CHAPTER 44

Niacinamide

Activities:
PAR-2 inhibition, anti-inflammatory, antioxidant, antiaging, photoprotective

Important Chemical Components:
Also known as nicotinamide (and 3-pyridinecarboxamide), molecular formula is $C_6H_6N_2O$

Origin Classification:
Natural vitamin constituent of various foods but the cosmetic ingredient is laboratory made

Personal Care Category:
Depigmenting, exfoliant

Recommended for the following Baumann Skin Types:
Is a superior choice for dry, sensitive and wrinkle-prone skin types. Best for DRNT, DRNW, DRPT, DRPW, DSNT, DSNW, DSPT, DSPW, ORPT, ORPW, OSPT, OSPW, OSNT, and OSNW.

SOURCE

Niacinamide, also known as nicotinamide, is the biologically active amide of niacin (vitamin B_3). This form of the vitamin is found naturally in a wide variety of foods, particularly root vegetables, mushrooms, yeasts, some fruits, peanuts, and seeds.[1,2] Significantly, the effects of niacinamide on pigmentation have been shown to be reversible (Table 44-1).[3]

HISTORY

Research on and the use of oral niacinamide dates back to the 1930s, but the data on the use of topical niacinamide are relatively new. The first use of topical niacinamide to ameliorate skin barrier function in individuals with pellagra, which is characterized by pronounced cutaneous sensitivity to sunlight, was reported in 1976.[4–6] For over 40 years, niacinamide has been used in dermatology for a broad array of disorders including acne, atopic dermatitis, autoimmune bullous dermatoses, excess sebum, as well as rosacea, and more recently to treat hyperpigmentation and to prevent photoaging and photoimmunosuppression.[7,8]

TABLE 44-1
Pros and Cons of Niacinamide

Pros	Cons
PAR-2 blocking agent	Not well known by consumers
Water soluble	Not as potent as hydroquinone
Easily tolerated	No organic or natural forms are available on the market
Anti-inflammatory	
Can be formulated in SPF	
No interactions with other ingredients	

CHEMISTRY

Niacinamide is an important part of the niacin coenzymes nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP+), and their respective reduced forms the antioxidants NADH and NADPH. These compounds contribute to cellular oxidation and reduction reactions as well as DNA synthesis and repair, are involved in over 200 enzymatic reactions, and may play a role in providing cosmetic benefits.[2,9–11] Surjana and Damian suggest that niacinamide is able to confer clinical effects because of its role as a cellular energy precursor, a modulator of inflammatory cytokines, and a suppressor of the nuclear enzyme poly(adenosine diphosphate-ribose) polymerase-1.[7] It has also been shown to increase intercellular lipid production.[3,12]

Niacinamide has been demonstrated to suppress melanosome transfer to epidermal keratinocytes, by up to 68 percent in an *in vitro* model, and to render improvement in undesired facial pigmentation.[9] This inhibition of melanosome transfer from melanocytes to keratinocytes is considered the primary method by which niacinamide lessens skin pigmentation.

ORAL USES

The nutritional value of niacin or niacinamide has been long understood. Niacinamide is found in various vegetables (particularly asparagus and root vegetables), mushrooms, yeasts, some fruits, peanuts, and seeds. Oral niacinamide is best known for curing pellagra, but it has also been linked to playing a role in preventing insulin-dependent diabetes mellitus development.[9,13] Evidence amassed during the last 15 years has also shown that oral niacinamide has prevented photocarcinogenesis in mice, as well as protected against photoimmunosuppression in humans and mice.[14–16] In addition, recent results of phase II double-blinded randomized controlled trials led by Surjana et al. indicate that oral niacinamide (500 mg) effectively diminishes actinic keratoses and shows potential for chemopreventive activity against skin cancer.[17]

TOPICAL USES

Niacinamide has been used for various indications in dermatology, including acne and rosacea.[18–20] This water-soluble vitamin is known to be a significant active ingredient in moisturizers intended to improve xerosis and stratum corneum (SC) barrier function.[4] In addition, it has recently been shown in topical form to protect against UVA and UVB radiation and is thought to be a promising agent to prevent against skin cancer.[21]

In a 2005 study, twice daily application of a 5 percent niacinamide preparation for 8 weeks yielded significant improvement in

hyperpigmentation as did the use of 3.5 percent niacinamide combined with retinyl palmitate.[22]

In 2013, Mohammed et al. studied the effects of twice-daily application of a niacinamide-containing formulation for 28 days on the left and right mid-volar forearms of 20 healthy volunteers in terms of transepidermal water loss (TEWL), corneocyte surface area and maturity, SC thickness, and selected protease activities. Overall, areas treated with niacinamide-containing formulations exhibited larger and more mature corneocytes, less inflammatory activity and TEWL, and greater SC thickness as compared to pre-treatment baseline and areas left untreated or treated with vehicle control. The investigators concluded that niacinamide displays unique SC barrier-bolstering qualities and merits consideration as a topical formulation adjunct.[4] During the last decade, though, its greatest application in dermatology has been thought to be in relation to its activity as a depigmenting agent.

Combination Therapy

In 2006, Hakozaki et al. studied the effects of combining high-frequency ultrasound with topical skin-lightening agents (ascorbyl glucoside and niacinamide) on facial hyperpigmentation in 60 Japanese women. They found in their four-week clinical trial that the use of ultrasound radiation along with skin-lightening gel significantly diminished facial hyperpigmentation spots as compared with no treatment and skin-lightening gel alone, which they attributed to the facilitating effect of ultrasound on the transepidermal transport of the topical agents.[23]

In 2009, Bissett et al. performed two double-blind, 10-week, left-right randomized, split-face clinical studies to ascertain if the combination of N-undecyl-10-enoyl-L-phenylalanine, which has reportedly lowered melanin production in cultured melanocytes, and niacinamide is more effective than niacinamide alone in diminishing facial hyperpigmentation. In one study, 80 Japanese women (76 of whom completed the study) randomized into two groups each applied one of two formulation pairs to the randomly assigned side of the face, a vehicle control and a 5 percent niacinamide formulation, or a 5 percent niacinamide and a 5 percent niacinamide plus 1 percent N-undecylenoyl phenylalanine formulation. In the other study, 152 Caucasian women (of whom 147 completed the study) applied either vehicle control, a 5 percent niacinamide formulation, or a 5 percent niacinamide and 1 percent N-undecylenoyl-phenylalanine combination formulation to the randomly assigned side of the face. The investigators found that the combination formulation was more effective than the vehicle or niacinamide alone in improving the appearance of hyperpigmentation in both studies. They concluded that this combination formulation is an effective antiaging agent for facial skin.[24]

Early in the next year, Jerajani et al. measured the effects in 246 Indian women (aged 30–60 years) with epidermal hyperpigmentation of the daily use of a lotion containing niacinamide, panthenol, and tocopherol acetate for 10 weeks. In this randomized, double-blind trial, which 207 women completed, those who used the well-tolerated test formulation experienced significant improvements in the appearance of hyperpigmentation, skin tone, and texture as compared to controls.[25]

Also in 2010, Kimball et al. conducted a 10-week, double-blind, vehicle-controlled, full-face, parallel-group clinical study in 202 women (aged 40–60 years) to evaluate the effects of a combination of niacinamide and N-acetyl glucosamine in a topical moisturizing formulation on irregular facial pigmentation. The evenly divided groups daily applied either a morning sun protection factor (SPF) 15 sunscreen moisturizing lotion and evening moisturizing cream each containing 4 percent niacinamide and 2 percent N-acetyl glucosamine or the SPF 15 lotion and cream vehicles. All measurement parameters revealed that the test formulation was significantly more effective in alleviating detectable hyperpigmentation than the control product and yielded results superior to using an SPF sunscreen alone.[26]

Niacinamide was also a key active ingredient in an SPF 30 moisturizing lotion used in a recent randomized, controlled comparative study on wrinkle reduction. In this eight-week parallel-group study of 196 women with moderate to moderately severe periorbital wrinkles, 99 women used the SPF moisturizer containing 5 percent niacinamide, peptides, and antioxidants; a moisturizing cream containing niacinamide and peptides; and a targeted wrinkle product containing niacinamide, peptides, and 0.3 percent retinyl propionate. The remaining cohort of 97 women used 0.02 percent tretinoin plus moisturizing SPF 30 sunscreen. The niacinamide regimen was significantly better tolerated and provided significantly improved wrinkle appearance compared to the tretinoin group.[27]

SAFETY ISSUES

Niacinamide is very well tolerated by the skin and has an excellent safety profile.

ENVIRONMENTAL IMPACT

Given the widespread availability of plants containing niacinamide, no discrete environmental toll is exacted in the culling of niacinamide specifically.

FORMULATION CONSIDERATIONS

Niacinamide is chemically stable, easily formulated, and compatible with various other potential cosmetic formulation ingredients.[28]

USAGE CONSIDERATIONS

Niacinamide can be used in conjunction with retinoids, sunscreens, hydroxy acids, and other ingredients without concern for cross-reactivity.

SIGNIFICANT BACKGROUND

In 2002, Hakozaki et al. examined the *in vitro* effects of niacinamide on melanogenesis and *in vivo* effects on 18 Japanese women with hyperpigmentation. In cultured melanocytes, niacinamide exerted no effect on mushroom tyrosinase catalytic activity or melanogenesis but significantly inhibited melanosome transfer in a keratinocyte/melanocyte coculture model and decreased cutaneous pigmentation in a pigmented reconstructed epidermis model. In the clinical trial over four weeks, the 18 participants with hyperpigmentation used 5 percent niacinamide moisturizer and a vehicle moisturizer in a paired design, and 120 subjects with facial tanning were assigned to two of three treatments (vehicle, sunscreen, and 2 percent niacinamide plus sunscreen). The investigators found that niacinamide significantly reduced hyperpigmentation and enhanced skin lightness in comparison to vehicle alone. They concluded that niacinamide effectively lightens skin by suppressing melanosome transfer from melanocytes to keratinocytes.[9]

In 2004, Bissett et al. conducted a 12-week, double-blind, placebo-controlled, split-face, left-right randomized clinical study with 50 Causcasian women (aged 40–60 years) to compare a moisturizer containing 5 percent niacinamide and a control moisturizer. The investigators found that the well-tolerated niacinamide formulation imparted significant improvements in fine lines/wrinkles, hyperpigmentation, skin texture, red blotchiness, and sallowness compared to the control product.[28]

The next year, Bissett et al. sought to clinically determine the antiaging effects of topical niacinamide in addition to the well-established improvement on hyperpigmentation. In this 12-week, double-blind, left-right randomized study, 50 white females with clinical signs of facial photoaging twice daily applied 5 percent niacinamide to half of the face and its vehicle control to the other half. The researchers observed that the niacinamide-treated areas demonstrated marked improvement in elasticity as well as in reducing fine lines and wrinkles, hyperpigmented spots, red blotchiness, and skin sallowness.[29]

Also in 2005, Greatens et al. used an *in vitro* melanocyte-keratinocyte coculture to find that both agents are reversible inhibitors of melanosome transfer at concentrations not affecting cell viability. In a related study, the investigators observed that topically applied niacinamide dose-dependently and reversibly diminished hyperpigmented lesions.[3]

CONCLUSION

Niacinamide, the biologically active amide of niacin (vitamin B_3), the dearth of which leads to pellagra, has long been known to play an important role in cutaneous health. This versatile vitamin exhibits its most dynamic dermatologic activity as a depigmenting agent. It is a safe and effective alternative to hydroquinone, though not as potent or effective as the standard-bearing depigmenting agent. However, niacinamide has a well-established role in dermatology and its range of indications appears to be broadening. Niacinamide is one of the author's favorite ingredients because of its utility in treating inflammation and pigmentation, and preventing of skin aging and skin cancer, as well as its tolerability.

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