Review

Considering Phytosphingosine-Based Ceramide Formulations for Atopic Skin Care

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Abstract: This review provides an overview of the structural and functional features of key phytosphingosine-based ceramides (CERs), notably CER[EOP], CER[NP], and CER[AP], and their role in atopic skin health. Herein, we discuss how these indispensable stratum corneum (SC) lipids maintain skin barrier homeostasis and contribute to the skin’s barrier function in terms of its cohesiveness and resilience. We also consider the usefulness of CER[EOP], CER[NP], and CER[AP] in preserving skin hydration and protecting and/or repairing dry, itchy, or sensitive skin. Next, we explore how and to what extent an imbalance or inadequate amounts of CER[EOP], CER[NP], and CER[AP] contribute to the hallmark characteristics of atopic skin diseases like eczema. Furthermore, we discuss the importance of complementary SC resident lipids such as cholesterol (CHOL) and free fatty acids (FFAs), which are crucial for optimal CER function. Studies have shown that delivering topical CERs in balanced and optimal combination with CHOL and FFAs—while supporting and boosting the endogenous biosynthesis of CERs using ingredients such as niacinamide and lactic acid—helps relieve symptoms of atopic diseases to provide some measure of relief. Finally, we look at some emerging ingredients that can complement the science of CERs in healthy and diseased skin.

Keywords: ceramides; eczema; hydration; lipids; moisturizers; phytosphingosine; skin barrier; topical formulation

1. Introduction

The skin is the body’s primary defensive mechanism against exogenous pathogens and injury, and its proper and efficient functioning is dependent on a myriad of cellular structures and endogenous mediators working together in harmony [1–3]. When it comes to the outermost layer of the skin, the stratum corneum (SC) [2–4], it is the interplay between the layers of flattened, dead corneocytes and the SC lipids/lipid matrix surrounding those corneocytes that dictates not only the permeability of the skin (both to external insults and loss of internal moisture/hydration) but also the skin’s functioning when affected by chronic skin conditions such as eczema (atopic dermatitis (AD)) [2–4].

The key structural components of the SC lipid matrix—namely ceramides (CERs); cholesterol (CHOL); and free fatty acids (FFAs), also known as non-esterified fatty acids (NEFAs)—exist in a highly organized, specific combination to allow for the healthy functioning of the skin. Any disruptions to this combination, as seen in eczematous skin (e.g., alterations to absolute and relative quantities of CERs, CHOL, and FFAs; disturbed structure, organization, and behavior; or CER chain length distribution), can significantly alter the effectiveness of the skin barrier and exacerbate skin sensitivity and existing skin conditions. With respect to CERs, the specific subclasses including CER[EOP] (esterified ω-hydroxy fatty acyl phytosphingosine), CER[NP] (non-hydroxy fatty acyl phytosphingosine), and CER[AP] (α-hydroxy fatty acyl phytosphingosine), among others, are known...
to play crucial roles in skin hydration, barrier support and repair, as well as atopic skin functionality [1–5].

Herein, we review phytosphingosine-based CER[EOP], CER[NP], and CER[AP] as the principal repositories for the skin CERs’ behavior and profile (Figure 1) in healthy and diseased skin (specifically eczematous skin) in terms of their absolute quantities, physicochemical character, distribution, complex interaction with CHOL and FFAs, and organization within the SC in order to decipher their key structural and functional roles.

Furthermore, we discuss how alterations in CER[EOP], CER[NP], and CER[AP] native profiles can interfere with the skin’s barrier function by affecting its ability to preserve hydration and protect and/or repair dry, itchy, or sensitive skin. Finally, we discuss how applications of optimized CER-dominant topical formulations can help to improve disease-affected skin by delivering topical CER[EOP], CER[NP], and CER[AP] to the skin in a balanced combination with CHOL, FFAs, well-known CER boosters, including niacinamide, lactic acid, and phytosphingosine, and some infrequently used CER boosters such as ceramide–magnesium (CER-Mg) and ursolic acid.

2. The Composition of the Stratum corneum and the Importance of Ceramides in Skin Health

The outermost layer of the skin’s epidermis, the SC, or the so-called ‘dead layer’ [4], is composed of two discrete structural components, each distinctively related to the functionality of the SC [2,3]: (1) polygonal-shaped, fully differentiated, non-nucleated and dead keratinocytes known as corneocytes (considered as the SC ‘building blocks’), and (2) a lipid matrix (considered as the SC ‘cement mixture or glue mixture’) that fills the gaps between corneocytes in order to hold them in place [2,3]. In comparison with an average skin thickness of 1.2–1.3 mm [3], the SC is only 10–30 µm thick [2,6] and consists of approximately 15–20 highly ordered layers of interconnected corneocytes [2,7] intertwined within a complex mixture of lipids arranged in highly ordered and coherent multilamellar lipid sheets [2,3]. Corneocytes adhere tightly to each other through corneodesmosomes to form a barrier that is responsible for the skin’s mechanical strength and stiffness. This barrier not only protects us from a range of environmental stressors, especially those related

Figure 1. Phytosphingosine-based CER[EOP], CER[NP], and CER[AP] are among the key players indispensable for skin barrier function and health and for optimized skin care. Abbreviations: AP, α-hydroxy fatty acyl phytosphingosine; CER, ceramide; EOP, esterified ω-hydroxy fatty acyl phytosphingosine; NP, non-hydroxy fatty acyl phytosphingosine.
to external factors such as solar ultraviolet (UV) radiation, pollution, pathogenic microbes, and exposure to allergens and (harsh) chemicals [8,9], but also acts synergistically with the lipid matrix to prevent transepidermal water loss (TEWL) from the skin’s surface [2,10]. The lipid matrix nourishes the skin with its distinctive combination of lipids (e.g., CERs, CHOL, and FFAs) that effectively supports the skin’s protective and reparative barrier function and governs the permeability barrier properties of the SC [2]. Therefore, it is the absolute and relative quantities, physicochemical characteristics, distribution, organizational and structural synergy, and the interaction between corneocytes and the lipid matrix that together account for the multiple functions of the SC [1].

In reference to the SC chemical composition, proteins account for about 75–80% of the SC weight, with the remainder being 5–15% lipids (i.e., CERs, CHOL and its derivatives, and FFAs) and 5–10% water and other substances [3,11,12]. The SC lipids that exclusively make up the SC lipid matrix are unique among biological membranes in terms of their composition, structural organization, and functionality. It is a phospholipid-free mixture of polar and non-polar lipids, predominantly composed of three key components in approximately equimolar concentrations [13,14]. The three major physiological lipid types of the healthy SC lipid matrix are (1) CERs (about 45–50% by mass), (2) CHOL (25% by mass), and (3) FFAs (10–20% by mass). In addition, there are small amounts of CHOL derivatives, namely CHOL esters (10% by mass) and CHOL sulfate (about 2–5% by mass), which, in particular, seem to play a critical role in the overall structural organization of the SC lipid matrix, thus contributing to normal barrier function [5,15,16]. CERs, CHOL, and FFAs organized in multilamellar lipid sheets parallel to the corneocyte surfaces assemble within the lipid layers into domains presenting two different densities [13,17]: (1) a dense, tight orthorhombic (ORTHO) lateral packing that predominates in healthy skin, and (2) a less dense and thus looser hexagonal (HEX) packing that predominates in diseased skin [13], indicating that the efficient filling of SC interstices is absolutely crucial for preventing the penetration of ‘external intruders’, as well as inhibiting excessive TEWL from the skin’s surface [17]. In the lamellar organization (specifically in healthy skin), the lipids are arranged predominantly in two lamellar phases with different periodicity. If the lipids’ lamellar-repeat spacing is in 6 nm intervals, the alignment is identified as a short periodicity phase (SPP). On the other hand, if the lipids’ lamellar-repeat spacing is in 13 nm intervals, the alignment is identified as a long periodicity phase (LPP) [18,19]. However, the SC lipids can also form a disordered liquid (LIQUID) state, where the molecular arrangement is greatly disturbed due to the randomly placed appearance of the CHOL molecule, rather than its periodic appearance, which is required to achieve a regular and stable arrangement [20]. From neutron diffraction studies, the presence of CER[NP] and CER[AP] in a specific structure—having three versus four hydroxyl groups (–OH) in the head group [21–23]—appeared to be crucial for the formation of the SPP and for the overall integrity of the barrier function of the SC [21,22]. Furthermore, a novel lipid organization (the packing of CERs, CHOL, and FFAs against and around each other) model centered on CERs as the predominant lipid type of the SC lipid matrix, based on hydrophobic matching and segregation, has been proposed as the optimal model in terms of packing of the SC lipids, with the FFA chain lengths matching the CER fatty acyl chains and CHOL matching the CER sphingoid chains [24]. Therefore, the highly organized lipid environment of the SC is imperative for maintaining the skin’s equilibrium and fortifying its protective barrier [13,20,24–33].

The ongoing emphasis on barrier repair management and/or therapy to restore barrier properties and clinical condition of skin after the disruption of normal, healthy skin [34] has revealed that most, if not all, of the barrier’s protective function comes from the SC (e.g., for example, altered corneocyte structure leads to a leaky and thus impaired barrier) and its lipid matrix composition and organization [13,34,35]. When the ratios or structural/conformational rearrangements of the SC lipids (e.g., CERs:CHOL:FFAs) are interrupted or altered in any shape or form, barrier function is rapidly compromised. These barrier alterations and/or disturbances give microbes, allergens, and substances of concern
unrestrained entrance to the deeper layers of the skin, ‘driving’ insufficient hydration, improper desquamation, and excessive inflammation and clinical scaling, thus resulting in (extremely) dry, flaky and itchy skin attributed to common skin conditions including eczema [2,5]. Therefore, the approaches aimed at the replenishment of the depleted or disturbed lipids (for example, the overall CER quantity; individual CER subclasses including CER[EOP], CER[NP], and CER[AP]; and the overall CHOL and/or FFAs quantity) or enhancing their presence and function by introducing their complementary and/or boosting ingredients are crucial in order to reinstate optimal skin barrier function [2].

Many current management and/or therapeutic approaches known as CER-dominant formulations include a combination of the key CER subclasses, namely phytosphingosine-based CER[EOP], CER[NP], and CER[AP], as well as CHOL and FFAs. For example, double-CER combination containing CER[EOP] and CER[NP], and triple-CER combination containing CER[EOP], CER[NP], and CER[AP]) [36–40] combined with (1) CHOL and/or FFAs [37–40]; (2) conventional moisturizers (e.g., glycerin) [37–40]; (3) frequently used CER precursors/promoters/boosters, including niacinamide, lactic acid and phytosphingosine [37–40]; and (4) sporadically used CER-Mg [41] and ursolic acid [2] can complement the science of CERs and ‘prompt’ skin into making CERs in order to initiate or more likely to accelerate skin barrier recovery and repair [14]. Topical formulations that contain a complete and equimolar physiological mixture (1:1:1) of triple-lipid CERs:CHOL:FFAs are not harmful to disturbed or compromised skin; however, incomplete or imbalanced mixtures can potentially aggravate underlying barrier defects, presumably by destabilizing the functional properties of the skin’s lipid-based barrier [14]. Lately, triple-lipid topical formulations that contain a 3:1:1 optimal molar ratio of CERs:CHOL:FFAs (preferably with longer chains) have been extensively used to maintain healthy skin barrier or more often to accelerate disease-affected skin barrier recovery and repair, thus improving skin barrier health in a timely and effective manner [14].

3. Characterizing the Key Skin Ceramides

3.1. Origin and Nomenclature

All CERs are usually synthesized by three pathways: (1) the de novo pathway, (2) the pathway activating sphingomyelinase and β-glucocerebrosidase, and (3) the salvage pathway. However, the de novo pathway is the major mechanism of CER biosynthesis in the epidermis, where CERs are synthesized by amide bond-mediated interactions between fatty acids (FAs)/fatty acyl chains and sphingoid bases (SBs) [4,42] (Figure 2A). The endoplasmic reticulum (ER) of the stratum spinosum layer within the SC is the primary site of the biosynthesis of CERs. The CERs produced in the ER are converted into glucosylCERs:CHOL:FFAs not harmful to disturbed or compromised skin; however, incomplete or imbalanced mixtures can potentially aggravate underlying barrier defects, presumably by destabilizing the functional properties of the skin’s lipid-based barrier [14]. Lately, triple-lipid topical formulations that contain a 3:1:1 optimal molar ratio of CERs:CHOL:FFAs (preferably with longer chains) have been extensively used to maintain healthy skin barrier or more often to accelerate disease-affected skin barrier recovery and repair, thus improving skin barrier health in a timely and effective manner [14].
stands for CER (non-hydroxy fatty acyl phytosphingosine); and CER[AP] (orange-shaded box) stands for CER (α-hydroxy fatty acyl phytosphingosine) \[6,18,22,45,46,48\] (Figure 2B).

3.2. Ceramide Identity, Functional Diversity, Complexity, and Specificity

Each of the many CER subclasses (e.g., CER[EOP], CER[NP], and CER[AP]) is characterized by its distinctive identity; however, each displays extreme complexity and polymor-
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Phic diversity due to a multitude of variable substructures, namely fatty acyl chains/FAs and SBs [44,49] (Figure 2A,B). It was initially believed that there were only nine distinct subclasses of CERs, namely the products of three species of FAs (N, A, and O) and three SBs (S, P, and H) (Figure 2B). However, later, this number increased to 12 and has continued to increase in recent years, now sitting at least 20 with the discoveries of dihydrosphingo-
sine (DS) [50]. Of these, at least 16 occur in the human SC [51]; however, the variability of fatty acyl chains/FAs and SBs significantly broadens the landscape of potential CER structures—indeed, hundreds or even thousands of different CER subclasses have been identified so far [5,42,52–54].

Both FAs and SBs can considerably differ in carbon chain length, degree of unsaturation, and number and position of –OH groups [47,52]. SBs are typically represented as having a great variability in chain length (represented by m) (Figure 2B) with aliphatic amines that have two or three –OH groups [47]. Furthermore, it seems that both SBs’ chain length and the number of –OH groups (hydroxylation pattern) are important for the integrity of the SC barrier function and retaining skin hydration [22,23]. FAs themselves are a group of chemical compounds with notable heterogeneity; thus, it is difficult to categorize them unequivocally. However, there are two commonly used classifications of FAs: (1) the first concerning the presence and number of double bonds—saturated (no double bonds present), monounsaturated (a single double bond), and polyunsaturated (multiple double bonds); and (2) the length of the carbon chain in the molecule (represented by n) (Figure 2B)—short chain (C2–C4), medium chain (C5–C11), long chain (C12–C20), very long chain (C21–C25), and ultra-long chain (>C25) [47]. Among all these different FAs, very long-chain FAs and ultra-long-chain FAs are among the main components of CERs responsible for the rigidity and impermeability of membranes, forming the chemically and mechanically robust SC barrier [47]. However, (ultra) very long FFAs (C32–C36) occur in low amounts [55]. All the aforementioned differences and alterations in the composition, quantity, structural organization, and functionality of CERs have a great potential to directly and negatively influence barrier properties and integrity [3,47]. The presence of long-chain CERs is strongly involved in the maintenance of barrier function, whereas an increase in short-chain CERs is commonly associated with barrier impairment [6,56]. The molecular composition of all CER subclasses, including phytosphingosine-based CER[EOP], CER[NP], and CER[AP], within the human SC is quite specific and unique, making them indispens-able (in their own right and/or in a combination with other SC lipids) for the integrity of SC barrier function [44,49].

3.3. Ceramide Conformational Features and Interactions with Cholesterol and Free Fatty Acids

As mentioned previously, the lipid lamellae consist of a complex, heterogeneous mixture of lipids that self-assemble into a multilayer arrangement. Precursor molecules, including sphingomyelins, glucosylCERs, phospholipids, and CHOL, initially form lipid stacks within lamellar bodies. These stacks later form lamellae in the extracellular space of the SC [53]. Lipid molecules are held together with non-covalent van der Waals forces between the non-polar hydrocarbon chains and hydrogen bonding between polar head groups, allowing for some movement within the lamellae [53,57]. The restructuring of the lipid molecules into lamellae expels excess water such that the only remaining water is bound to polar head groups, in a manner like ligand–receptor binding [58]. It is believed that there is no free water in the lamellae [53].

There are two primary packing conformations within the lipid lamellae: (1) orthorhom-
bic packing (ORTHO) and (2) hexagonal packing (HEX). The unit cell/subcell of each of these conformations is shown in Figure 3. A third conformation, the liquid crystalline (LIQUID) conformation (Figure 3), also occurs, but there is no lateral organization and therefore, no defined unit cell/subcell in this conformation [53]. Of these, the ORTHO conformation involves the tightest packing arrangement of lipid molecules, and for this reason, it is the preferred conformation to maximize barrier integrity and minimize TEWL [59]. It is important to note that although our discussion is primarily focused on CERs, the system
also includes CHOL and FFAs, which are also indispensable for the characteristic SC organization as they are likely to participate in the ORTHO lattice, provided their chain lengths are compatible [53]. The HEX conformation adopts a slightly looser (less dense) packing arrangement and allows for some rotational mobility about the z-axis (where the surface of the lamellar sheet lies on the x and y axes) but is also more permeable. The LIQUID conformation is the most disordered, with both rotational and translational mobility, and, if present to a high degree, results in the breakdown of the skin barrier integrity [60].

Figure 3. Lateral organization of stratum corneum (SC) lipids from most to least densely packed, namely Qortho (ORTHO), Hexagonal (HEX), and Liquid-crystalline (LIQUID) structures, showing molecular distances (in nm nanometers) within the unit cells/subcells [13,20,42,53,54].

Interactions between CERs, CHOL, and FFAs within the lipid layers are complex and not completely understood; however, it appears that in the process of hydrophobic matching and segregation, CHOL molecule chains match with CER SB chains, while CER fatty acyl chains match with FFAs in order to minimize the total potential energy of the configuration [24]. CHOL and FFAs alone do not mix in the absence of CERs or other sphingoid lipids [61], and CHOL plays an important role in making the packing tighter, and it is also involved in the formation of the SPP and LPP lipid organization, thus minimizing packing defects. Interestingly, a stacked monolayer arrangement, in which extended CERs bridge lipid layers, appears to be equally energetically favorable but is not observed in practice. This may be due to the lipid layer structure being carried through from precursor lamellar bodies during the formation of the lamellae [24]. CER head groups, the extent of hydrogen bonding between them, and the specific chain length structures of the CERs all have an effect on LPP/SPP behavior, packing density, and miscibility [62]. Interactions between specific CER head groups can be approximated through various computer models [62], but it can be speculated that increased amounts of CERs with high H-bonding potential (such as CER[EOP], CER[NP], and CER[AP]) may increase resilience to lipid changes that induce changes in packing conformation or LPP-to-SPP transition.

3.4. CER[EOP]

CER[EOP] (Figure 4) is the product of an esterified ω-O-hydroxy fatty acyl chain [EO] and phytosphingosine [P] (Figure 2B). It contains three –OH groups in the SB portion. Esterified ω-hydroxy CERs, including CER[EOP] and CER[EOS], are specific to the epidermis [51] and are generally protein-bound to the corneocyte envelope (a shell that surrounds each corneocyte), where they form a hydrophobic layer [53]. When protein-bound, ω-OH-CERs are attached via an ester link of the terminal –OH group (at R4 position) (Figure 2A) to the structural protein involucrin [63]. Structurally, CER[EOP] and CER[EOS] are almost identical, with EOP only having one additional –OH group on the sphingoid backbone, making it slightly larger and more polar. Both CER[EOP] and CER[EOS] are found in lower concentrations in atopic skin [64]. These CERs contain acyl groups derived from linoleic acid and are known to play an important role in the formation and stabilization of the LPP of the lamellar sheets [65]. While CER[EOS] is thought to be more important for LPP formation [66], based on an in vitro study [65], increased CER[EOP] also promoted the formation
of the LPP. However, raising CER[EOP] beyond normal levels or artificially replacing all CER[EOS] with CER[EOP] resulted in the breakdown of the LPP and the formation of crystalline CER[EOP] domains [65]. While precise effects remain unclear, current evidence supports the notion that esterified ω-hydroxy CERS promote LPP formation when in the correct ratio and with sufficient diversity of chain lengths.

![Molecular structures of phytosphingosine-based CER[EOP], CER[NP], and CER[AP] and their –OH groups](image)

**Figure 4.** Molecular structures of phytosphingosine-based CER[EOP], CER[NP], and CER[AP] and their –OH groups [23,44,45,48]. Abbreviations: AP, α-hydroxy fatty acyl phytosphingosine; EOP, esterified ω-hydroxy fatty acyl phytosphingosine; n, a range of carbon atoms—chain length variation; NP, non-hydroxy fatty acyl phytosphingosine.

Even though the percentage (represented as the mean percentage of total CERS) of the phytosphingosine-based CER[EOP] in the human SC is on the lower side (approximately 0.9–2.7%) [46] (Figure 2B), it seems that CER[EOP] is critical for the integrity of the SC lipid matrix. CER[EOP] with its long chain length acts as a connector between the SC multilamellar lipid sheet/lipid layer architecture and plays an important role in the organization of lipids (lipid matrix) in the SC [49]. As CERS, including CER[EOP], play an important role in corneocyte envelope formation, natural (or relatively higher levels) of CER[EOP] exhibit a positive correlation with good skin health status, especially with acidic pH, whereas reduced levels of CER[EOP] have a negative correlation with TEWL and strongly reflect the degree of skin barrier defects [67] in atopic skin [18]. Thus, it is crucial to maintain normal levels of CER[EOP] in the skin. Overall, skin-identical phytosphingosine-based CER[EOP], CER[NP], and CER[AP] (which are usually present in the R configuration, the natural configuration observed in the skin) contain more –OH groups in their polar head group than other CERS, meaning that they could form more hydrogen bonding with the surrounding CERS and SC lipid components. The number of –OH groups in the head group of the CERS appears to play a critical role in skin health for the integrity of the SC barrier function and retaining skin hydration. Furthermore, it is also crucial for the stability of a dense lateral packing that predominates in healthy skin [2,13,23]. For example, one study demonstrated that CER[EOP] and CER[NP] acted synergistically in an emulsion to improve skin hydration and reduce TEWL in skin pre-treated with the irritant sodium lauryl sulfate (SLS), an effect that would have great potential in combating dry skin and reducing itch [68]. The extra –OH group and ‘bulkier’ CER[EOP] polar head group structure make an important contribution to the behavior and structure of the SC lipid matrix as it strongly influences the lamellar repeat distance and lipid chain packing [49]. Thus, when present in the correct ratio and with sufficient diversity of fatty acyl and/or sphingoid chain lengths, CER[EOP] plays an indispensable role in the formation and stabilization of the LPP of the SC lamellar sheets [65].

3.5. CER[NP]

CER[NP] (Figure 4) and CER[NH] are the two most abundant CERS in human SC [51], at approximately 22.1–24.2% (by mass) and 14.5–23.7% (by mass), respectively (Figure 2B),
based on measurements from the inner forearm [5]. Although the specific functions of these CERs are not fully understood, both play an important role in skin barrier formation and function. In atopic skin, both lesional and non-lesional, the ratio of CER[NP] to CER[NS] is significantly decreased, compared to healthy skin [69]. A similar change was observed in the ratio of CER[NP] to CER[AS], and these effects exhibited a strong correlation with increased TEWL, an indication of a weakened skin barrier [69]. Some other studies have also shown decreased levels of CER[NP] in patients with eczema [2,70]. One recent study demonstrated that a lipid mixture enriched with CER[NP] and FAs could help recover barrier function impaired by topical corticosteroid use [71]. Furthermore, CER subclasses including both CER[NP] and CER[AP] play key roles in the morphology of the lipid layers for the proper formation of stable SC multimellar lipid sheets/structures [21].

3.6. CER[AP]

With four –OH groups in its SB head unit, CER[AP] (Figure 4) is the most polar CER, giving it a very strong hydrogen bonding potential. Skin conditions such as eczema, where a weakened skin barrier is a key feature, typically exhibit an increased proportion of sphingosine at the expense of phytosphingosine, which reduces the strength of hydrogen bonding throughout the lipid matrix [72]. Also, it was reported that although an artificial CER[EOP-AP] model favored the formation of lateral lipid packing, there was strong hydrogen bonding and reduced barrier permeability, indicating that although the ORTHO conformation is preferred, some degree of unfavorable HEX conformation appears to be present; thus, under specific circumstances, the coexistence of HEX packing cannot be ruled out from the lateral lipid organization [72]. Other studies have shown that topical products containing a CER blend with CER[AP] can help restore barrier function in people with eczema-prone skin [38,39,73].

4. Altered Ceramide Levels in Eczematous Skin

Altered CER levels have been observed in many common skin diseases, indicating the delicate nature of the lipid balance within the skin barrier and its importance for maintaining normal function. For example, decreased levels of total CERs are a common feature of eczema, psoriasis, lamellar ichthyosis, and xerosis [2], but the involvement of specific CERs and its derivatives, including CER[EOP], CER[NP], and CER[AP] (or other SC lipids), varies [2]. One of the most widely studied skin conditions with regard to CER involvement is eczema. Eczema is a chronic relapsing inflammatory skin disease characterized by a broad spectrum of clinical manifestations such as erythema, dryness, and intense pruritus/itch [74]. It affects 15% to 20% of children and 1% to 3% of adults, and its prevalence is increasing rapidly, especially in developed countries [75]. Eczema interferes with sleep and other activities, significantly affecting the quality of life of the patient and their family [76]. The pathogenesis of eczema is multifactorial, involving genetic, immunologic, and environmental factors that lead to a dysfunctional skin barrier and dysregulation of the immune system [74]. Widespread regions of dry itchy skin are one of the most prominent clinical features of eczema [74]. Involuntary scratching provoked by severe itching (referred to as the itch–scratch cycle) can lead to a physical disruption of the SC, thereby exacerbating the intrinsic weakness in the barrier. A damaged skin barrier has been found in patients with eczema in parallel with disease severity, with clinically uninvolved skin also exhibiting abnormal barrier function [77,78]. This results in excessive TEWL [79] and predisposes the skin to the development of microfissures and cracks in the SC, which favors the entry of allergens and microorganisms [80]. A variety of factors associated with eczema directly contribute to impaired barrier function, including a decrease in some CER subfractions in the SC, an altered ratio of the lipid composition of the SC intercellular lipid matrix, altered activity of some enzymes, and defective filaggrin production. Since filaggrin brings together structural proteins in the cells of the SC to form compact and cohesive bundles and flattens those cells to create a strong barrier, its
defective production strongly correlates with genetic mutations present in some patients with eczema [81].

CER deficiency has been clearly linked to eczema, with many studies now showing decreased overall CER levels in both lesional and non-lesional atopic skin [82–84]. The deficiency is not uniform, however, and while some CERS decrease significantly, others are found in proportionally higher amounts (Figure 2B). Multiple studies [64,70,83,85–87] have shown a relative decrease in CER[EOP], CER[NP], and CER[EOS] but increases in CER[NS], CER[AS], and CER[NH] (Figure 2B), although it should be noted that not all studies were in agreement, indicating either limitations in current methodologies or the complexity and multifactorial nature of this disease. The composition of the lipid matrix is not the only observable change in atopic skin. Other studies [88,89] have found that patients with atopic skin conditions have a higher proportion of short-chain lipids and reduced long-chain lipids [88,89]. This in turn shifts the lipid packing equilibrium away from the more favorable ORTHO conformation and toward the unfavorable HEX packing, resulting in a weakened skin barrier and increased TEWL [90]. The epidermis of atopic skin also exhibits reduced levels of protein-bound ω-hydroxy CERS compared to healthy skin. Macheleidt and coworkers [63] measured the amount of protein-bound ω-hydroxy CERS in healthy forearm epidermis and compared this with non-lesional and lesional eczematous skin, which decreased from 46–53% to 23–28% and 10–25% by weight, respectively [63]. Thus, the insufficiency of SC CERS [83], including phytosphingosine-based CER[EOP], CER[NP], and CER[AP], has been identified as a key etiological factor in atopic skin characterized by dryness, roughness, scaliness, decreased hydration, pruritus, increased TEWL, and impaired skin barrier function and integrity [18].

5. Ceramide-Dominant Skin Care Evolution for Skin Barrier Maintenance, Recovery and Repair

The management of eczematous skin in both adults [91] and children (including neonates and infants) [92] is mainly aimed at reducing signs and symptoms (e.g., flaky, dry, irritated, and itchy skin) of the disease and preventing/reducing recurrence while maintaining the skin hydration [91,93,94]. The most common approach is to improve skin barrier function with the regular use of conventional moisturizers that contain (1) emollients (substances that help smooth, soften, and lubricate the skin as well as increase moisture levels in the skin) such as light liquid paraffin; (2) humectants (substances that act like molecular sponges that attract and hold water in the outer layers of the skin) such as glycerin; and (3) occludents (substances that form a near-waterproof film on the skin that keeps water in, reducing TEWL) such as petrolatum [40,91] and are free from all potential allergens or irritating ingredients [91,93]. In contrast to conventional moisturizers [95,96] that can help maintain skin’s barrier hydration and integrity, topical formulations containing a mixture of the three main SC lipids consisting of CERS:CHOL:FFAs in optimal proportions (3:1:1) [97] can help to restore balance of the epidermal barrier (including SC barrier) lipids, therefore making those CER-dominant formulations superior to most non-CER containing ones [14,34].

More recently, CER-dominant moisturizers that contain a combination of conventional moisturizing components, CHOL and FFAs, as well as specific CER subclasses including phytosphingosine-based CER[EOP], CER[NP], and CER[AP], have been developed [37,73,98]. Such CER-dominant physiological lipid-based moisturizing cleansers and/or creams can help to ameliorate the signs and symptoms of (mild to moderate) eczema in adults in about 28 days compared to the placebo [37]. Also, these (or similar) CER-dominant topical formulations safely restore ‘optimal’ skin permeability without compromising barrier integrity and function [37]. Furthermore, a similar CER-dominant lotion and cream that contains CER[EOP], CER[NP], and CER[AP] exhibited superior levels of skin moisturization (by forming a layer on the skin surface) and effectively reduced the signs of skin dryness [38,39] of eczema-prone skin [73,99] compared to controls. These results have notable implications for clinical practice given the conventional
use of ‘undecorated/straightforward’ moisturizing topical formulations (e.g., cleansers, lotions, and creams) for the management of dry, itchy [38,39], eczema-prone sensitive skin [73,99]. Given that irritants are important triggers for eczema lesions, the effects of the CER-containing [100] and, more specifically, CER-dominant topical formulations on the skin barrier could potentially help maintain and/or repair skin, reduce symptom intensity, skin dryness, and a propensity for inflammatory lesions, thus diminishing the burden of managing eczema [73,99].

6. Considering Ceramide-Dominant Topical Skin Care Formulations

Adding CERs [14,34] and/or even adding CER boosters such as niacinamide [39,40], lactic acid, phytosphingosine [37,38,40], CER-Mg [41], and ursolic acid [2] to conventional moisturizers or making CER-dominant moisturizers similar to natural skin lipids has beneficial effects, as these types of moisturizers act as a barrier repair, formulated to mimic the natural CER composition found in healthy skin [14]. Therefore, depending on the lipid type and its concentration (i.e., CER, CHOL, and FFAs), as well as the CER subclasses present and their proportions in the mixture, the skin barrier recovery either slows, proceeds as usual, or accelerates [14] (Figure 5). These findings imply that topically applied CER, together with CER boosters integrated into CER-dominant topical formulations, can augment SC endogenous CER levels and thus ameliorate barrier integrity more efficiently [2]. Therefore, CERs are most effective when combined with other skin-replenishing ingredients like CHOL, FFAs, conventional moisturizers, and CER boosters in order to deliver a positive impact on barrier homeostasis [14,40] (Figure 5).

<table>
<thead>
<tr>
<th>Evolution of CER-dominant topical formulations</th>
<th>Impact on skin barrier homeostasis</th>
</tr>
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<tbody>
<tr>
<td><strong>1. Traditional/Conventional formulations (without CERs)</strong></td>
<td>Maintains and/or improves barrier integrity</td>
</tr>
<tr>
<td>Using a combination of emollients (e.g., light liquid paraffin), humectants (e.g., glycerin) and occlusants (e.g., petrolatum)</td>
<td></td>
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| **2. Prototypical CER-dominant formulations** | |
| Using a combination of CERs, FFAs and CHOL: | |
| - Triple moisturising system | Maintains and/or improves barrier integrity |
| - Single lipid species | |
| - Dual lipid species | |
| - Tripe lipid species (CERs/CHOL/FFAs equimolar ratio 3:1:0) | |
| - Triple lipid species (CERs/CHOL/FFAs optimal ratio 3:0:1) CER-dominant (Phytosphingosine-sodium CERs + EOP + NT) + AP | |
| **3. Emerging CER-dominant formulations** | |
| Using a combination of emollients (e.g., light liquid paraffin), humectants (e.g., glycerin) and occlusants (e.g., petrolatum) | Maintains and/or improves barrier integrity |
| - Triple moisturising system | |
| - Physiological lipid dominant moisturisers | Accelerates barrier recovery and repair |
| Triple lipid species (CERs/CHOL/FFAs optimal ratio 3:0:1) CER-dominant | |
| - CER boosters | |
| Using a combination of CER boosting ingredients (e.g., niacinamide, lactic acid, CER-Mg, ursolic acid phytosphingosine) | |

**Figure 5.** The evolution of CER-dominant maintenance, recovery, and barrier repair topical formulations and their impact on skin barrier homeostasis. Abbreviations: AP, α-hydroxy fatty acyl phytosphingosine; CER(s), ceramide(s); CHOL, cholesterol; EOP, esterified ω-hydroxy fatty acyl phytosphingosine; FFA(s), free fatty acid(s); NP, non-hydroxy fatty acyl phytosphingosine.

6.1. Niacinamide

Niacinamide (also known as nicotinamide or vitamin B3) serves as a precursor in the synthesis of the nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, which act as coenzymes in many biochemical reactions [101,102]. When used on the skin, niacinamide helps improve several skin characteristics, including the appearance
of fine lines and wrinkles, pore size, and skin texture [103]. Niacinamide also helps maintain moisture levels in the SC, supporting barrier function, and it may help counteract some of the harmful effects of UV radiation [103]. For example, niacinamide (and its derivatives) is able to improve skin barrier functions by stimulating the de novo biosynthesis of all CERs (by 4–5 fold), FFAs (by 2.3 fold), and CHOL (by 1.5 fold) attributed to the upregulation of serine palmitoyltransferase activity—the rate-limiting enzyme in sphingolipid synthesis [101]. Moreover, niacinamide was shown to significantly decrease TEWL and effectively increase SC hydration in atopic dry skin when compared to white petrolatum [102]. In randomized, controlled, comparative studies of the SC integrity, moisturizers containing niacinamide in combination with glycerin yielded more rapid and sustained improvement in dryness and SC barrier than conventional moisturizers containing predominantly various levels of lipids (e.g., petrolatum, mineral oil, etc.) [104]. Therefore, topical formulations that contain niacinamide go beyond skin moisturization to improve the integrity and elasticity of the SC; their application results in enhanced skin benefits over time [104].

6.2. Lactic Acid

Lactic acid is an alpha-hydroxy acid (AHA) and a naturally occurring humectant in the SC, where it is a component of the skin’s natural moisturizing factor (NMF) at a level of about 12% [2,95]. Lactic acid and its salt, sodium lactate, have been shown to increase water-holding capacity and extensibility of skin [95]. After the treatment of the skin, it was found that lactic acid increased the levels of SC CERs in keratinocytes. The increase in CER biosynthesis was associated with the metabolism of lactic acid to acetyl CoA, which is utilized as a carbon source for lipid biosynthesis [105]. Another study showed that a lotion containing 12% lactic acid or lactate reduces the severity of dry skin [106]. Lately, a lotion containing 15% lactic acid, and CER[EOP], CER[NP], and CER[AP] provided a statistically significant and clinically meaningful improvement in desquamation, resulting in enhanced moisturization as well as improved texture and appearance of dry skin [38]. Therefore, from these results, it can be concluded that lactic acid can be used in topical formulations to stimulate de novo CER biosynthesis [107], thus leading to increased SC CER levels, which result in a superior lipid barrier and a more effective resistance against dryness [105].

6.3. Ceramide–Magnesium (CER-Mg)

In a recent study [41] the efficacy of a CER-Mg cream was compared side by side with two other creams, which are often used in the treatment of mild and moderate eczema: (1) a low-potency topical corticosteroid (containing 1% hydrocortisone acetate) and (2) a commonly used over-the-counter emollient, also known as cold cream [41]. This CER-Mg cream, which contains CER[EOP], CER[NP], and CER[AP] and a complex of Mg and zeolites (structurally ordered minerals), was found to be more effective in improving skin hydration and maintaining levels of NMF than hydrocortisone or emollient [41]. Even with such encouraging findings, the main question that arises from this study is whether—and to what extent—each of these individual components (e.g., CER subclasses and Mg) can beneficially influence the skin barrier, realizing that not only the amount but also their balance is crucial for the skin barrier [41]. One potential answer is that the penetration of CERs through the impaired skin barrier is enhanced in eczema, thus enhancing their efficacy in improving the skin barrier [41]. An alternative answer is that the effectiveness of such CER-Mg cream derives from Mg itself, which is known to be involved in the biosynthesis of CERs, where Mg ions are required for the sphingomyelinase enzyme activity [108]. However, it is still not clear if the effect of the CER-Mg cream could be assigned to the presence of CERs alone, Mg alone or a combination of Mg and CERs, or even some other constituents (e.g., conventional moisturizers) in the CER-Mg cream, such as glycerin [41]. In a different study, significant improvement in skin barrier properties (i.e., decreased TEWL, increased hydration, and reduced skin roughness and erythema) was observed when patients soaked in 5% dead sea salts (rich in Mg) daily compared with tap water alone [109]. Nevertheless, CER-Mg topical formulations may offer an alternative
maintenance approach, leading to improved adherence to eczema management, as well as a non-steroid alternative for the treatment of mild-to-moderate eczema by improving clinical symptoms and restoring the skin barrier [41].

6.4. Phytosphingosine

Phytosphingosine is one of the five major sphingoid backbones found in CERs in human skin [3,6,18,43–47]. Among these sphingoid backbones, phytosphingosine is somewhat skin-specific, as it is rarely found in other human organs [110]. In addition, phytosphingosine-based CERs such as CER[NP] and CER[AP] are among the most abundant CER subclasses present in human SC [46]. In addition, a few CER subclasses containing a specific fatty acyl chain and phytosphingosine, for example, phytosphingosine-based CER[EOP], CER[NP], and CER[AP], have been extensively used for the development of moisturizers formulated specifically for the management of mild-to-moderate eczema by improving skin barrier function and protecting against irritation in patients with dry, eczema-prone skin [36,38–40,73,99].

6.5. Ursolic Acid

Ursolic acid is a naturally occurring, non-toxic triterpenoid found in a variety of medicinal plants [2]. When incorporated into liposomes, ursolic acid can produce changes in human skin cells that are indicative of anti-aging effects [111]. Firstly, ursolic acid was found to stimulate collagen production in cultured dermal fibroblasts by reducing cell differentiation markers [111]. Secondly, the treatment of the forearms of human volunteers with a lotion containing 0.3% or 1% ursolic acid liposomes resulted in an induction of CERs, with more increased levels of hydroxy CERs than of non-hydroxy CERs [2,111]. Perhaps ursolic acid has the potential to be used in CER-containing and/or CER-dominant topical formulations to either maintain, boost, or even restore skin CER content.

7. Conclusions and Future Perspective

Skin CERs are heterogeneous and complex lipid entities that are fundamental for maintaining skin barrier function. Barrier dysfunction in skin conditions and diseases including eczema occurs as a result of alternative pathophysiology and diverse changes to skin lipids, including phytosphingosine-based CER levels and their composition, structure, organization, and function. Many current barrier-protective CER-based formulations incorporate phytosphingosine-based CERs since when applied exogenously, they may help to maintain or restore skin CER levels, which in turn may help improve skin barrier function through reduced TEWL and increased skin hydration. As CERs become more ubiquitous, it is essential to understand not only their importance to skin functionality but also find the best way to correctly incorporate them into skincare products—and subsequently into the existing SC membrane/lipid structures—in order to support and maintain proper barrier function, not hinder it. With this understanding, in the near future, it may be possible to specifically formulate a wide range of atopic skincare products with sufficient (appropriate concentrations) CER diversity in a balanced, optimal combination with conventional moisturizers, CHOL, FFAs, and CER boosting ingredients for a specific condition or disease. It seems that the best approach is to not only supply the skin with the correct CER subclasses in the correct ratio to support barrier function and repair but also to support endogenous production of CERs by including complementary ingredients such as niacinamide and lactic acid.

Although CERs play a crucial role in the integrity of SC, further research and stronger scientific evidence are fundamental to clearly pinpoint why and under what conditions CER-based formulations could be more effective than formulations lacking CERs.

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supervision of the manuscript preparation. All authors have read and agreed to the published version of the manuscript.

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**Abbreviations**

A, α-hydroxy fatty acyl chain/fatty acid; AD, atopic dermatitis; CER(s), ceramide(s); CER[AP], α-hydroxy fatty acyl phytosphingosine; CER[EOP], esterified ω-hydroxy fatty acyl phytosphingosine; CER-Mg, ceramide–magnesium; CER[NP], non-hydroxy fatty acyl phytosphingosine; CHOL, cholesterol; DS, dihydro sphingosine; EO, esterified ω-hydroxy fatty acyl chain/fatty acid; FA(s), fatty acid(s); FFA(s), free fatty acid(s); H, 6-hydroxyphosphoglycerine; HEX, hexagonal lateral structure/organization; LIQUID, liquid crystalline lateral structure/organization; LPP, long periodicity phase; N, non-hydroxy fatty acyl chain/fatty acid; NMF, natural moisturizing factor; O, ω-hydroxy fatty acyl chain/fatty acid; ORTHO, orthorhombic lateral structure/organization; P, phytosphingosine; S, sphingosine; SB, sphingoid base; SC, stratum corneum; SD, 4,14-sphingadiene; SPP, short periodicity phase; TEWL, transepidermal water loss.

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