RESEARCH PAPER

A comprehensive review on ceramide cosmeceutical cream for treatment of atopic dermatitis, psoriasis, and Netherton's syndrome and their regulations.

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ABSTRACT

The largest organ in the human body, the skin, keeps the body hydrated, maintains homeostasis, and blocks out toxins. The stratum corneum, the outermost layer, is characterized as a structure in which the extracellular lipid matrix between keratinocytes serves as the "mortar" and keratinocytes (KCs) as the "bricks." The skin barrier serves many unique purposes. The stratum corneum (SC) creates the physical barrier by combining multiple levels of complex defense systems, such as the skin microbiome that regulates the growth of pathogens and the acidity buffering capacity that shields us from chemical aggressions. Atopic dermatitis (AD), sometimes referred to as atopic eczema, is a clinically characterized, inflammatory, chronic condition that primarily affects the skin and significantly impairs the quality of life for those who suffer from it. Netherton's syndrome's clinical spectrum, frequent relationship with atopy, and lack of consistent immunological abnormalities are all demonstrated in a clinical and immunological examination of seven patients. Different regulatory frameworks in different markets present difficulties for the global sector because they are not harmonized, which limits innovation and market expansion. These distinctions also impede the function of regulatory bodies and have an impact on international trade. Regulation (EC) No. 1223/2009.

Keywords: Ceramide, Atopic dermatitis (AD), Regulations, cosmeceuticals, psoriasis

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Introduction:

The largest organ in the human body, the skin keeps the body hydrated, maintains homeostasis, and blocks out toxins. The epidermis and dermis are its two components. The former is made up of the stratum corneum, stratum lucidum (which is only seen in thick areas), stratum spinosum, stratum granulosum, and stratum basal. The stratum corneum, the outermost layer, is characterised as a structure in which the extracellular lipid matrix between keratinocytes serves as the "mortar" and keratinocytes (KCs) as the "bricks." The long periodicity phase (LPP) and the short periodicity phase (SPP) are the names given to these lipids, which are arranged into two coexisting laminar structures with repeating spacing of 12–13 nm and 5–6 nm (1). a dynamic sector known as cosmeceuticals has emerged as a result of the increased integration of pharmaceuticals and cosmetics in the worldwide skincare business in recent years. By providing physiological benefits to the skin, such as anti-aging, photoprotection, depigmentation, hydration, and barrier repair, these bioactive chemicals, which are located at the nexus of cosmetics and therapies, provide more than just surface enhancement (2).All sphingolipids, including glycosphingolipids and phosphosphingolipids, are made up of ceramides, a kind of sphingolipid. Ceramides are the main lipid component of the stratum corneum's intercellular gaps, which comprise the epidermal permeability barrier, along with cholesterol, free fatty acid, and other minor components, despite being a tiny component of cellular membranes (3).Because of its lengthy fatty acid chain and waxy texture, ceramide, a form of sphingolipid, is named after the Latin words "amide" and "cera," which

meaning wax. Ceramides play an early function in skin development because they are found in vernix, the protective layer of foetal skin (4).In general care as well as specialised and emergency care, dermatological consultations are frequently requested for skin conditions including atopic dermatitis (AD), psoriasis, or xerosis (Citation1). The quality of life (QoL) of patients is adversely affected by these disorders, which frequently present with a substantial symptom burden. Severe pain or itching can interfere with sleep, and more obvious symptoms can make people feel self-conscious and possibly socially isolated, which can impair their general psychological and physical condition (5). Ceramides are now included in skin care products due to their significance in the operation of the skin barrier. Clinicians treating patients with skin illnesses must have a thorough awareness of ceramides' function in the skin and how they are used in skin care products, given their increasing usage in these products. Ceramides are now included in skin care products due to their significance in the operation of the skin barrier. Clinicians treating patients with skin problems must have a thorough awareness of ceramides' function in the skin and how they are used in skin-care products due to their increasing utilisation (6).Regardless of skin state, trypsin-like serine protease activity was consistently higher than that of atopic dermatitis (AD) patients and healthy controls. Although not as much, chymotrypsin-like activity was also increased (7).Dysfunctional skin is permeable, frequently feels extremely dry, has compromised immunity, and lets in more allergens and irritants, all of which can contribute to the development and exacerbation of long-term dermatological conditions (8). a licensed topical therapy for plaque psoriasis, activates the transcription factor known as the aryl hydrocarbon receptor (AHR). During development, keratinocytes create ceramides (CER), which are essential lipid components of the stratum corneum (SC) (9).Ceramides, free fatty acids, and cholesterol and its esters make up the majority of extracellular lipids. Ceramides are essential for the epidermal barrier layer's lamellar organization. Ceramides make up around 40–50% of the total lipid mass of the stratum corneum, while cholesterol and free fatty acids make up 25% and 10%, respectively (10).

Mechanisms and Formulations of Ceramide Cosmetics:

The skin barrier serves many unique purposes. The stratum corneum (SC) creates the physical barrier by combining multiple levels of complex defence systems, such as the skin microbiome that regulates the growth of pathogens and the acidity buffering capacity that shields us from chemical aggressions. The keratinocytes' detoxifying and antioxidant capability, as well as the skin's local immune system's ability to fend off microbial infection, complete this outermost barrier(11). Ceramide metabolism, which is controlled by both total abundance and the distribution of barrier-critical subclasses, such as ultra-long-chain (ULC) and ω-O-acylceramides, is a crucial factor in determining the integrity of the epidermal barrier. De novo synthesis, salvage recycling, sphingomyelin hydrolysis, and post-secretory processing that promotes acylceramide maturation and corneocyte lipid envelope (CLE) development are the main mechanisms that maintain ceramide homeostasis (12). Thus, ceramides, fatty acids, cholesterol, and hydrocortisone (HC) have been suggested as therapeutic or protective agents against atopic dermatitis (AD) and xerosis. However, due to the skin's superior barrier function, topical administration of these drugs remains difficult (13). CERs have been added to both traditional and innovative carrier systems in recent years in order to deliver CERs topically and restore the skin's barrier function. However, because to their high molecular weight and extremely lipophilic nature, CERs' ability to penetrate deeper layers of the skin is also a contentious topic(14). The stratum corneum contains nine ceramide subclasses, each of which combines a fatty acid with a sphingoid base.19 Ceramides are essential for preserving the integrity of the skin barrier. It has been demonstrated that the majority of skin ailments with dry skin, like atopic dermatitis, have changed or lowered ceramide profiles in the stratum corneum, which lowers barrier performance (15).

Cer 3 and/or Cer 6 were selected for the cerosome formulation. Due to their affordability and availability in large quantities, these ceramides are frequently utilised in commercial treatments for skin renewal and repair. Both ceramides have highly varied and unique physicochemical features regarding H-bonding ability and miscibility with other SC lipids, even though their molecules only differ in the presence of one OH group (16). Several sphingolipid-metabolizing enzymes work together to produce endogenous ceramides at the cytosolic side of the endoplasmic reticulum. Ceramides can be synthesised or derived from natural sources for commercial bulk manufacture. Despite the fact that synthetic versions of natural ceramides and pseudo-ceramides typically lack the ideal three-dimensional molecular structure, their equivalent absolute worth makes them valuable

commercially (17). There are two distinct processes that manufacture CERs: the salvage pathway and the de novo pathway.13 The skin produces CER through the de novo process.14, 15 3-keto dihydrosphingosine is formed by condensing serine and palmitoyl-coenzyme-A (CoA), and then it is transformed into dihydrosphingosine(18).When compared to untreated skin, ceramide-containing emulsions enhanced the function of the skin barrier. There was some evidence that the ceramides 1 and 3 in emulsion C may have a positive synergistic effect on skin biochemical characteristics, including TEWL and skin moisture, and that they are essential to the defence mechanism against SLS irritation (19). 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, glucosyl CERs, phospholipids, and CHOL, initially form lipid stacks within lamellar bodies (20).

Clinical Support for Particular diseases:

The pathophysiology of numerous skin conditions is significantly influenced by malfunctioning of the skin barrier. While inappropriate selection may worsen disease or increase skin irritation from topically applied medications, appropriate selection of skin care products that target SC dysfunction might improve treatment effects. Both the formulation and the ingredients must be taken into account when selecting topical skin care solutions. Even while two products have nearly identical component lists, their formulations may differ significantly, which could have an impact on their tolerance, efficacy, and cosmetic acceptance (21). For the treatment of psoriasis, using a specific cream and cleanser that contains ceramide or keratolytics, either separately or in combination, resulted in a high degree of patient approval(22).

Atopic Dermatitis (AD):

Atopic dermatitis (AD), sometimes referred to as atopic eczema, is a clinically characterised, inflammatory, chronic condition that primarily affects the skin and significantly impairs the quality of life for those who suffer from it. In western countries, it affects up to 3% of adults and 20% of children.3 In addition to the personal affection brought on by the persistent itching, sleeplessness, difficulty focusing, and missed work, the economic cost of AD has skyrocketed in recent decades (23). Eczematous and itchy lesions at the flexural folds and other characteristic distributions are caused by atopic dermatitis (AD), a chronic skin condition based on skin barrier malfunction, environmental variables, and numerous immune system modifications 1. The course is marked by intense itching, chronic eczematous skin lesions on dry skin, and acute flare-ups and exacerbations (24). Chromosome areas that overlap with inflammatory and autoimmune illnesses as well as other skin conditions have been identified using genome screens of AD families. These offer fresh perspectives on the pathophysiology of AD when combined with candidate gene research (25). Most AD therapeutic studies have lasted less than a year. Under ideal conditions, a research should be controlled, and both the skin's barrier function and inflammation should be under long-term management. The subclinical inflammation associated with AD cannot be controlled by flare treatment alone, making such a perfect situation impossible (26). AD is the most prevalent inflammatory skin condition in the developed world and one of the most prevalent chronic diseases globally. It affects people of all ethnicities, both men and women, children, and adults, and it frequently runs in families with other atopic conditions, including bronchial asthma and/or allergic rhinitis (27). Although AD was once thought to be an allergic skin condition, the role of allergic reactions in the development of AD is now questioned, and it is suggested that allergy is actually a result of AD in individuals who also have an underlying atopic constitution (28). Due to the poor response to current treatments, AD is still difficult to treat
(29). In a subset of AD patients, allergens expressed by the yeast Malazessia furfur, which is a part of normal skin flora, have also been linked to disease development (30).

Psoriasis:

A prevalent chronic inflammatory skin condition, psoriasis is increasingly being identified as a systemic inflammatory disorder. One well-known comorbidity of psoriasis is psoriatic arthritis. Additional connections between psoriasis and cardiometabolic diseases, gastrointestinal disorders, kidney disease, cancer, infection, and mood disorders are supported by a fast growing body of research in a variety of groups and contexts(31). The treatment of psoriasis must be multidisciplinary. It involves diagnosing and treating addictions, psychological illnesses, and related metabolic and cardiovascular conditions (32). According to the study, autoimmune illnesses share a similar genetic or environmental aetiology. Additional research on people with multiple autoimmune illnesses may provide crucial insights into the disease's genesis

and pathophysiology (33). The findings show that cutaneous immunological conditions such urticaria, atopic dermatitis, and allergic contact dermatitis are under-represented in psoriasis patients when compared to age-matched control patients without the condition(34). Timely diagnosis and adequate care with safe and effective topical medicines and other medical and psychological interventions, if necessary, would be made easier by the recognition of psoriasis and its related medical and psychiatric comorbidities (35). The most often reported medications that cause psoriasis include beta-blockers, tetracyclines, lithium, anti-malarials, and non-steroidal anti-inflammatory drugs (36). In particular, screening for CV risk factors (blood pressure, 2.6%; glucose, 1.2%; cholesterol, 4.3%; and BMI, 9.7%) was uncommon among dermatologists. Similarly, less than half of 127 US dermatologists surveyed in 2015 checked for diabetes, dyslipidaemia, or hypertension in psoriasis patients (37). Psoriasis has an effect on HRQL that is comparable to that of other serious illnesses (38). The development of erythematous, indurated, scaly, itchy, and frequently painful skin plaques is the hallmark of psoriasis, a chronic, systemic immune-mediated illness (39). Sterile pustules are the hallmark of pustular psoriasis, a unique phenotype that can be either acutely widespread (generalised pustular psoriasis, GPP) or restricted to the fingers (acrodermatitis continuous of Hallopeau, ACH) or palms and soles (palmoplantar pustulosis)(40).

Netherton's Syndrome:

The skin, hair, and immune system are all impacted by the uncommon but severe autosomal recessive form of ichthyosis known as Netherton syndrome.The search for causative mutations in Netherton syndrome patients and families was made possible by the discovery that SPINK5, which codes for the serine protease inhibitor LEKTI, is the gene causing the condition (41). Pathogenic mutations in the SPINK5 gene produce Netherton syndrome (NS), a rare genodermatosis with an autosomal recessive inheritance pattern. Atopic diathesis, ichthyosis linearis circumflexa, and anomalies of the hair shaft are its three defining characteristics. Atopic dermatitis and Ichthyosis linearis circumflexa can be mistaken for one another, delaying diagnosis (42). The limited literature on systemic treatment results in children and adults with NS reflects the disease's rarity. Research revealed significant variation in outcome metrics (43). Mutations in the serine protease inhibitor Kazal-type 5 (SPINK5) gene, which codes for lymphoepithelial Kazal-type-related inhibitor (LEKTI), which is expressed in hair follicles and the granular layer of the epidermis, cause NS(44). Ichthyosis linearis circumflexa, which is quite specific but not always present, frequently develops from ichthyosiform erythroderma (45). Netherton syndrome due to worries about the drug's enhanced systemic absorption (46). Netherton syndrome (NS) is a rare inherited skin condition characterised by severe and persistent allergy symptoms as well as a significant skin barrier deficiency (47). Because increased absorption of topically applied corticosteroids directly affects the renal tubules and hinders renal reabsorption or improves the free excretion of amino acids, the normal results of clinical investigations and a study of the literature imply that the aminoaciduria may have been artifactual (48). Netherton's syndrome's clinical spectrum, frequent relationship with atopy, and lack of consistent immunological abnormalities are all demonstrated in a clinical and immunological examination of seven patients (49). Significant cutaneous improvement was seen in this first case series documenting the use of anti-IL-17 medication in NS, especially in two paediatric patients with erythrodermic phenotypes(50).

Tolerability and safety:

Improving skin condition by lowering inflammation and irritation is the aim of using moisturisers and moisturisers containing ceramides as an adjuvant acne treatment (51). In dermatological research, the Investigator Global Assessment (IGA) acne scale is frequently used to assess the severity of skin conditions, especially those associated with inflammatory skin diseases like acne. (52). Comparing the impact of the therapies on the intensity of symptoms as measured by the EASI at day 28 to the baseline was the main effectiveness outcome. With a composite score ranging from 0 to 72, the EASI takes into account the degree of skin involvement at four body regions (head/neck, upper limbs, trunk, and lower limbs) as well as the severity of the four eczema signs (redness, thickness/swelling, itching, and lichenification) (53). safe treatment for individuals whose underlying skin condition has not been successfully controlled by other regimens or who refuse to use those methods (54). Information on the application of skin care products containing MVE ceramide in cases of rosacea, acne, and eczema is available and may be taken into consideration (55). Three quarters of atopic dermatitis sufferers found the trial cream to be satisfactory. After using the cream, patients who accepted it had less pruritus and an overall improvement in their quality of life (56). The majority

of participants (71%) just took the ceramide-dominant and did not take the supplementary medication that was given (57). Ceramide-containing emollients enhance barrier function and may influence microbial communities through immunological modulation, hydration, and stratum corneum lipid regulation (58). At week 12, the patient-reported outcome included satisfaction. The occurrence of unwanted events was the safety endpoint (59). enhanced the stratum corneum's natural barrier function, indicating that it might be used as a therapy for AD patients (60).

Regulatory and Policy Environment:

Since they may come under several regulatory categories, such as cosmetics, pharmaceuticals, medical devices, and other chemical products, the presentation of the items and their mode of action define the regulatory requirements and the approval process (61). For dermocosmetic bioactive to be safe and effective, worldwide harmonisation, regulatory reform, and the use of cutting-edge technology are crucial. A cohesive strategy will preserve consumer safety while fostering innovation (62). Europe Functional cosmetics, also known as medication delivery systems or nanocarriers, are a novel class of products. Through the Cosmetics Regulation (EC No. 1223/2009), the European Commission regulates cosmetic products in Europe. The consumer has a high level of safety thanks to this directive. Notifying the Commission is required when a cosmetic ingredient satisfies the requirements outlined in Article 2 (1) (k) of the European Cosmetic Regulation for nanomaterials (figure 1) (63). By dividing the regulatory obligations that apply to new and old sources, the federal environmental statutes exacerbate the inequities (64). This changing environment offers chances for innovation while highlighting how crucial it is to uphold regulatory compliance in order to safeguard consumers and guarantee long-term prosperity in the cosmetics sector (65). The report also notes a lack of empirical data to show how recent regulatory changes have actually affected innovation and market access in the real world (66). Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, often known as the Cosmetics Regulation (CR), which went into effect on July 11, 2013, contains the primary standards and definitions (table1) (67). However, a small number of studies have shown possible hazards that have not yet been verified. Regulatory agencies have actively debated and discussed the possible risk of NMs in cosmetics, and various regulatory bodies are moving toward harmonisation (68). China's new cosmetic ingredient regulations have gone through two different stages of development. Prior to 2021, uniform registration management applied to all new substances. Only 14 new chemicals were accepted by regulatory bodies between 1989 and 2020 indicating a very cautious approach that prioritised risk avoidance but may have limited the introduction of innovative, safe, and effective materials (69). Patients with occupational skin illnesses may benefit from educational programs that teach fundamental principles for maintaining the proper skin barrier (70).

Table1: Demonstration of regulatory discrepancies, comparing what is foreseen in the European regulation and what occurs in practice.

Expectation	Reality
By carrying out an appropriate safety evaluation, the RP has a record of the CSR and the PIF proving the product is safe.	It is unlikely that this condition will be broken.
There are only goods on the market that are safe when used in typical and generally predictable circumstances.	Authorities may have purposefully overlooked this to prevent damaging businesses or sales.
The SCCS published guidelines to direct the testing and safety assessment of cosmetic components.	There is a need for the SCCS to also provide a practical interpretation of the guidelines, as it is hardly feasible to comply with all the proposed requirements.
Market surveillance activities are out by the MS regulatory body to identify non-compliant goods.	Market surveillance is ineffective due to its non-standardized methodology.
The SCCS updates the safety data for substances used in cosmetics on a regular basis.	Animal studies are frequently used in the SCCS re-evaluation, which has no set periodicity.

It makes it possible for regulatory choices to be more logical and scientific, guaranteeing the stable and healthy functioning of the cosmetics industry. Establishing a comprehensive evidence-based system for safety and efficacy has become an inevitable trend

due to the cosmetics industry's ongoing expansion and the growing needs of customers (71) The report emphasises how important it is to improve regulatory frameworks and increase consumer knowledge (72). The solution under investigation reduced facial redness in a short amount of time, balanced the amount of sebum and skin hydration, and had a positive calming and reassuring effect on people with sensitive skin (73). Many anti-aging cosmetic products that include ceramides have been developed because it is known that the amount of ceramides in the skin decreases with age (74). This barrier also includes a mechanism for controlling body temperature, electrolyte balance, and feeling. Disease states may disrupt the barrier, delay repair, or change the kinetics of repair even though the barrier is self-maintaining and replaces itself every 14 days (75). Ceramides could be one of the essential lipid to restore barrier function and maintain the buffer system of the skin, resulting in regulation of physiological environment for skin repair itself and skin surface pH, leading to acidic pH (76). Innovation in dermatology may be severely hampered by laws, particularly with regard to topical treatment products (77). Certain substances can be produced by bacteria in reaction to environmental stress. These bacterial chemicals are typically utilised in cosmetics, medicine, and even athletics. Certain probiotics modify the symptoms of many illnesses and have immunomodulatory properties (78). The classification and regulation of herbal creams in dermatology are still unclear and inconsistent. Citation79 Herbal creams are primarily used or classified as cosmetics or traditional remedies in the majority of states, suggesting that they are more permissive than real medication. For instance, the Federal Food and Drug Administration (FDA) in the US regulates herbal creams primarily as cosmetics; if they don't make specific medicinal claims, they are considered over-the-counter medications (79). Therefore, our clinical investigation with tnano-emulsion clearly implies that the up-regulated barrier function in AD skin is less important than the increased water content in reducing scaling and itching (80).

Global Harmonisation challenges:

In the EU, the European Commission has the overall responsibility for cosmetic legislation and each member state designates a competent authority to enforce that same legislation. Nowadays, the cosmetic regulatory framework is provided by Regulation (EC) Nº 1223/2009 which replaced the previous Directive 76/768/EC, adopted in 1976 (81). According to Global Data (2023), in the first two years following the implementation of the legislation, Middle Eastern cosmetics producers who did not adjust to halal regulations had a margin reduction of up to 30%. (82). In the end, a design space that satisfies the predetermined QTPP requirements was created, defining the ideal operating ranges for the most important variables and undoubtedly minimising product variability (83). The evaluation found considerable diversity in study design, sample size, duration, and outcome reporting, making direct comparisons challenging despite methodological advancements in TEWL measurement and skin barrier assessment (84). Macroalgal metabolites' bioactivity, safety profile, and regulatory status all play a role in their successful conversion into cosmetic uses. Phlorotannins and MAAs are two families of chemicals that are particularly interesting due to their biological effects and restricted regulatory approval (85). Different regulatory frameworks in different markets present difficulties for the global sector because they are not harmonised, which limits innovation and market expansion. These distinctions also impede the function of regulatory bodies and have an impact on international trade. Regulation (EC) No. 1223/2009, the European Union's (EU) cosmetics regulatory framework, guarantees consistency among member states and keeps up with technological advancements (86). The paper offers a current summary of the difficulties, developing regulatory frameworks, and topical medicinal potential of CBD. Through interactions with the skin's endocannabinoid system (ECS), CBD demonstrates a variety of biological benefits, such as anti-inflammatory, antioxidant,

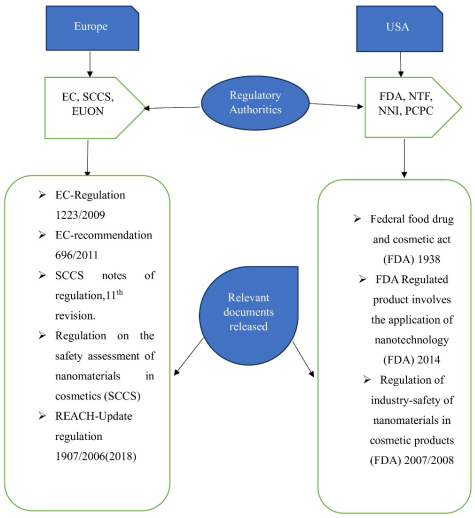

Fig 1 cosmetic regulation of Europe and USA

antibacterial, analgesic, lipostatic, antiproliferative, moisturising, and anti-aging qualities (87). This review outlines a translational route toward clinically dependable, sustainable, and customised nano cosmeceutical solutions that bridge the gap between medicine and aesthetics by fusing breakthroughs in nanomaterial science with dermatological knowledge and regulatory guidelines (88). Cosmetics and pharmaceuticals are combined to form the term "cosmeceuticals." It indicates that they have both medicinal and cosmetic qualities (89). The difficulty of producing increasingly natural and high-performance goods presents problems for the cosmetics sector, including raw material oxidation. Organoleptic changes, especially in colour and odour, may result from this (90).

Conclusion: the above review concludes that, barrier repair, these bioactive chemicals, which are located at the nexus of cosmetics and therapies, provide more than just surface enhancement. The pathophysiology of numerous skin conditions is significantly influenced by malfunctioning of the skin barrier. Regulatory agencies have actively debated and discussed the possible risk of NMs in cosmetics, and various regulatory bodies are moving toward harmonisation. In the EU, the European Commission has the overall responsibility for cosmetic legislation and each member state designates a competent authority to enforce that same legislation.

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