The roles of ceramides and multivesicular emulsion (MVE) technology in atopic dermatitis: a narrative review

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a highly prevalent chronic inflammatory skin condition. In Malaysia, a prevalence of 13.4% was reported for children between one and six years of age, one of the highest prevalence rates of AD in Asia. Many guidelines recommended moisturisers as the mainstay of treatment strategy for AD. Selecting an effective and suitable moisturiser for people with AD plays a crucial role in avoiding acute exacerbation of AD and achieving remission.

Materials and Methods: Given that an array of active ingredients and topical vehicles for moisturisers are available in the market, this review summarised the roles of ceramides and multivesicular emulsion (MVE) technology in managing AD to help guide treatment decisions.

Results: Ceramides are essential in maintaining the skin permeability barrier and hydration, modulating skin immunity through anti-inflammatory and antimicrobial defence system, and regulating cellular functions. Low levels and altered structures and composition of ceramides, compromised skin permeability barrier and increased trans-epidermal water loss were commonly observed in AD patients. Most clinical studies have shown that ceramide-dominant moisturisers are safe and effective in adults and children with AD. MVE technology offers an attractive delivery system to replenish ceramides in the SC, repairing the compromised skin permeability barrier and potentially improving patient compliance.

Conclusion: Recommending clinically proven therapeutic moisturisers with the right ingredients (level, ratio, structure and composition), alongside an effective sustained release delivery system, to AD patients is one key strategy to successful disease control and flare prevention, subsequently reducing the disease burden to patients, families and societies.

KEYWORDS:
Ceramide; multivesicular emulsion; atopic dermatitis; eczema; moisturisers

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a highly prevalent chronic inflammatory skin condition. In Asia, the AD prevalence varies with countries, ranging from 4.3 to 19.6% in children and 1 to 4.6% in adults. In Malaysia, a prevalence of 13.4% was reported for children aged between one and six years, one of the highest prevalence rates of AD in Asia.[1] AD is characterised by intense itching, dry skin and inflammation. AD follows a relapse-remitting course, with periods of acute worsening ('flares') alternating with relative quiescence after proper treatment.[2]

While AD has long been attributed to immunological abnormalities, it is now recognised that a defective skin permeability barrier is one key driver of disease activity in AD (i.e., barrier-initiated pathogenesis of AD). Firstly, disruption of the skin permeability barrier alone directly stimulates the production of proinflammatory cytokines (e.g. IL-1b, IL-6 and IL-8) in the epidermis as a repair response, triggering skin inflammation and producing AD symptoms.[3-5] Besides that, the genes encoding skin barrier structural components (filaggrin and loricin) are expressed in response to the impaired skin permeability barrier, leading to excessive inflammation and tissue hyperplasia. Impaired skin permeability barrier also increases trans-epidermal water loss (TEWL) and reduces skin hydration, further stimulating the release of proinflammatory cytokines and compromising the skin permeability barrier function. Lastly, as the skin permeability barrier forms a protective layer against exogenous substances, skin permeability barrier dysfunction increases the risk of pathogen colonisation, particularly Staphylococcus aureus[6], resulting in infections and subsequent IL-17 and IL-22-mediated inflammation.[3,4,6] Therefore, maintaining an effective and functional skin permeability barrier is essential to prevent acute exacerbation of AD and achieve disease remission.

Stratum corneum (SC), the outermost layer of the skin, develops before birth and becomes visible at 34-week gestational age. After birth, SC maturity continues up to about 4 years of age.[7,8] SC is composed of two distinct compartments: hydrophilic corneocytes (dead and terminally differentiated keratinocytes) and extracellular hydrophobic lipid matrix (lipid lamellae). The lipid lamellae are composed of ceramides (~50%), cholesterol (~25%), and free fatty acids (~15%), with smaller quantities of phospholipids and cholesterol sulphate. These hydrophobic lipids are tightly packed and arranged in multiple bilayers (lamellae) within the extracellular domains of the SC to prevent TEWL and invasion of environmental irritants, pathogens, and allergens.[5,9] The corneocytes, which are composed of filaggrin and a collection of water binding molecules known as natural moisturising factor (NMF), absorb water from epidermis to SC and prevent TEWL from SC to keep the skin

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Table I: The main types of ceramides in human SC

Fatty acid / Sphingoid	Non-hydroxy fatty acid (N)	α-hydroxy fatty acid (A)	Esterified ∞-hydroxy fatty acid (EO)
Dihydrosphingosine (DS)	CER (NDS) Ceramide 10	CER (ADS) Ceramide 11	CER (EODS) Ceramide 12
Sphingosine (S)	CER (NS) Ceramide 2	CER (AS) Ceramide 5	CER (EOS) Ceramide 1
Phytosphingosine (P)	CER (NP) Ceramide 3	CER (AP) Ceramide 6	CER (EOP) Ceramide 9
6-hydroxy sphingosine (H)	CER (NH) Ceramide 8	CER (AH) Ceramide 7	CER (EOH) Ceramide 4

hydrated.[4] These corneocytes are held in place by a highly cross-linked protein structure called cornified envelope (CE), which binds covalently with a monolayer of insoluble lipids, mainly ceramides, forming the cornified lipid envelope (CLE). The CLE works like a scaffold, supporting the corneocytes within extracellular lipid lamellae and plays an important role in maintaining the skin permeability barrier function.[5,9]

Infant skin differs from adult skin at the microstructural, functional and compositional levels, and these differences lead to different water-holding properties and clinically observed differences between infant and adult skin.[8] In infants, the SC is thinner. Despite higher SC hydration in infants compared with adults, infant TEWL is significantly higher than adults and the levels of NMF and lipid components are significantly lower in infants up to 1 years of age.[7,10] These parameters change rapidly over the 1st year of life and are stabilised towards adult values by 3–5 years of age.[8] These developmental changes impacted the skin permeability barrier in children, resulting in a more sensitive and permeable skin that is susceptible to irritation and inflammation.[10] The age-dependent changes in children skin permeability barrier, which are believed to be fully matured to adult values by approximately 5 years of age, explained the higher prevalence of AD amongst children relative to adults.[8,10]

Due to robust clinical evidence demonstrating that regular use of moisturisers reduces the severity of AD, prolongs the time to next flare, and reduces the need for rescue topical corticosteroid (TCS),[11] many guidelines including American Academy of Dermatology (AAD),[2] and Malaysia Clinical Practice Guideline[12] recommended moisturisers as the mainstay of treatment strategy. Moisturisers increase skin hydration and ameliorate skin dryness by exerting humectant, occlusive, and emollient effect. While humectants (e.g., glycerine, hyaluronic acid, urea) mimic the NMF in corneocytes to attract and bind water from deeper epidermis to SC, occlusives (e.g., lanolin, mineral oil, olive oil, petrolatum) act like the intercellular lipid bilayers to form a hydrophobic film and slow down TEWL from the SC whereas emollients (e.g., collagen, colloidal oatmeal, shea butter, glyceryl stearate, isopropyl palmitate, stearic acid) function like natural lipids on the SC, filling the cracks between the corneocytes and smoothening the skin.[13]

Various topical vehicles and formulation technologies were designed to sustainably deliver active ingredients to the targeted skin site at an appropriate level. Common vehicles included chemical penetration enhancers (e.g., propylene glycol, oleic acid, isopropyl myristate, ethanol) or physical occlusives (e.g., lipids and hydrocarbons ointment). Physical occlusives increase the skin hydration and markedly increase skin penetration of applied ingredients. Chemical penetration enhancers facilitate both the partitioning into and the passage of ingredients through the skin. Besides physical occlusives and chemical penetration enhancers, other formulation technologies such as liposomes, noisomes, nanoparticles, transferosomes, ethosomes, and multi-vesicular emulsions (MVE) were introduced to enhance the delivery of active ingredients to the skins. Given that selecting an effective and suitable moisturiser with the right active ingredients and topical vehicles at the right levels plays a crucial role for people with AD in achieving remission and avoiding acute exacerbation of AD, this study aims to review the roles of ceramides and the latest multivesicular emulsion technology in managing AD.

THE ROLES OF CERAMIDES IN ATOPIC DERMATITIS

Ceramide comprises fatty acids (FA) and sphingosine bases (SB) (Fig. 1).[5] Ceramides are classified by a combination of the abbreviations of FA and SB (Table I).[5,14]

There are five types of FAs in human SC: non-hydroxy (N), α-hydroxy (A), esterified ω-hydroxy (EO), ω-hydroxy (O), and β-hydroxy (B), each contributing to 59.4%, 32.5% 6.3%, 1.6%, 0.17% of the human ceramides, respectively.[14] While there are five types of SBs in human SC: dihydrosphingosine (DS), sphingosine, (S) phytosphingosine (P), 6-hydroxy sphingosine (H), and 4,14-sphingadiene (SD), SD-type ceramide is present in small amount in human SC (0.4%). In the human SC, the most abundant ceramides were Ceramide 3, Ceramide 8, and Ceramide 7 (24.2%, 23.7%, and 18.0% of total ceramides, respectively), followed by Ceramide 6, Ceramide 10, Ceramide 2, Ceramide 5, Ceramide 4, Ceramide 1, Ceramide 9 and Ceramide 11 (in descending order, 1 to 9%). Other ceramide classes constitute lower than 1% of human SC.[14]

Many studies consistently found that the total ceramide levels were markedly reduced in patients with AD compared with those with healthy skin, suggesting that low levels of ceramides in the SC impaired the skin permeability barrier, allowing irritants and allergens to permeate the skin, initiating the inflammatory process of AD.[15] Specifically, Ceramide 1 and 3 levels were significantly lower in AD patients than in healthy skin.[12,15] Ichikawa et al.[15], who used a more precise liquid chromatography-mass spectrometry, observed that the levels of Ceramide 4, Ceramide 8 and

Table II: Summary of clinical evidence for ceramide-dominant moisturisers

Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Gupta et al. (2023)[20]	RCT (double-blind, vehicle-controlled)	Children (<18 years)	Aqua Oat Moisturizing Cream vs. Olesoft Max Cream (paraffin-based cream)	- The mean change in SCORAD at 3 months in the ceramide-based and paraffin-based moisturizer groups was 22.1 and 21.4, respectively (p = 0.37). - The change in CDLQI/IDLQI, TEWL over forearm and back, amount and days of topical corticosteroid required, median time to remission and disease-free days at 3 months were similar in both groups. - Both the paraffin-based and ceramide-based moisturizers were comparable.
Na et al. (2010)[21]	Cohort study	Children (aged 5 to 19 years)	Atobarrier cream (no comparator)	- The SCORAD value decreased dramatically after 4 weeks of moisturizer application (p = 0.000). - The TEWL was not changed, but the SC hydration increased significantly (p = 0.000). No significant adverse effects were observed. - Moisturizer containing lipid granules effectively controlled atopic dermatitis.
Danby et al. (2016)[22]	Cohort study	Adults (aged ≥ 60 years)	Balneum cream vs. Aquamol cream	- Treatment with the test emollient for 28 days significantly reduced TEWL and skin surface pH by an average of 1.07 ± 0.29 g/m2/h and 0.15 ± 0.07 pH units compared to the untreated control site, respectively. - Hydration was increased significantly (+2.09 ± 0.95 units) compared to the untreated control despite the last application being ≥12 h previously. - Neither treatment adversely affected lipid chain conformation.
Koh et al. (2017)[23]	Cohort study	Children (aged 6 months to 6 years)	Ceradan Cream (no comparator)	- The mean change in SCORAD and PEST scores from baseline to week 12 was -11.46 (p<0.0001) and -1.33 (p<0.0001) respectively. - The ceramide-dominant therapeutic moisturizer used was safe and effective in the management of AD in young children.
Shindo et al. (2022)[24]	RCT (double-blind, vehicle-controlled)	Adults (23–64 years old)	Ceramide-care Cream vs. water in oil type emulsion	- Both moisturizers improved the visually evaluated skin symptoms and skin hydration. - No statistically significant difference in skin hydration and TEWL between treatment and control arms at week 4. - Moisturizer containing pseudo-ceramide and the eucalyptus extract significantly improved cutaneous barrier function and significantly increased the ceramide level in the stratum corneum
Draelos et al. (2008)[25]	RCT (investigator-blind)	Children and adult (aged 5 to 80 years)	CeraVe Hydrating Cream/Cleanser + fluocinonide cream vs. CeraVe Hydrating cleanser + fluocinonide cream vs. bar cleanser + fluocinonide cream	- The incidence of clearing at week 4 increased from 15% (fluocinonide cream 0.05%+ bar cleanser) to 76% (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser + moisturizing cream) with P=0.0001, and to 37% (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser) with P=0.0001. - The time to clearing was 3.0 weeks in treatment group 3 (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser and moisturizing cream), 3.4 weeks in treatment group 2 (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser), and 3.7 weeks in treatment group 1 (fluocinonide cream 0.05% + bar cleanser). - For all signs and symptoms, treatment group 3 experienced the fastest onset and greatest improvement at all time points, followed by treatment group 2 and treatment group 1. - No adverse events and tolerability issues reported by either the investigator or the subjects.
Lynde et al. (2014)[26]	Cohort study	Adult and Children (aged 2 to 88 years)	CeraVe Hydrating Cream (no comparator)	- At day 42, SCORAD scores for group 1 (≥12 years old) and group 2 (<12 years old) showed significant improvement (P=0.0001). - No adverse effects were reported during the 6-week of evaluation. - Ceramide-containing cleanser and moisturiser regimen substantially improved skin condition and clinical outcomes related to AD severity as well as QOL aspects.
Danby et al. (2020)[27]	RCT (double-blind, intrapatient- and vehicle-controlled)	Adult (aged ≥ 18 years)	CeraVe Hydrating Cream/Lotion vs. Zerobase/Epimax/Aquamax Cream	- The test cream and lotion both significantly increased skin hydration and reduced skin dryness for at least 24 hours following a single application compared to a no treatment control site. - Compared to three reference emollient creams the test cream and test lotion were the only products capable of sustaining clinically meaningful improvements in skin moisturiza- tion for 24 hours. - The sustained moisturization imparted by the test products reduces the need for frequent emollient application, often requiring 3–4 applications per day for tradi- tional emollients, and should reduce the high burden of managing dry skin conditions like AD.
Danby et al. (2022)[28]	RCT (observer-blind, intrapatient- and vehicle-controlled)	Adult (aged ≥ 18 years)	CeraVe Hydrating Cream vs Zerobase cream (paraffin-based cream)	Skin barrier integrity was greater at sites treated with the test cream (effect size for area under the transepidermal water loss curve -162, p< 0.0001). Skin sensitivity to sodium lauryl sulfate was reduced (-5 points visual redness, p< 0.0001), as was transepidermal water loss (-15.3 g/m2h, p< 0.0001) compared with the reference. - Sites treated with the test cream displayed enhanced lipid chain ordering, which was significantly associated with skin barrier integrity (r = 0.61). Compared with the reference, treatment with the test cream increased hydration (8.61 capacitance units, p< 0.0001) and decreased signs of dryness.

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Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Hon et al. (2013) [29]	Cohort study	Children (aged < 18 years)	Cetaphil Restoraderm Skin Restoring Lotion (no comparator)	- Two thirds of the patients reported very good or good acceptability of the LMF moisturizer, whereas one third reported fair or poor acceptability. - The objective SCORAD score, pruritus score, and sleep disturbance score were lower in the very good/good acceptability group than in the fair/poor acceptability group. - The mean objective SCORAD score improved (from 31.5 to 25.7; p = 0.039) and skin hydration improved from 30.7 to 36.0 (p = 0.021) in the very good/good acceptability group.
Simpson et al. (2013) [30]	RCT (investigator-blinded, intrapatient-controlled)	Adults (aged 18 to 65 years)	Cetaphil Restoraderm Moisturizer vs. no treatment	- After 4 weeks of treatment, significantly greater reduction of TEWL and clinical dryness scores, and increased skin hydration (all p < 01) in the CRM-treated than untreated area. - A significantly higher level of ceramide (p < 05) and a trend toward increased water content was observed in the SC for CRM than for the control. - There were no related AEs.
Ma et al. (2017) [31]	RCT (investigator-blinded, parallel-group, controlled study)	Children (aged 2 to 12 years)	Cetaphil Restoraderm Skin-restoring moisturizer and cleanser vs. no moisturiser and cleanser only	- A significantly earlier onset of action in terms of fewer flares favoring moisturizer was found at week 4 (31 vs. 59%, respectively, p = 0.022), and after 12 weeks, fewer flares occurred (50 vs. 72%). - At week 12 for flare-free subjects, nearly half in both groups had clear IGA, and an emollient effect in terms of less dryness or burning was more marked for moisturizer/body wash. - Both products led to high patient satisfaction and were well tolerated. - A regimen incorporating a moisturizer plus body wash delayed AD flares by nearly 2 months compared to body wash alone, and yielded high patient satisfaction.
Leshem et al. (2020) [32]	RCT (observer-blind, intrapatient- and vehicle-controlled)	Children and adults (aged ≥ 12 years)	Cetaphil Cream vs Aveeno Moisturizing Cream vs CeraVe Moisturizing Cream vs Vaseline	- Mean TEWL improved in the treated forearm and worsened in the untreated one, but the difference was not significant. - There was no significant change in pH or in TEWL after tape stripping. - Capacitance significantly improved in the moisturizer forearm. - The effects of moisturizers on nonlesional AD skin were small and need to be addressed when powering future studies.
Hon et al. (2011) [33]	Cohort study	Children (aged 5 to 18 years)	Curel Moisture Cream (no comparator)	- Four weeks following the use of the cream, skin hydration improved significantly and fewer patients were using topical corticosteroids. - There was no deterioration in transepidermal water loss, eczema severity, or quality of life.
Seghers et al. (2014) [34]	Cohort study	Children and adults (aged 7 to 60 years)	Curel Moisture Cream (no comparator)	- The objective scoring atopic dermatitis decreased from 29.1 at week 0 to 22.0 at week 4 (p < 0.001). - There was no detectable difference in TEWL after 4 weeks. - However, SC hydration was significantly increased from 39.7 at week 0 to 49.2 after 4weeks (p < 0.001). - Both Dermatology Life Quality Index and patient-oriented eczema measure showed significant improvement at week 4 (p < 0.001). - The moisturizer was well tolerated with no serious adverse events recorded.
Mori et al. (2018) [35]	RCT (single-blind)	Female with mild AD (≥ 18 years)	Curel Moisture Gel Lotion vs. no treatment	- Skin dryness and scaling significantly improved with or without application of the moisturising gel. - However, the improvement in dryness of the treated group was significantly higher than that of the nontreated group. - Erythema and itchiness were significantly improved only in the treated group. - The skin hydration on the forearm increased significantly only in the treated group. - Accompanying those improvements, the quality of life of the subjects, evaluated by Skindex-16®, was significantly improved.
Koppes et al. (2016) [36]	RCT (double-blind, vehicle-controlled)	Adults (aged ≥ 18 years)	Dermalex Eczema Cream (Cer-Mg) vs. hydrocortisone acetate cream 1% vs. unguentum leniens (cold cream)	- After 6 weeks, group I (Cer-Mg + Hydrocortisone) showed comparable significant improvement in SCORAD and TEWL between Cer-Mg sites and Hydrocortisone sites, while in group II (Cer-Mg + emollient), the decrease in SCORAD and TEWL was significantly greater at Cer-Mg sites compared with emollient-sites. - Cer-Mg cream was more effective in improving skin hydration and maintenance of levels of NMF than hydrocortisone and emollient.
Sugarman et al. (2009) [37]	RCT (investigator-blinded, vehicle-controlled)	Children (unspecified)	EpiCeram Skin Barrier Emulsion vs. Cutivate cream (fluticasone)	- EpiCeram reduced clinical disease severity, decreased pruritus and improved sleep habits both 14 and 28 days after initiation of therapy. - Although the fluticasone-treated group showed significantly greater improvement at 14 days, SCORAD, pruritus and sleep habit scores for EpiCeram did not differ significantly from the fluticasone-treated group by 28 days.
Kircik et al. (2011) [38]	Cohort study	Children and adults (all ages)	EpiCeram Skin Barrier Emulsion (no comparator)	- Approximately half of the subjects achieved success with investigator global assessment (clear or almost clear scores) after 3 weeks of treatment with test cream monotherapy or in combination with another treatment. - A large proportion of subjects (75%) and investigators (77%) reported satisfaction after three weeks of treatment. Pruritus and quality of life improved during the study.

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Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Miller et al. (2011)[39]	RCT	Children (aged 2 to 17 years)	EpiCream vs. Atopiclair (Glycyrrhetinic-acid containing barrier repair cream) vs. Eucerin cream (petroleum-based skin protectant moisturizer)	- All three groups showed improvement in Investigator's Global Assessment (IGA), the Petroleum-based group was the only group to demonstrate statistically significant improvement in all assessments, including IGA, Eczema Area and Severity Index (EASI), visual analog scale (VAS) for itch intensity, and body surface area (BSA) involvement by day 21 (P <0.05). - No statistically significant difference for any clinical efficacy assessment was found between the three groups at each time point. - However, Petroleum-based cream was found to be at least 47 times more cost-effective than Glycyrrhetinic aicd- or Ceramide-based cream.
Weber et al. (2015)[40]	RCT	Children (aged 3 months to 12 years)	Eucerin Eczema Relief Body cream (maintenance) and Eczema Relief Instant Therapy (acture flare) vs. no treatment	- The incidence of flare was significantly lower in the moisturizer group compared with the control group (21% vs 65%; P=0.006), while the median time to flare was shorter in the control group (28 vs >180 days). - Risk of flare was reduced by 44.1% after 6 months of Body Cream application. - Flare Treatment reduced overall eczema symptom severity at week 2 and week 4; 78.9% of flares had improved or cleared at week 4.
Ishida et al. (2011)[41]	Cohort study	Adults (aged 29 to 71 years)	Extemporaneous preparation with psuedoceramide (no comparator)	- Four weeks of treatment with pseudoceramide cream significantly reduced skin symptoms, accompanied by significant decreases in transepidermal water loss and increases in water content. - TEWL values decreased significantly at week 2 and 4 during the 4 weeks of treatment with the psuedoceramide lotion and remained at a lower level at day 3 in the regression phase in the AD lesional skin. - The level of pseudoceramide that penetrated into the SC was significantly correlated with the SC water content but not with transepidermal water loss.
Draelos et al. (2018)[42]	Cohort study	Children and adults (aged 1 to 86 years)	NeoCera cream (no comparator)	- Use of the ceramide cream resulted in a 100% improvement in IGA scores and a 67% improvement in overall subject skin assessment scores after 4 weeks of treatment and the improvements were statistically significant. - Statistically significant improvements were also observed in transepidermal water loss, water content of the skin, and skin smoothness. - Adverse events were not observed.
Spada et al. (2021)[43]	RCT (double-blind, placebo-controlled)	Adults (aged ≥ 18 years)	QV Intensive Cream vs. placebo cream	- Eczema area severity index score decreased significantly across all time points in both groups compared to baseline (P < .0001), however, this decrease was not significant between groups at day 28 (P = .7804). - In contrast, TEWL and skin hydration significantly improved over time in the active group, while it either stayed the same or worsened in the placebo group (P = 0.0342 and P < 0.0001, respectively). - There was no difference in the use of mometasone furoate as rescue medication over time between groups (P = .1579). - Dermatology life quality index scores improved significantly in both groups (P <0 .0001), with no difference between groups (P = 0.5256). - However, patient satisfaction was greater in the active compared to the placebo group for several parameters including relief of itch, dry skin, skin softness and smoothness (all P < 0.05). - No patients withdrew from the study due to adverse events (AEs) and there were no serious AEs.
Berardesca et al. (2002)[44]	RCT	Children and adults (unspecified)	Repositol vs. Alfason Repair vs. Locobase Repair vs. Nouriva Repair	- Both treatment groups statistically improved all parameters considered at week 4 and 8 as compared to baseline. - Between the 2 treatment groups, there was a statistically significant difference in favour of combined therapy: erythema, pruritus and overall disease severity; erythema and pruritus; erythema, pruritus, fissuring and overall disease severity. - No statistically significant difference was found for: dryness, scaling and fissuring; scaling, fissuring and overall disease severity; dryness and scaling.
Chamlin et al. (2002)[45]	Cohort study	Children (aged ≤ 12 years) with stubborn-to-recalcitrant AD	Tricream (no comparator)	- SCORAD values improved significantly in 22 of 24 patients by 3 weeks, with further progressive improvement in all patients between 6 and 20 or 21 weeks. - TEWL, which were elevated over involved and uninvolved areas at entry, decreased in parallel with SCORAD scores and continued to decline even after SCORAD scores plateaued. - Both SC integrity (cohesion) and hydration also improved slowly but significantly during therapy. - Finally, the ultrastructure of the SC, treated with ceramide-dominant emollient, revealed extracellular lamellar membranes, which were largely absent in baseline SC samples.

Table III: Recent advances in topical formulation technology over the years

Year	Formulations	Components	Mechanism of actions/functions
1964	Liposomes [47]	Self-assembled (phospho)lipid-based drug vesicles that form a bilayer (unilamellar) and/or a concentric series of multiple bilayers (multilamellar) enclosing a central aqueous compartment.	• protect the encapsulated active ingredients from physiological degradation • control the release of active ingredients • extend the half-life of the active ingredients • selectively deliver the active ingredients to the targeted site, thus decreasing the systemic side-effect, elevating the maximum-tolerated dose, and improving therapeutic benefits
1970s	Noisomes [48]	Self-assembled vesicles from non-ionic surfactants with cholesterol that forms lamellar structures	• act as a depot, releasing the drug in a controlled manner • delay clearance from circulation and protect the entrapped active ingredients from the biological environment • enhance the bioavailability of active ingredients and restrict their effects to target cells
1990s	Nanoparticles [49]	Lipid molecules with particle size on the nano- to sub-micron scale (50–1000 nm) after active ingredients encapsulation and are composed of biocompatible and biodegradable components which do not require the use of organic solvents for their assembly	• improve intracellular permeation and increase bioavailability of active ingredients • allow efficient delivery and control release of active ingredients to the targeted sites
1991	Transferosomes [50]	Ultradeformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core	• able to reach intact deeper regions of the skin after topical administration, delivering higher concentrations of active substances and making them a successful drug delivery carrier for transdermal applications
1997	Ethosomes [51]	Soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water	• enable active ingredients to reach the deep skin layers and / or the systemic circulation as ethanol is an efficient permeation enhancer
2004	Multivesicular emulsion (MVE)[52]	Concentric layers of oil-in-water emulsions where one vesicle is contained within another inside the MVE.	• enhance the effectiveness of individual ingredients used on the skin, with time-released or sequential delivery after initial application

Ceramide 9 were also significantly reduced in AD patients on top of the Ceramide 1 and Ceramide 3 levels that have been previously reported. In contrast, the level of Ceramide 5 was elevated in AD patients. Most importantly, this study found that low levels of all ceramides (except Ceramide 2, 5 and 11) increased TEWL and reduced skin hydration, while all ceramide levels (except Ceramide 2 and 5) correlated with skin permeability barrier function. Notably, Ceramide 2 has a unique contribution to AD. While the short-carbon-chain Ceramide 2 was commonly found in AD patients, the long-carbon-chain Ceramide 2 level was reduced in AD patients, suggesting that the structures of ceramides affect the skin permeability barrier.[15] A more recent Japanese study reported a significant difference in Ceramide 6 between AD non-lesional and lesional skins, and between non-lesional and normal skins,[16] providing more granularity to the importance of maintaining the level of Ceramide 6 in AD skins.

Besides the right level and structure of ceramide, the composition of ceramide is important in maintaining the permeability barrier functions. Unique changes in ceramide composition were observed in AD patients. AD patients had significantly lower ratios of several ceramide subclasses (Ceramide 3:2, Ceramide 8:2, Ceramide 3:5, Ceramide 8:5, Ceramide 10:5, Ceramide 7:5, Ceramide 9:5) compared to healthy patients.[5,14] The changes in ceramide composition disrupted the structure of the lipid lamellae and the corneocyte lipid envelope, impaired the functionality of the skin permeability barrier, increased TEWL and reduced skin hydration.[5,14]

While most moisturisers reduce cytokine production by improving skin permeability and restoring SC hydration, ceramides and their metabolites (sphingoid base, sphingosine-1-phosphate and ceramide-1-phosphate) also modulate skin immunity. Firstly, the FA and sphingosine exhibit potent activity against bacterial, yeast, and viral pathogens, and such inhibition of pathogen colonisation reduce superantigen-initiated inflammation.[3,6] Secondly, the ceramide metabolites stimulate innate immunity by increasing the synthesis of antimicrobial peptides in response to external stress, such as ultraviolet irradiation and other types of oxidative stress, protecting the skin against external stressors in the absence of microbial infection.[17] Thirdly, ceramide metabolites activate two acidic pH-dependent enzymes, which increase the production of ceramides required to form the extracellular lamellar bilayers. Lastly, ceramide metabolites inactivate kallikreins, which are activated at high pH skin of AD patients to disrupt the SC integrity.[18] The critical role of ceramides in the anti-inflammatory pathway explained the reason behind altered ceramides levels and compositions commonly observed in lesional skin compared to non-lesional skin.[15]

Apart from forming the basis of SC's physical and chemical defence system, ceramides and their metabolites regulate cellular functions, including cell cycle arrest, differentiation and apoptosis. They add anti-mitotic and pro-cell death features to cells, including in keratinocytes,[17] potentially reducing the risk of skin lichenification in patients with persistent AD. Upon topical application, ceramides not only

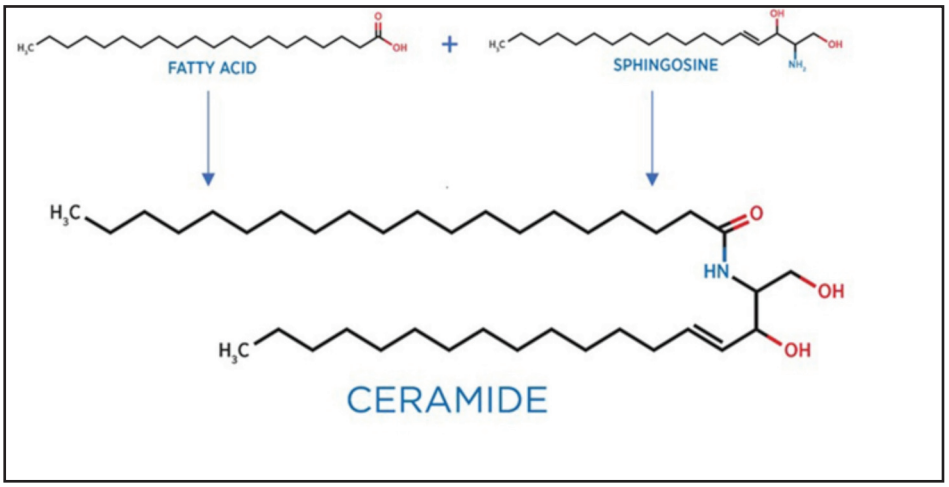

Fig. 1: Ceramide composition.

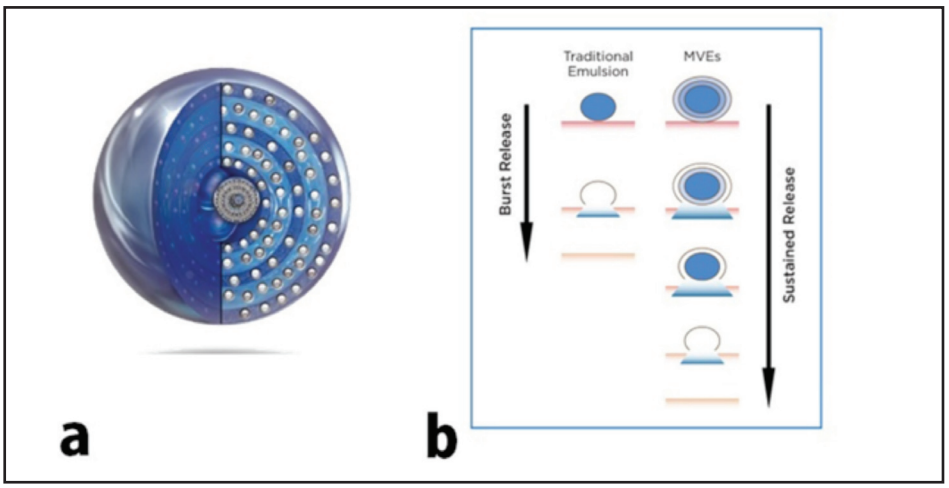

Fig. 2: Multivesicular emulsion (MVE) (a) and its sustained release mechanism of action (b).

form liquid crystalline structures, lamellar liquid crystalline, and gel structures with other chemicals formulated in the agent, strengthening the skin permeability barrier, they were incorporated into lamellar bilayer structures to enhance barrier integrity. Lastly, they penetrate nucleated layers of epidermis and the absorbed ceramides are hydrolysed to the metabolites (a sphingoid base and fatty acid), which are utilised in endogenous ceramide synthesis.[17] The metabolites amplify the production and delivery of ceramide and other lipids to the SC extracellular spaces, replenishing the lamellar bilayers essential for permeability barrier, skin hydration, antimicrobial, anti-inflammatory and cellular function.[18]

CLINICAL EVIDENCE OF CERAMIDES IN ATOPIC DERMATITIS

Based on the well-deciphered physical and biochemical roles of ceramide in AD, ceramide-dominant moisturiser seems an appealing treatment option to replenish the ceramide levels in SC of AD patients, enhancing the recovery of compromised skin permeability barrier in AD patients.[3] Numerous ceramide-dominant moisturisers with unique blends of ingredients in varying levels and ratios have been developed and introduced to the market. Although commercially available moisturisers may appear safe to be applied on the skin, animal studies have demonstrated that some products could potentially bring more harm than benefits.[19] Also, the absorption rate of ceramides often depends on the formulations and vehicle technologies.[17] Therefore, all moisturisers should be clinically proven for their safety and effectiveness before being prescribed to AD patients.

Given the heterogeneity in the study design, study population, intervention (different active ingredients and formulations), comparator used, and outcomes, this review did not pool the outcomes via meta-analysis but narratively reported individual studies. Our review shows that ceramide-dominant moisturisers are safe for children and adults with AD (Table II).

Most clinical studies have demonstrated favourable outcomes for ceramide-containing moisturisers (ceramides, pseudo-ceramides and ceramide precursors) in patients with AD, except Gupta et al.[20] and Miller et al.[39] Improved SCORAD (SCORing Atopic Dermatitis)[21,23,26,29,36,37,45], decreased TEWL[21,22,27-30,36,41,43,45], increased skin hydration[30,33-36,43-45] and reduced signs of dryness[27,28,30,31,35,43,44] were often reported after the treatment of

ceramide-dominant moisturisers. Two studies[31,40] reported a lower incidence of flare in the treatment arms while one reported a significantly shorter time to clear after the treatment of ceramide-dominant moisturisers and cleanser compared to the control arm.[25] Notably, four studies[21,24,32,33] observed inconsistent outcomes, such as positive outcomes in symptoms only but no significant difference in signs such as TEWL and skin hydration or vice versa.

This review included both cohort and randomised controlled trials. All cohort studies were limited by their non-randomisation nature and lack of control arms while most RCT studies were of small study size and short duration of follow-up. Deliberate assessments of each study's clinical effectiveness and safety are needed before prescribing ceramide-dominant moisturisers. The long-term safety and efficacy of ceramide-dominant moisturisers remained to be observed.

The findings in this review supported the guideline recommendation[2,12] for moisturisers to be incorporated as an integral part of the AD management plan, not only to improve AD signs and symptoms, but also to accelerate the skin repair process, delay incidence and time to flares and reduce the need for rescue TCS therapy.[11] Choosing the right physiological lipid moisturiser therapy with the optimal 3:1:1 molar ratio (ceramide, fatty acid, cholesterol) that suits individual AD patients is an art. Besides safety and effectiveness, moisturisers with high patient acceptability and dosing convenience could potentially improve patient compliance, providing additional value for AD patients in their roadmap to achieving long-term remission.

THE ROLE OF MULTIVESICULAR EMULSION (MVE) IN ATOPIC DERMATITIS

Over the years, several formulation technologies (Table III) were introduced to enhance the delivery of active ingredients into the skins, including moisturisers. Different formulation technologies exhibit distinct pharmacokinetic and pharmacodynamic properties which affect the therapeutic response; therefore it is of utmost importance to characterise the right formulation technologies for active ingredients intended to be delivered to the targeted sites.[46]

Multivesicular emulsion (MVE) is a unique emulsion technology that differs from the traditional water-in-oil and oil-in-water emulsion.[25] It is manufactured using behentrimonium methosulfate, a cationic quaternary amine salt emulsifier, which allows the formation of the multilamellar concentric spheres of oil and water (Fig. 2). The alternating hydrophilic and hydrophobic concentric layers encapsulate the active ingredients, such as ceramides, phytosphingosine, FA, cholesterol, dimethicone, glycerol, and hyaluronic acid, in either the lipid layers or within the aqueous compartment, depending on their compatibility.
The distinctive MVE structure allows the active ingredients to be delivered to the skin surface, rather than to be absorbed into the deeper epidermis and circulation. When used in ceramide formulations, the MVE structure allows the ceramides to be released in a controlled manner, forming a long-lasting occlusive layer. The occlusive barrier sustainably prevents TEWL, maintaining skin hydration up to 24 hours and avoiding invasion of irritants and pathogens. On top of that, MVE acts to continuously stimulate intracellular ceramide synthesis, enhancing skin permeability barrier repair.[25,28] In addition to improving the delivery of active ingredients, MVE itself displays skin barrier protective and moisturising properties[4], highlighting the potential for MVE to be used alone or as a topical vehicle to enhance the therapeutic effect of other active ingredients.

CLINICAL EVIDENCE OF MVE IN ATOPIC DERMATITIS

Given that the MVE technology is purported to provide sustainable skin hydration over an extended period, a double-blind intra-subject vehicle-controlled single open-application randomised clinical trial was conducted to compare the duration of skin hydration imparted by the MVE-based moisturisers (both cream and lotion formulations) and by three paraffin-based emollient therapies commonly prescribed in the UK among AD patients (reference). Results showed that MVE-based moisturisers provide clinically meaningful improvements in skin hydration and reduction in skin dryness that is sustained over 24 hours.[27] While patient compliance to moisturisers is prudent for changing the trajectory of AD diseases, offering sustained release once-daily application moisturisers to patients with low compliance could potentially reduce the incidence of AD flares, moving one step towards achieving long-term remission.

Besides that, several clinical studies have confirmed the clinical effectiveness and safety of MVE technology in delivering ceramides to the skin.[25-28] Compared to the areas treated with a reference cream, AD skins treated with ceramide-dominant MVE-based moisturisers were found to have greater skin permeability barrier integrity, as observed from the significant reduction in TEWL and enhanced lipid lamellar arrangement after 4 weeks of treatment. While the signs of dryness had resolved in areas treated with the MVE-based moisturisers, they persisted in areas treated with the reference cream. Signs of redness were resolved similarly in moisturiser-treated regions, suggesting that ceramide-dominant MVE-based moisturisers allow more effective and rapid skin permeability barrier repair and hydration, protecting the skin against irritation compared with the reference test cream.[28]

It is a common practice to combine the use of TCS in emollient vehicles with separate moisturisers in the treatment of AD. However, little is known about the potential interaction between moisturisers and the TCS. Upon application, the TCSs are often stored in the SC for up to 14 days depending on the vehicle formulation and the time that SC takes to regenerate. Any skin occlusion by the moisturisers may result in a second dose as the TCSs reservoir in the SC are slowly absorbed into the deeper skin layers. Besides that, moisturisers containing chemical penetration-enhancers such as propylene glycol and butylene glycol tend to increase the skin permeability and indiscriminately facilitate the permeation of TCS into the epidermis and dermis for systemic absorption. While moisturisers could potentially augment the effects of TCS, there are also concerns that moisturisers may reduce TCS responses by forming an occlusive barrier against potential irritants including TCS, or diluting the dose or

competing with the absorption of TCS. In the absence of clinical evidence, it is not possible to confirm the efficacy and safety of moisturisers and their vehicles when used in combination with TCS.

Draelos et al. conducted a randomised controlled trial on 60 subjects, aged between 5 to 80 years with mild to moderate AD, to examine the safety and efficacy of combination therapy with a high-potency TCS (i.e. fluocinonide cream 0.05%), MVE-formulated ceramide-containing moisturising cream and MVE-formulated ceramide-containing liquid cleanser. When MVE-moisturising cream and cleanser were used in combination with the highly potent TCS, the incidence of clearing at week 4 increased significantly from 15 to 76%. Greater AD signs and symptom improvement, and shorter time to clearing were also observed in the treatment group receiving combination MVE-moisturising cream and cleanser (3 weeks) compared with the treatment group receiving TCS alone (3.7 weeks). Moreover, there were no adverse events and tolerability issues reported by either the investigator or the subjects, suggesting the potential for MVE-moisturising cream and cleanser to be used concomitantly with highly potent TCS without significant interactions.[25]

Apart from effectiveness and safety, a cost-effectiveness study in the US reported that MVE-based moisturiser (CeraVe) is the most cost-effective emollient therapy, compared with other ceramide-dominant moisturisers.[53] As daily use of moisturisers is needed even after remission to achieve long-term remission, a cost-effective moisturiser could potentially improve compliance, subsequently overall patient outcomes.

Although this review may fail to capture all studies related to ceramide and MVE-formulated moisturisers due to the lack of an independent screener and publication bias, we extensively summarised the roles of ceramides and MVE technology in AD and described the most up-to-date clinical evidence of ceramide-dominant moisturisers and MVE technologies in managing AD, providing solid evidence to inform treatment decisions. Upon the availability of more clinical data, future study could meta-analyse the effect of ceramides and MVE technology in AD.

CONCLUSION

Ceramides are essential components in maintaining the skin permeability barrier and hydration, modulating skin immunity through anti-inflammatory and antimicrobial defence system, and regulating cellular functions. Most studies have shown that ceramide-dominant moisturisers are safe and effective in adults and children with AD. MVE technology offers an attractive delivery system to replenish ceramides in the SC, repairing the compromised skin permeability barrier and potentially improving patient compliance. Recommending clinically proven therapeutic moisturisers with the right ingredients (level, ratio, structure and composition), alongside an effective sustained release delivery system, to AD patients is one key strategy to successful disease control and flare prevention, potentially reducing the high disease burden to patients, families and societies.

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