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 ORIGINAL ARTICLE 

# Going Beyond Ceramides in Moisturizers: The Role of Natural Moisturizing Factors

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## ABSTRACT

Xerosis is experienced by almost everyone at some time in their lives and the foundation of management of dry skin (both consumer- and healthcare professional-directed) rests on the use of moisturizers. Given the wide range of available moisturizers, counseling patients about selecting the optimum moisturizer for their individual situation relies on knowledge of ingredients and formulations. Traditionally, the main focus for many moisturizers centered on the core functional and structural role of ceramides within the epidermal barrier. However, while a key aspect of transepidermal water loss and other skin barrier functions, components other than ceramides are equally essential in increasing moisturization. The skin's natural moisturizing factors (NMFs) are a complex mixture of water-attracting compounds such as amino acids, urea, lactate, pyrrolidone carboxylic acid (PCA), and electrolytes which play a fundamental role in preserving physiologic function by regulating the water content of the stratum corneum. By facilitating water retention, NMFs contribute significantly to the suppleness, elasticity, normal desquamation, and overall integrity of the skin barrier. Incorporation of NMFs into moisturizers addresses critical deficiencies in the skin's moisture balance that exist in xerotic and atopic skin, and in many skin disorders, mitigating signs and symptoms associated with xerosis and promoting optimal skin health. The biochemical composition of NMFs and the intricate interplay with epidermal homeostasis translate to a central role in moisturizers used for prophylactic and therapeutic management of various dry skin conditions, beyond ceramides alone.

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## INTRODUCTION

The majority of people experience xerosis during their lifetime and the condition can be acute or chronic.[1,2] Both endogenous and exogenous factors contribute to the development of xerosis (Figure 1).[3] Xerosis can occur due to changes in the environment, skincare regimen, age, medications, hereditary disorders such as ichthyosis, or secondary to inflammatory skin conditions such as atopic dermatitis, psoriasis, and seborrheic dermatitis.[2,4-6] Clinically, signs of xerosis include scaling, white/flaky skin, cracks and fissures, erythema, hyperkeratosis, and lichenification. Symptoms of xerosis commonly include pruritus, which can be a significant and chronic problem in older individuals.[7] Other signs and symptoms of xerosis range from the physical sensation of dryness or discomfort of the skin to pain or stinging.[8] Deficiencies of several individual molecules and structural components in the epidermis can contribute to xerosis, including NMFs and ceramides; abnormalities in the skin's moisture network also play a role.[9,10]

The impact of xerosis is increasingly appreciated by healthcare professionals, particularly as the population ages, since dry skin in older patients can lead to problems that can be significant.[11] For example, excoriation of dry, pruritic skin can lead to infection, fragile and dry or cracked skin in individuals with poor mobility can lead to pressure ulcers, and in those with insulin-dependent diabetes, dry skin can be a precursor to foot erosions and infections.[11] Dry skin may also be a sign of malnutrition among elderly individuals.[11]

### Role of Moisturizers in Xerotic Conditions

Moisturizers serve as the foundation of the management of xerotic conditions.[8] These products can have both short- and long-term effects on skin hydration, barrier function, skin texture, elasticity, and appearance.[8] Incorporation of specific ingredients into moisturizer formulations can enhance some of these beneficial effects.[12] Over the years, there have been significant advances in the development of moisturizers, from occlusives formulated as basic skin barrier protection to humectant-enriched moisturizers developed for hydrating care.[8] Occlusives are substances that form a confluent layer on the skin surface, physically blocking the evaporation of water (transepidermal water loss) and can shield the skin from irritants, allergens, and pathogens. Commonly used occlusives include oils (eg, soybean oil, olive oil, and mineral oil), waxes (eg, carnauba and beeswax), dimethicone, lanolin, and petrolatum.[8] Emollients are saturated and unsaturated lipids (eg, colloidal oatmeal, shea butter, and isopropyl palmitate)

**TABLE 1.**

**Mechanisms of Actions of Moisturizing Ingredients. Adapted from Purnamawati, et al.[8]**

| | Emollients | Humectants | Occlusives | Protein Rejuvenators |
|---|---|---|---|---|
| Mechanism of Action | Saturated and unsaturated hydrocarbons, including colloidal oatmeal, shea butter, and isopropyl palmitate, which improve skin barrier function, membrane fluidity and cell signaling which results in overall improvement of skin texture and appearance.<br><br>Often combined with emulsifier(s). | Low molecular weight substances, including ceramides, amino acids, alpha hydroxy acids, hyaluronic acid and others, with capability to attract water to the stratum corneum and hydrate skin.<br><br>Frequently used with other compounds which may retain the water content. | Oils (olive oil, soybean oil, mineral oil) waxes (carnauba, beeswax), dimethicone, lanolin, and petrolatum, that form an inactive layer on the skin surface, physically blocking water evaporation from skin (transepidermal water loss). Occlusives also shield skin from irritants. | Small molecular weight proteins, thought to aid skin rejuvenation by replenishing essential proteins |
| Indication | Routine skin care, dry and rough skin, papulosquamous skin disease | Xerosis, ichthyosis | Prevention of contact dermatitis, xerosis, atopic dermatitis | Photodamaged skin, skin rejuvenation |
| Possible Adverse Effects | Contact irritation (seldom) | Irritation (lactic acid, urea) | Oily application, cosmetically disagreeable, folliculitis (mineral oil), contact dermatitis (lanolin), acneiform eruption | Contact dermatitis |
| Substance | Fatty acids, fatty alcohols, cholesterol, ceramides, squalene, pseudoceramides (synthetic ceramides) | Urea, sorbitol, panthenol, glycerol, propylene glycol, NMF, hyaluronic acid, alpha hydroxy acid, lactic acid | Mineral oil, petroleum jelly, beeswax, silicones, zinc oxide | Collagen, elastin, keratin |

which improve skin barrier function, membrane fluidity, and cell signaling, resulting in overall improvement of skin texture and appearance.[8] Humectants are substances (eg, ceramides, amino acids, alpha hydroxy acids, and hyaluronic acid) that attract water to the stratum corneum and hydrate the skin.[8] Finally, protein rejuvenators, such as low molecular weight collagen, keratin, and elastin, replenish essential proteins in the skin, bestowing a rejuvenated appearance.[8] Along with their unique mechanisms of action, each of these moisturizing ingredients is associated with potential side effects and may be more effective for patients with certain dry skin conditions (Table 1). The best moisturizers today provide a combination of protection and hydration, helping to support endogenous barrier repair mechanisms. They also have anti-inflammatory, antipruritic, and wound-healing effects, all housed within a well-designed vehicle that is chemically and functionally compatible with its ingredients.[8]

Ceramides and the complex of molecules collectively known as natural moisturizing factors (NMFs) have been shown to contribute benefits when added to moisturizer formulations.[13] Ceramides are well-established active ingredients in moisturizers and are essential for healthy skin barrier function.[14] They account for approximately 30 to 40% of the lipids within

**FIGURE 1.** Pathophysiology of xerosis.[3]

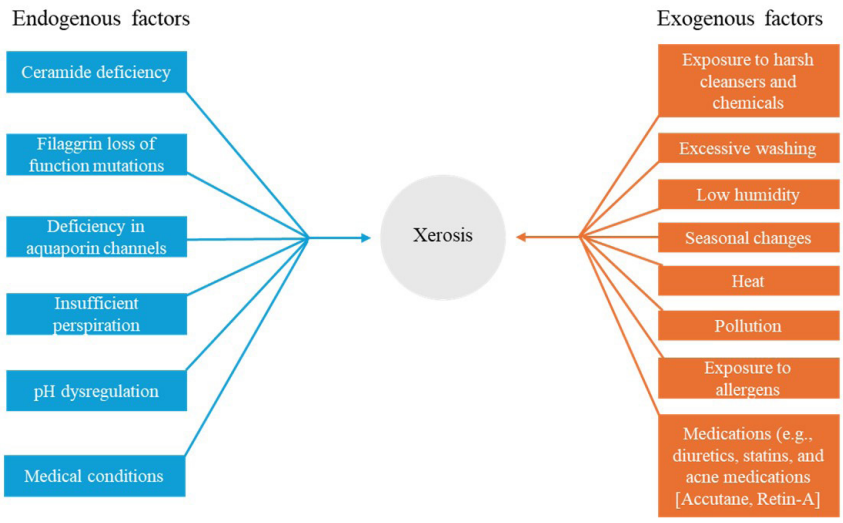
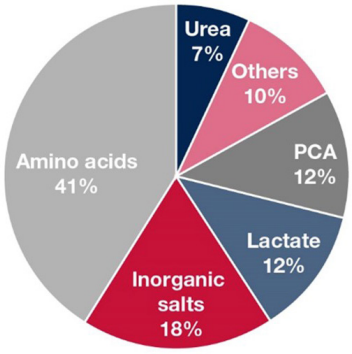


**FIGURE 2.** Composition of endogenous NMFs.




The components of endogenous NMFs. Compounds listed as "Others" include inorganic acids, peptides, and some unidentified compounds.
PCA, pyrrolidone carboxylic acid.

the stratum corneum, are highly lipophilic, and poorly water-soluble.[14] Skin lipids, including ceramides, arrange themselves in a highly ordered lamellar structure that is essential to barrier function. When aligned in this way, lipids help regulate and prevent excessive TEWL; aberrations in the amount and organization of lipids lead to barrier defects and skin disorders.[14] NMFs are often omitted from many available moisturizers; however, their inclusion can significantly enhance the overall benefits of ceramides alone.

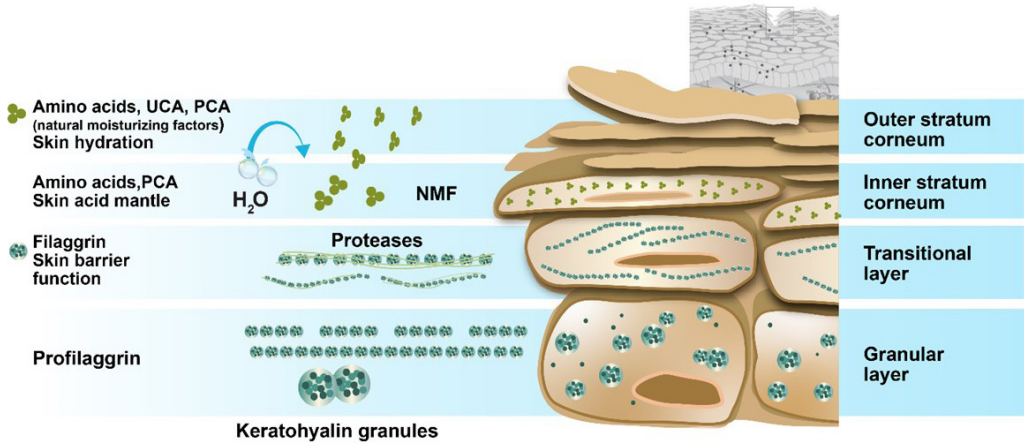
**Appreciating the Benefits of NMFs**

Cutaneous water loss is highly regulated and water retention in the stratum corneum depends on both the orderly lipid arrangement discussed above and the presence of water-attracting agents within corneocytes which are collectively known as NMFs.[15] The chemical composition of NMFs is shown in Figure 2. The molecules are breakdown products of filaggrin: primarily amino acids and their derivatives (pyrrolidone carboxylic acid, lactate, and urea) and inorganic salts.[10]

NMF production begins with profilaggrin (Figure 3), which is insoluble and found within keratinocytes of the granular layer.[10] As the keratinocytes transition into corneocytes, profilaggrin undergoes dephosphorylation and proteolysis to become soluble filaggrin.[10] Filaggrin then interacts with keratin, aggregating keratin into microfibrils which help prevent premature proteolysis of filaggrin.[10] However, filaggrin eventually does undergo proteolysis in the upper layers of the stratum corneum, forming highly efficient NMFs that can act as humectants to attract, bind, and retain both atmospheric and endogenous water.[10] The water bound by NMFs provides skin with elasticity and allows appropriate functioning of hydrolytic enzymes for desquamation.[10] The timing and depth of filaggrin degradation depends on both water activity within corneocytes and environmental humidity.[10] In high humidity there are few drying effects and filaggrin breakdown occurs close to the outer surface of the skin.[10] In lower humidity environments, filaggrin proteolysis occurs earlier and at deeper skin layers so that the NMF products can prevent the skin from excessive drying.[16,17] Ultraviolet light has also been associated with reduced natural degradation of filaggrin into NMFs. Additionally, NMFs within the skin diminish with age due to reduced profilaggrin levels and impaired barrier function.[15,18]

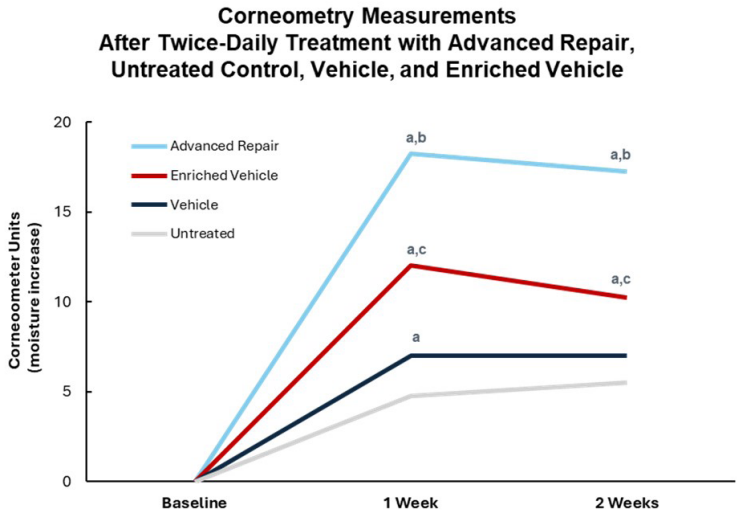
Decreases in endogenous NMFs in the skin lead to dehydration and concomitant skin dryness, roughness, and pruritus.[10] Reduced levels of NMFs within the stratum corneum have been linked to cutaneous disorders such as atopic dermatitis, psoriasis, and xerosis.[1] Loss-of-function mutations in *FLG* (the gene encoding profilaggrin and filaggrin), have been implicated in the etiology of ichthyosis vulgaris, and are strong predisposing factors in atopic dermatitis and xerosis. It is estimated that roughly 10% of people carry these mutations.[20]

**FIGURE 3.** The process of NMF production. Adapted from Fowler.[19]




*UCA=urocanic acid; NMF=natural moisturizing factor; PCA=pyrrolidone carboxylic acid.

**FIGURE 4.** Change in skin hydration with NMF moisturizer superior to vehicles and control. From Weber T, et al.[1]




[a]Significantly higher than untreated control ($P<0.05$).
[b]Significantly higher than vehicle and enriched vehicle ($P<0.05$).
[c]Significantly higher than vehicle ($P<0.05$).
NMFs, natural moisturizing factors.

**Topical Supplementation of NMFs**

The majority of water in the stratum corneum is free, and it has been estimated that just one-third is bound by NMFs. The bound water is what confers elasticity to the skin; merely increasing free water concentrations does not affect skin elasticity.[21] NMF levels have been shown to be significantly reduced in patients with xerosis, atopic dermatitis, ichthyosis, and psoriasis.[22-24] Thus, supplementing NMFs in the skin through topical application of NMF-containing moisturizers is a logical approach to optimizing skin hydration, both for patients with healthy skin and those with skin barrier disorders. Indeed, ongoing research indicates that the combination of the humectant actions of NMFs and other active ingredients such as ceramides can synergistically improve dry skin relief.[10]

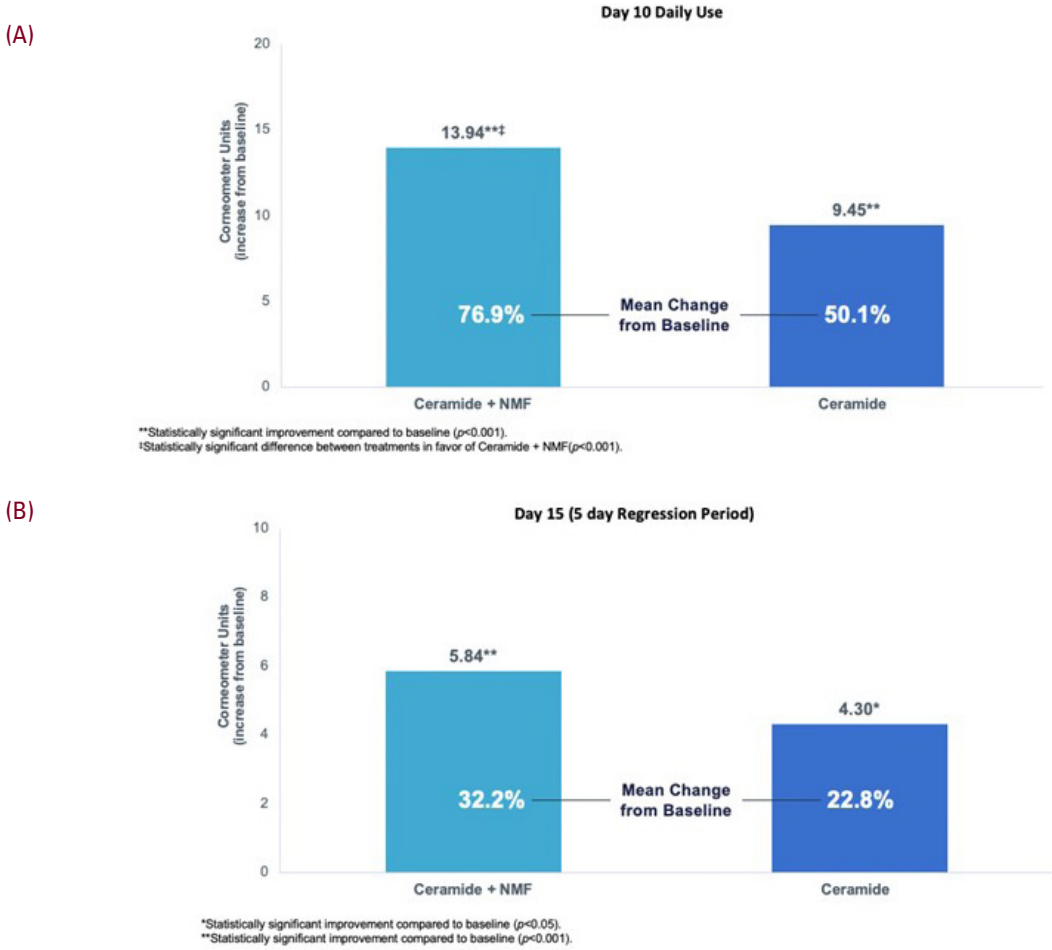
Some NMFs have long been used in dermatology, even before their mechanisms of action within the skin were well understood. For example, urea has been added to moisturizing creams since 1943 but cutaneous urea levels were not compared in healthy skin and skin affected by atopic dermatitis until 1966.[16,25] Moisturizers containing urea have been shown to improve barrier function and reduce TEWL; additionally, urea can reduce irritant reactions and bolster antimicrobial defenses in the skin barrier.[10,26,27] Urea can even act as an endogenous humectant, which can attract water in conditions of low humidity.[28] It has been hypothesized that the actions of urea may correlate with reduced keratinocyte proliferation and subsequent increases in corneocyte size.[10]

Lactate and lactic acid have also been in use as a moisturizing treatment for ichthyosis since the 1940s and are associated with superior improvement in signs and symptoms compared to lactate-free moisturizers.[16,29-31] As an alpha hydroxy acid, lactic acid has been shown to improve dry skin, influence skin cell renewal, improve winter dry skin, and have anti-aging effects.[10] Topical PCA has also been associated with beneficial reductions in dry skin signs and symptoms.[16]

Several active- and vehicle-controlled studies have evaluated an NMF-containing moisturizer with 5% urea (Eucerin Advanced Repair Lotion®, Beiersdorf).[1] In the vehicle-controlled study, the NMF moisturizer was compared with two vehicles (one containing lipids plus ceramides and the second enriched with urea and lactate) or untreated control in subjects with dry skin.[1] Subjects (N = 36), aged 51-76 years old, with Fitzpatrick skin types I-III applied treatment to their inner forearms twice a day in a double-blinded, randomized fashion for two weeks. Moisturization was assessed via skin hydration (corneometer) and barrier function (TEWL) at week 1 and week 2 of the study.[1] The study demonstrated progressive improvement from the most basic vehicle to vehicles with more hydrating ingredients added, ultimately leading to the best hydration observed with NMF moisturizer (Figure 4).[1] In addition, clinical grading results showed significant decreases in visible skin dryness and tactile skin roughness for subjects using the enriched vehicle lotion or the NMF moisturizer.

A double-blind study evaluated the skin hydrating abilities of an NMF cream compared to a ceramide-based cream.[32] In this head-to-head study, subjects (N = 35) applied either the NMF cream or the ceramide-based cream to the lower legs once daily for ten days with a five-day regression phase. Skin hydration

**FIGURE 5.** Clinical evaluation of skin hydration after (A) 10 days of daily moisturization and (B) after a 5-day regression period (no additional moisturization). From Baldwin et al.[32]




was evaluated by corneometry. At day 10, subjects receiving the NMF cream had a 76.9% increase in hydration compared to baseline ($P$<0.001), and subjects receiving the ceramide-based cream had an increase in hydration compared to baseline of 50.1% ($P$<0.001; Figure 5). Notably, subjects receiving the NMF cream retained more of the increased hydration from baseline (32.2%, $P$<0.001) than did subjects receiving the ceramide-based cream (22.8%, $P$<0.05) following the 5-day regression phase (Figure 5). The superior results with the NMF-ceramide cream were attributed to the inherent properties of NMFs in maintaining barrier function and reducing TEWL.

## CONCLUSION

In recent decades, scientific advances have led to a more detailed understanding of filaggrin processing, as well as the genetic/environmental factors that can affect both filaggrin and NMF levels and humectant activity. NMFs have an essential role in healthy skin and the lack of NMFs is associated with cutaneous disorders. Clinical data indicate that moisturizers that incorporate NMFs may be able to restore the hydration commonly lost in patients with skin barrier conditions, significantly better than ceramides alone.

## DISCLOSURES

Dr Baldwin has served as an advisor and speaker for Galderma, Bausch, Sun, Almirall, L'Oreal, La Roche-Posay and EPI, as well as an advisor and investigator to Sol-Gel Technologies Ltd. Dr Del Rosso has served as a consultant, investigator, and/or speaker for Abbvie, Almirall, Amgen, Arcutis, Bausch Health (Ortho Dermatologics), Beiersdorf, Dermavant, EPI Heath, Ferndale, Galderma, Incyte, JEM Health, LaRoche Posay, LEO Pharma, Lilly, Loreal, MC2 Therapeutics, Novan, Pfizer, Regeneron, Sanofi, Sente, SolGel, Sun Pharma, UCB and Unilever.

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