benefits to the epidermal barrier. Those results were confirmed in *in-vivo* studies applying 2% niacinamide.

Niacinamide up-regulates markers of epidermal differentiation, which should have a significant positive impact on ageing epidermal tissue. It stimulates basal epidermal keratinocytes and increases the biosynthesis of epidermal intermediates critical to the formation of a fully functioning stratum corneum.

Niacinamide helps to prevent UV-induced deleterious molecular and immunological events, supporting work in animal models demonstrate clearly the ability of niacinamide to significantly reduce photoimmunesuppression.

Niacinamide inhibits the transfer of melanosomes from melanocytes to keratinocytes. This could lead to a reduction in pigmentation with time, without inhibitory effects on melanocyte tyrosinase activity.

Niacinamide is delivered effectively from a range of vehicles. From various formulations, approximately 10 to 29% of the starting dose was detected after 1 to 2 days.

***In-vivo* studies:**
Niacinamide in concentrations of 2 to 5% reduces human skin hyperpigmentation and facial spots formation.

Niacinamide regulates sebaceous lipid and consequently acne. Topical niacinamide in the form of a commercial 4% gel has been shown to provide potent anti-inflammatory activity in the treatment of acne vulgaris while bacterial resistance is lacking. *In-vitro* Niacinamide produced significant dose-dependent reductions in total sebaceous lipogenesis and reductions in both triglyceride and fatty acid synthesis.

Niacinamide exerts multiple benefits on the appearance of ageing and photodamaged skin. A significant improvement in skin texture appearance over the application of a 5% niacinamide product was seen in women aged 35 to 60 years. The appearance shifted towards the finer, anisotropic features characteristic of younger skin while the appearance of hyperpigmented spots was significant improved.

Niacinamides effect on skin pigmentation
Niacinamide inhibits transfer of melanosomes from melanocytes to keratinocytes
Skin pigmentation results in part from the transfer of melanized melanosomes synthesized by melanocytes to neighboring keratinocytes, and niacinamide can inhibit this transfer.

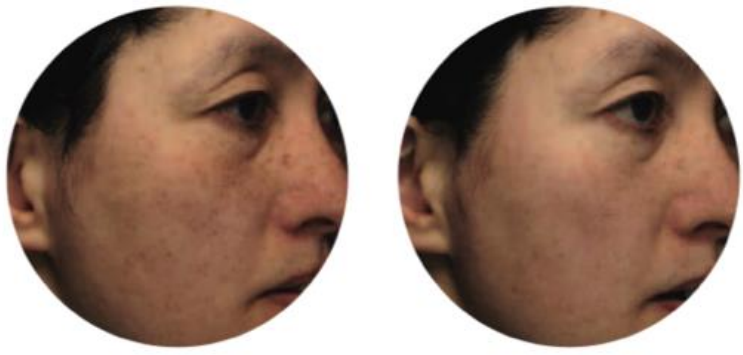
Boissy and colleagues[14] first showed these effects in co-cultures of human melanocytes and keratinocytes, using immuno-linked celltype-specific dyes to separate and count

keratinocytes, melanocytes and keratinocytes containing transferred melanosomes. The addition of niacinamide to the cultured cells significantly inhibited the transfer of melanosomes from melanocytes to keratinocytes (by 25–45%; $p<0.05$). Niacinamide had no inhibitory effect on melanocyte tyrosinase activity.

Niacinamide reduces human skin hyperpigmentation

The findings by Boissy and colleagues on inhibition of melanosome transfer suggest that treating human skin *in vivo* with topical Niacinamide would lead to a reduction in pigmentation with time via this novel, elegant mechanism. A follow-up study by Boissy et al.[15] confirmed this, assessing the effect of niacinamide on facial hyperpigmented spots in a human clinical trial with a split-face, vehicle-controlled design. The results demonstrated a dose-dependent and reversible reduction in hyperpigmented lesions with Niacinamide treatment. *In vitro* and *in vivo* data show that when Niacinamide treatment stops, the melanosome transfer and hyperpigmentation will resume.

This report is consistent with two previously reported studies, both by Hakozaki and colleagues[16], involving a total of 138 Japanese women in a split-face design trial comparing 5% niacinamide to control vehicles over 8 weeks. In the first study, comprising 18 females with hyperpigmented facial spots, 5% niacinamide induced a significant ($p<0.05$) reduction in spot area at 4- and 8-week time-points and significantly reduced ($p<0.05$) graded visible spot pigmentation at 8 weeks. In the second study, involving 120 female Japanese subjects with facial tanning, niacinamide induced a significant ($p<0.05$) increase in skin lightness at 4- and 6-week time-points, and a significant ($p<0.05$) increase in graded visible skin lightness at 4 weeks.



Niacinamide reduces skin yellow appearance of hyperpigmented spots

Anti-Acne properties

Regulation of sebaceous lipid and acne by niacinamide

Topical niacinamide in the form of a commercial 4% gel has been shown to provide potent anti-inflammatory activity in the treatment of acne vulgaris, and many practitioners use the treatment for its combination of efficacy and unlikeliness of causing bacterial resistance.

In a study reported by Shalita and colleagues[17], 82% of subjects with inflammatory acne showed an improvement in global evaluation after 8 weeks of usage, accompanied by significant reductions in papules/pustules (-60%) and acne severity (-52%). The authors postulated these effects may be due to niacinamide's apparent antihistaminic effect, its activity as an electron scavenger, or its inhibition of 3'-5' cyclic-

AMP phosphodiesterase activity. However, recent data suggest a more fundamental role for topical niacinamide in acne treatment.

Notably, Biedermann and coworkers[18] used viable human facial biopsies (from face-lift surgery) to measure the effect of niacinamide on sebaceous lipogenesis. Cultured biopsies were treated with Niacinamide or trans-retinoic acid (tRA) for 4 days, and then incubated with 14C-acetate. Niacinamide produced significant dose-dependent reductions in total sebaceous lipogenesis (–42% at 25mM; $p<0.01$), and the reduction induced by 25mM niacinamide was equivalent to that produced by 1µM tRA (-32%; $p=0.01$). Furthermore, Niacinamide produced marked reductions in both triglyceride and fatty acid synthesis vs. the control (-52% and -46% respectively for 25mM niacinamide; $p<0.05$). Given that triglycerides represent by far the largest proportion of sebaceous gland lipids (50–60%), the effect of niacinamide on total lipogenesis is likely attributable to triglyceride reduction.

This has important implications for acne pathogenesis. It is accepted that acne is a disease involving the pilosebaceous duct and *Propionibacterium acnes*. Regardless of the exact interplay of these factors, a significant reduction in both total sebaceous lipids and in the triglyceride fraction would be expected to benefit acne-form skin.

SUMMARY

Niacinamide has been shown to be a cosmetic ingredient with an extraordinary breadth and history of cutaneous benefits.

These include:

- Anti-ageing effects, including normalization of age-associate depletions of nicotinamide coenzymes; stimulation of collagen synthesis; up-regulation of epidermal sphingolipids, particularly ceramides, and improvement of epidermal barrier function;
- Beneficial effects on skin pigmentation, including up-regulation of keratinocytes differentiation markers; prevention of UV damage; inhibition of melanosome transfer, and reduction of hyperpigmentation;
- Anti-acne properties, including reduction of total sebaceous lipids and triglycerides in particular;
- Multiple benefits on ageing skin appearance.

The fundamental role of niacinamide as a precursor of reduced nicotinamide coenzymes such as NADH and NADPH is believed to be pivotal to its observed effects. It displays distinct advantages over other ingredients with similar benefits, such as retinol, in that it is well tolerated, is not subject to oxidation or photolysis, and is chemically stable and compatible with other anti-ageing technologies. In short, the multiplicity of effects and formulation benefits seen with niacinamide make it an ideal choice for a variety of cosmetic products targeting young and old skin.[19]

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Niacinamide – Research update

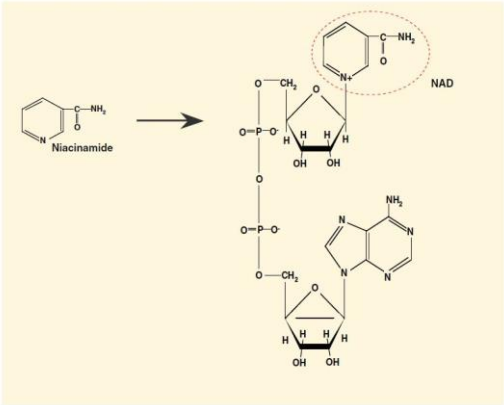
The protective cutaneous effects of vitamin B3 and its physiologically active form, niacinamide, have been a subject of scientific interest for nearly a hundred years, ever since B3 deficiency was identified as the reason for an early 20th century epidemic of pellagra, a chronic wasting disease with severe cutaneous symptoms. In recent years, a dramatic increase in clinical research with topical niacinamide has provided growing evidence for its beneficial effects on skin health, from helping maintain barrier integrity to diminishing and perhaps even reversing the signs of ageing. At the same time, continuing research in *in vivo* and cell culture models is helping elucidate the cellular and molecular mechanisms underlying the well-documented cutaneous physiological activity of niacinamide.

History and Background

Niacinamide is the water-soluble form of vitamin B3, which is sometimes called "vitamin PP," for "Pellagra-Preventive." The pseudonym stems from its association with pellagra, a disease that swept the southern United States in epidemic proportions in the early 1900s.1 Pellagra patients presented with a variety of debilitating symptoms including, significantly, a spectrum of cutaneous lesions.

Pellagra was eventually recognized as a disease caused by vitamin B3 deficiency, both treatable and preventable by simple dietary supplementation. In 1937, it became clear that nicotinic acid and its derivatives (including niacinamide) were the protective "PP" factors. Since then, a host of dermatological therapeutic benefits and mechanisms have been ascribed to niacinamide, (also known as nicotinamide, 3-pyridinecarboxamide) when used as a topical agent. These include its apparent role as an anti-acne active, and as a moderator of photo immune-suppression and accompanying tumorigenesis. Niacinamide also has demonstrated benefits on the stratum corneum barrier, including the up regulation of epidermal sphingolipids (particularly ceramides) and biomarkers of epidermal differentiation and dermal proliferation.

More recently, fresh evidence points to a role in modifying the cosmetic appearance of skin through suppression of epidermal melanosome transfer with subsequent effect on skin pigmentation and a role in modifying epidermal surface topography.

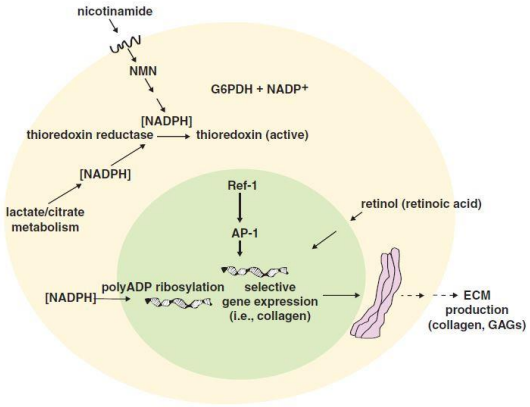


Structure of niacinamide and inclusion within NAD molecule

The mechanisms for these cutaneous effects are still unclear. However, since niacinamide is an important precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) and their reduced high-energy forms (NADH and NADPH), it has been postulated that topical application of niacinamide may promote this broad spectrum of reported activity by correcting local homeostatic balance of these two nucleotide coenzymes.

Physiological role of Niacinamide

The substituted pyridine derivative niacinamide is an essential constituent of the oxidoreduction coenzymes NAD and NADP. During glycolysis and the TCA cycle, 10 molecules of NAD + (per molecule of glucose) are reduced to 10 NADH by the transfer of a hydride ion to the 4-position of the niacinamide ring. The hydride ion of NADH serves effectively as an energy storage unit, giving up a pair of high energy electrons to the mitochondrial electron transport chain when needed. In this process of oxidative phosphorylation, electron pairs are transferred from NADH to a final acceptor (oxygen) via a series of electron carriers. This transfer of electrons is thermodynamically favorable, i.e., ΔG is negative, and is coupled to the pumping of protons out of the mitochondrial matrix. The flow of protons back into the matrix, in turn, catalyzes the production of ATP by F_0F_1ATP-synthase. Total energy yield (ΔG') for this process is high (–52.7kcal).



Hypothesized involvement of NADPH on AP-1 activity

Whereas NADH is involved in catabolism, NADPH tends to serve as an electron (hydride ion) donor in anabolic processes, that is, biosyntheses. For example, NADPH is the reducing co-factor used by fatty acid synthetase in lipid biosynthesis and by desmolases and hydroxylases in steroid biosynthesis.

Given their functions, the nicotinamide coenzymes NADH and NADPH can be viewed as fundamental energy "currency" units within cells, driving the metabolism of cells involved in both catabolic and anabolic processes.

Niacinamide and Skin ageing

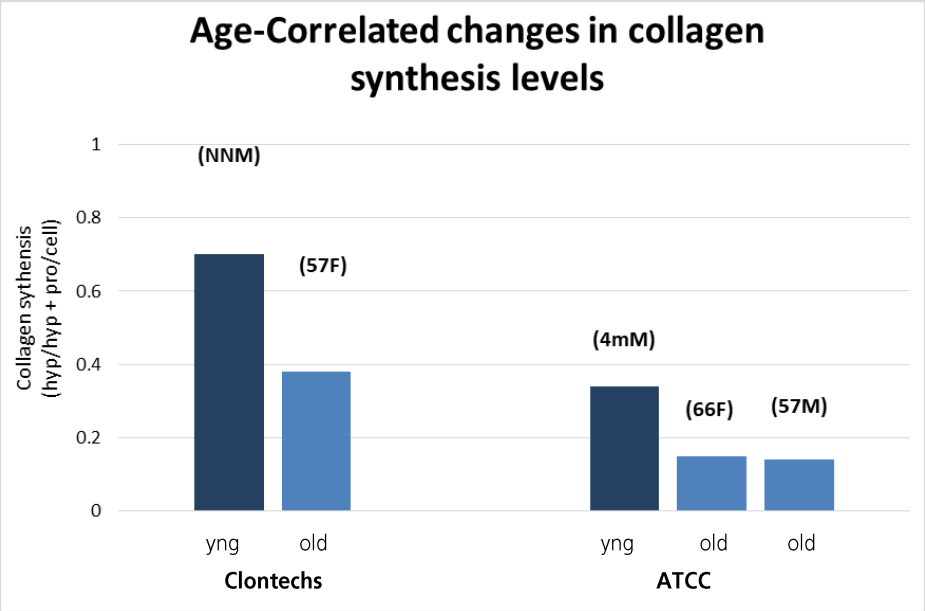
Niacinamide can help normalize age-associated depletions of nicotinamide coenzymes in skin

There is increasing evidence that systemic and intracellular concentrations of the nicotinamide coenzymes NADH and NADPH decline with age in human and animal models.[2] [3] [4] Recent data appear to confirm this, including a 2001 study by Oblong and

colleagues[5] that found an age-associated reduction in nicotinamide coenzymes. Using human dermal fibroblast cell lines from a 7-year-old and a 72-year-old, the authors measured endogenous NADPH/NADP+ ratios and total NADPH + NADP+ levels, finding lower NAD redox ratios and lower total NADPH + NADP+ levels in the aged fibroblasts compared to the young cells (-51% and -28%, respectively).

Importantly, when the authors supplemented the aged fibroblast cultures with 14C-niacinamide and 14C-nicotinic acid (a niacinamide precursor), intracellular concentrations of NADPH increased. This suggests that a localized supply of niacinamide can be utilized by aged cutaneous cells to restore intracellular nicotinamide coenzyme homeostasis.

It is well established that net collagen production decreases as a function of age and photo-damage in the dermis of mammalian skin. Recent data[5] demonstrate that niacinamide supplementation stimulates collagen synthesis in human dermal fibroblasts.



To address the question of age-related decline in collagen content, Oblong and colleagues examined collagen protein secretion from cultured human dermal fibroblasts taken from a young (7-year-old) and aged donor (72-year-old). Dermal fibroblasts from the aged donor secreted significantly ($p<0.05$) less collagen than those from the young donor. Furthermore, NADPH/NADP redox ratios were lower ($p<0.05$) in fibroblasts from the aged donor (results were normalized to the cell number from the respective culture well).

Supplementing the aged cell culture with niacinamide significantly increased total collagen secreted (by 54%), total protein secreted (by 41%), and total number of cells (by 20%), relative to a control vehicle. Importantly, there was also a significant 35% increase in the collagen/total protein ratio, indicating some specificity for collagen biosynthesis and secretion. These data suggest that treatment with niacinamide has a positive impact on the dermal compartment, both in terms of its connective tissue and gel matrix components – effects that would be of particular significance in aged and photo-damaged skin.

Niacinamide and Epidermal barrier function

Niacinamide up-regulates epidermal ceramide synthesis with concurrent epidermal barrier benefits

Sphingolipids and other stratum corneum lipids, particularly ceramides, are known to play central roles in the structural and functional integrity of the epidermal permeability barrier, and are reportedly decreased in aged and atopic skin.[6] Growing evidence suggests that topical niacinamide augments the barrier properties of the skin, with accompanying clinically relevant benefits, by up-regulating endogenous biosynthesis of epidermal sphingolipids, including ceramides in particular. These augmentation benefits appear to extend even to skin that is compromised by disease.

In one study, Tanno and colleagues showed that niacinamide induced up to a 5-fold up-regulation in ceramide synthesis ($p<0.05$), in a dose dependent fashion, in cultured human epidermal keratinocytes.[7] Further work by the same group showed up-regulation of other sphingolipid fractions (glucosylceramide, by 7.4-fold, and sphingomyelin, by 3.1-fold), as well as free fatty acid and cholesterol synthesis (by 2.3- and 1.5-fold, respectively), with niacinamide supplementation. The data suggest that niacinamide-induced increases in levels of intra-cellular acetyl-CoA (the precursor common to epidermal lipid synthesis) and expression of serine-palmitoyltransferase may be the underlying mechanism for these effects.

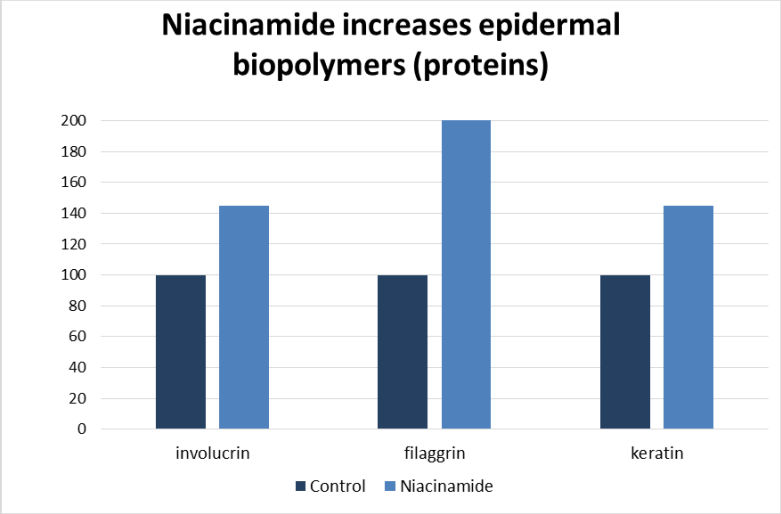
To demonstrate the *in vivo* clinical significance of these findings, Tanno and coauthors[8] topically applied 2% niacinamide to dry lower legs over 4 weeks, observing a significant increase ($p<0.05$) in recovered stratum corneum ceramide and free fatty acid lipid fractions, vs. a control vehicle. This was accompanied by a significant reduction in transepidermal water loss (TEWL) vs. control vehicle (-27%; $p<0.05$).

In other research, Ertel and colleagues[9] demonstrated that a moisturizing vehicle containing 2% niacinamide produced significant reductions in TEWL vs. a vehicle control, and that this was accompanied by an increased rate of stratum corneum turnover (as measured by dansyl chloride assay). Research has also shown TEWL reduction and increased resistance to barrier damage by sodium lauryl sulfate (SLS) on forearm.[10] Draelos and coworkers[11] demonstrated a significant improvement in global condition (assessed) in 96% of 48 female subjects with stage I/II rosacea who were treated for 4 weeks with a moisturizing vehicle containing 2% niacinamide.

Niacinamide up-regulates biosynthesis of markers of keratinocyte differentiation

Niacinamide has been shown both to stimulate basal epidermal keratinocytes and up-regulate biosynthesis of epidermal intermediates critical to the differentiation and formation of a fully functioning stratum corneum, namely, filaggrin and involucrin. (Filaggrin plays a vital role in aggregation and alignment of keratin tonofilaments in granular cells; filaggrin is also a precursor to low molecular weight components collectively called natural moisturizing factors which bind water in the stratum corneum. Involucrin is an essential precursor in the formation of the insoluble cornified envelope surrounding terminal keratinocytes.) These effects would be expected to have a significant positive impact on ageing epidermal tissue *in vivo*.

Oblong and coworkers used cultured normal human epidermal keratinocytes (NHEK) supplemented with a medium containing niacinamide. Following a 24-hour incubation, the number of niacinamide-treated NHEK had increased significantly ($p<0.05$) relative to a control vehicle, and the niacinamide-treated NHEK showed up-regulation in both involucrin and filaggrin biosynthesis (by 45% and 100%, respectively) vs. that induced by a control vehicle. The authors postulated that the effects were due to niacinamide-induced increases in intracellular levels of nicotinamide coenzymes.



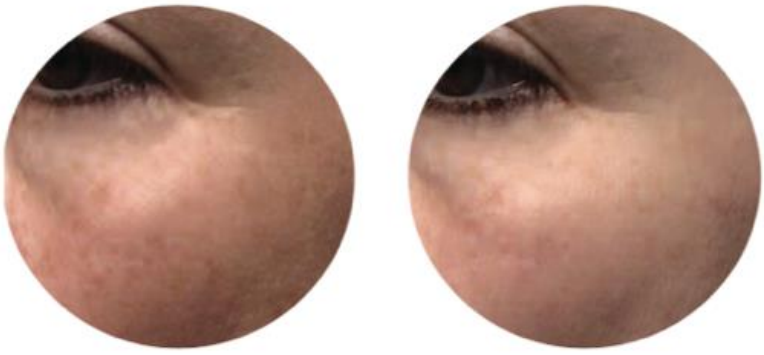
Niacinamide helps prevent UV-induced deleterious molecular and immunological events

The protective role of niacinamide against UV-induced damage is supported by data in animal models and human cell lines. For example, recent work in cultured normal human keratinocytes by Shen and colleagues[12] demonstrated that niacinamide can protect against damage from reactive oxygen species induced by UVC irradiation or exposure to hydrogen peroxide. Niacinamide treatment significantly attenuated apoptotic morphological changes ($p<0.05$) in a dose dependent manner. Niacinamide-treated cells also had decreased p53 induction and a reduction in DNA ladders vs. those treated with a control vehicle. These data are consistent with other research[13] demonstrating the ability of niacinamide to significantly reduce both induction of photocarcinogenesis and photoimmunesuppression, though the mechanism by which niacinamide exerts these effects is not yet clear.

Skin appearance

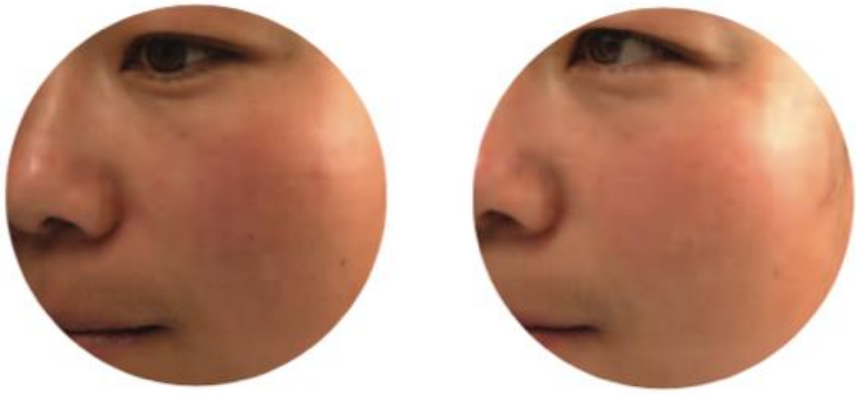
Niacinamide exerts multiple benefits on the appearance of ageing/photo-damaged skin, *in vivo*

Several double-blind clinical studies reported by Bissett and colleagues[19] studied the effects of 5% topical niacinamide vs. a control vehicle in ageing human facial skin. In one, a 12-week randomized, split-face trial involving 40 female subjects (ages 35-60), found significant improvements in niacinamide-treated skin in terms of skin texture appearance at both 4 and 12 weeks ($p<0.1$, <0.05, respectively), and in hyperpigmented spot appearance at 8 weeks ($p<0.05$).



Baseline 12 weeks

In another study, 50 female subjects (ages 40-60) applied blind-coded products split-face and randomized for 12 weeks. Image analysis revealed significant improvements in several facial parameters, including reduction in skin yellowing ($p = 0.02$ at week 8 and 0.0004 at week 12), fine lines/wrinkles ($p = 0.06$ at week 8 and 0.0005 at week 12), hyperpigmented spots ($p = 0.002$ at week 8 and $p = 0.006$ at week 8), and red blotchiness ($p = 0.03$ at week 12). In an additional study, in which 88 female subjects aged 35-60 applied blind-coded products split-face for 8 weeks, the niacinamide-containing treatment provided a significant improvement in skin texture appearance relative to the vehicle control at the 8-week time-point, thus confirming the results of the first study.



Baseline 4 weeks

Before and after treatment with niacinamide-containing product

The reported effect on skin surface texture is consistent with that found in a 10-week clinical study in which Matts and Solechnick[20] used multiple-angle reflectance spectrophotometry to measure the diffuse component of skin reflection. After 10 weeks of treatment, the diffuse component was significantly increased in dorsal hand skin treated with 5% niacinamide vs. a control vehicle ($p<0.05$), suggesting a shift in texture toward finer, anisotropic features characteristic of younger skin. These results paralleled blinded self-rated preferences for texture appearance in treated skin over vehicle control ($p<0.05$).

Another appearance problem is skin sallowness (yellowing). A mechanism contributing to this problem is glycation, the spontaneous oxidative cross-linking reaction of sugar with protein. The glycation product is yellow in color, and such collagen products accumulate in skin. Since glycation involves oxidation, antioxidants have potential to affect the process. Since NADH and NADPH are endogenous antioxidants and niacinamide is a precursor to them in skin, topical niacinamide has potential to be effective against skin sallowness. Recent research with 50 Caucasian women (ages 40-60), as previously noted, demonstrated that an oil in water emulsion with a 5% niacinamide concentration visibly diminished skin yellowing at 12 weeks vs. a placebo that did not contain niacinamide.[19]