Chandrashekar BS, Luger T, Rajendran SC, Parathasaradhi A, Thomas J, Ganjoo A, Sharma D, Damishetty R, Ruby N, Sujay V, Sriram S, Udare S, Shah D, Rajgopal J. Role of Actives in Emollients in Atopic Dermatitis. J Dermatol & Skin Sci. 2024;6(1):16-23

Journal of Dermatology and Skin Science

Review Article Open Access

Role of Actives in Emollients in Atopic Dermatitis

B. S. Chandrashekar[1], Thomas Luger[2], S. C. Rajendran[3], Anchala Parathasaradhi[4], Jayakar Thomas[5], Anil Ganjoo[6], Divya Sharma[7], Rajetha Damishetty[8], Nazima Ruby[9], Vijayalakshmi Sujay[10], Snehal Sriram[11], Satish Udare[12], Dhara Shah[13], Jayesh Rajgopal*[14]

[1]Chief Dermatologist / Medical Director: Cutis, Academy of Cutaneous Sciences, Bengaluru
[2]Department of Dermatology, University of Muenster, Muenster, Germany
[3]Director and Senior Consultant Dermatologist at Cosmetic Skin Care Clinic, Koramangala, Bengaluru
[4]Senior Consultant Dermatologist at Anchala's Skin Institute, Hyderabad
[5]Professor & Head, Chettinad Hospital and Research Institute, Chennai
[6]Director, Skinnovation Clinics, New Delhi
[7]Chief Consultant at Dr Divya's Skin and Hair Solutions, Bangalore
[8]Additional Medical director, Oliva chain of 23 Hair and Skin Clinics
[9]Consultant Dermatologist, Radiant Skin Clinic, Bengaluru
[10]Consultant Dermatologist and Cosmetologist, Shree Skin and Cosmetic Clinic, Bengaluru
[11]Consultant and Head of Cosmetic Dermatology Department at Nahar Medical Center, Mumbai
[12]Medical Director of 'Sparkle' Skin and Aesthetic Centre, Vashi and 'Disha Skin and Laser Institute' Thane, Mumbai
[13]Head Medical Affairs, Mylan Pharmaceuticals Private Limited - A Viatris Company
[14]Senior Medical Manager, Mylan Pharmaceuticals Private Limited - A Viatris Company

Article Info

Article Notes
Received: April 15, 2024
Accepted: May 30, 2024

***Correspondence:**
* Dr. Jayesh Rajgopal, Mylan Pharmaceuticals Private Limited - A Viatris Company, Bengaluru, India; Orcid Id: 0009-0003-4251-1394; Tel: (+91) 99771 38848;
Email: jayesh.rajgopal@viatris.com.

Keywords:
Atopic dermatitis
Emollients
Anti-inflammatory
Atopic eczema
Emollient plus

Abstract

The prevalence of atopic dermatitis (AD) in India is 2.7% (age 6–7 years) and 3.6% (age 13–14 years). Emollients remain mainstay treatment for atopic dermatitis. The present review article focuses on the role of active ingredients in emollients towards the management of AD. Article were selected by searching in database like Google Scholar and PubMed and were reviewed by the authors. Daily use of emollients from birth may significantly reduce the incidence of AD in a high-risk population. Emollients with a variety of active ingredients to target AD pathophysiology have been developed which contain active ingredients like liquorice extract (anti-inflammatory and anti-pruritic), niacinamide (restoration of barrier function), sterols (restoration of barrier function), laureth-9-polydocanol (anti-pruritic), xylitol (microbiome maintenance) and galacto-oligosaccharide (GOS) (microbiome maintenance). Emollient plus may be a useful adjunct to pharmacological therapy in AD and as maintenance therapy, providing rapid and significant improvements in skin moisture, epidermal barrier function, and signs and symptoms of AD.

Introduction

Atopic dermatitis (AD) also known as atopic eczema (AE), is a chronic inflammatory, relapsing, and pruritic skin disease that affects patients of all age groups and ethnicities.[1] It is characterized by recurrent eczematous lesions [1], and intense itch [1] and is often associated with elevated serum immunoglobulin E (IgE) levels.[2] It affects up to approximately 2.4% of the population worldwide [3] and can also appear in adults.[1] Onset of AD usually presents by the age of five years, but timely diagnosis and treatment will avoid future complications and improve patients' quality of life.[4] As per the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of atopic dermatitis in India is 2.7% (age 6–7 years) and 3.6% (age 13–14 years).[5] AD can have a profound, negative effect on the quality of life (QoL), including on social life, education, and work.[6]

Emollients remain the mainstay treatment for atopic dermatitis as they improve the epidermal barrier function, maintain skin

integrity and appearance, reduce trans epidermal water loss, and restore the lipid barrier's ability to attract, hold, and redistribute water.[2] The Indian guidelines also recommend the use of Moisturizers & Emollients as a first-line treatment for AD.[2] Emollients contain a humectant or moisturizer (promoting stratum corneum hydration) and an occludent (reducing evaporation such as lipids or petrolatum). Emollients containing moisturizers are better compared to those without, for reducing investigator-reported severity and leading to fewer flares and reduced usage of topical corticosteroids (TCS).[7] Daily use of emollients from birth may significantly reduce the incidence of AD in a high-risk population [8] although this was not confirmed in a clinical trial done in 1394 infants.[9]

Emollient Plus is a category of emollients that include extra skin-protecting ingredients. Emollients Plus contains active, non-medicated substances which can improve AD lesions through several synergistic modes of action, including preserving barrier lipid[10]. Use of Emollient Plus significantly improves clinical signs and symptoms, increases skin hydration, and improves the quality of life of subjects with mild AD as soon as 28 days. In addition, Emollients Plus has corticosteroid-sparing effect in subjects with mild to moderate AD[11]. This review primarily focuses on the role of active ingredients in emollients towards the management of AD.

Methods

The relevant articles were searched on databases like Google Scholar and PubMed using keywords "Atopic Dermatitis", "Emollient Plus", "Actives in Emollients", "Atopic dermatitis management". Articles which were primarily based on only emollients (without any active ingredients) were excluded from the review. The selected articles were reviewed by the authors and then included in the present article.

New Pathogenic Concepts of AD

The pathogenesis of AD is complex and multifactorial, driven by genetic, immune, and environmental factors.[12] A healthy epidermal barrier has a complex composition comprising of structural proteins and epidermal lipids that provide a physical protective barrier against immunological, neuro-sensory, and microbial barrier, and ultraviolet (UV) light injury.[13,14] Dysfunction of this epidermal barrier is a characteristic feature of the pathophysiology of AD, attributed to abnormalities in the formation of structural proteins (e.g., filaggrin) and lipid metabolism.[15] This disruption allows the entry of external antigens that induce impaired innate immune responses leading to persistent skin inflammation and in turn, further damaging the skin barrier.[16,17]

Two hypotheses have been proposed for inflammatory lesions in atopic dermatitis which are (i) an imbalance of adaptive immune system; and (ii) defective epidermal barrier.[18] An imbalance in T regulatory cells and T-helper cells type 1, 2, 17 and 22 causes an imbalance in the adaptive immune system. The Th2 differentiation of naive CD+4 (Cluster of differentiation) T-cells predominates causing increased production of interleukins (IL) IL-4,

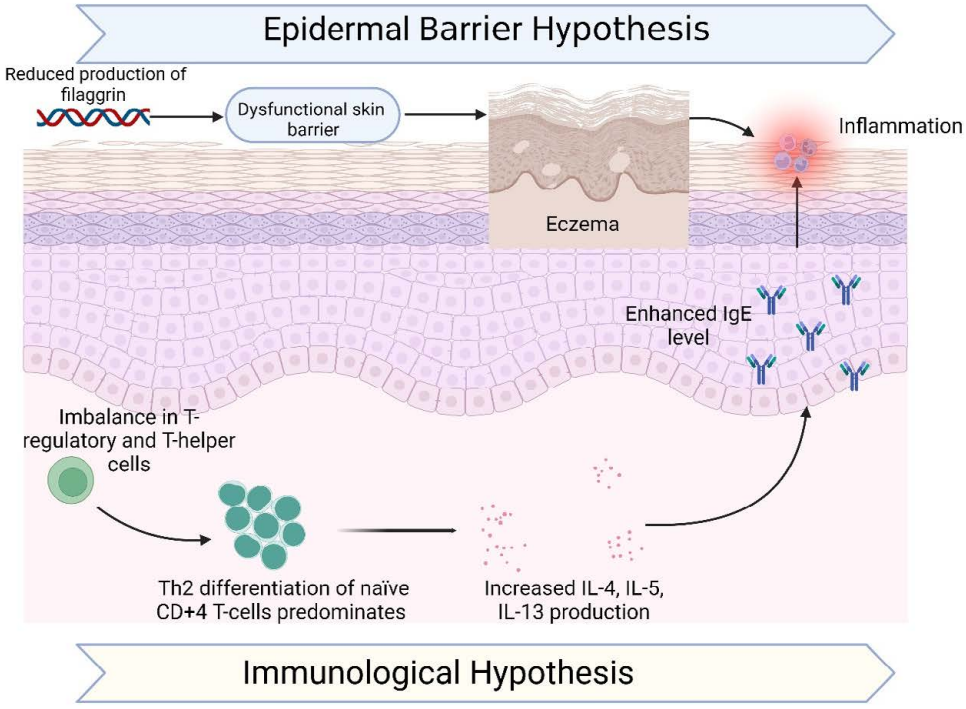

Figure 1: Mechanism of atopic dermatitis

IL-5 and IL-13 leading to enhanced IgE level and Th1 differentiation is correspondingly inhibited.[18] A defective epidermal barrier occurs due to reduced production of filaggrin and trans epidermal loss of water causing eczema (Fig. 1). Dry skin leads to increased penetration causing allergic sensitization, asthma, and hay fever.[18]

Claudin-1 is a tight junction protein homogenously expressed in the stratum granulosum, [19] which is reduced in patients with AD. Restoring claudin-1 expression is important for preserving tight junction integrity.[20] Involucrin is a cornified envelope-associated protein; reduced expression disturbs barrier function, so increasing involucrin may be beneficial in the skin of patients with AD.[21] Caspase-14 is a late epidermal differentiation protein that is reduced in patients with AD. It catalyzes the degradation of pro-filaggrin; thus, is key to the formation of the SC.[22] Keratin-16 is a type 1 intermediate cytoskeletal protein expressed in keratinocytes in response to epidermal barrier challenges. Keratin-16 is induced in AD and reducing its expression may help modulate the epidermal innate immune response.[23]

Preventive Strategies and General Measures

According to European guidelines (EuroGuiDerm) on atopic eczema, therapy with TCS (class II) or topical calcineurin inhibitors (TCI, e.g., Pimecrolimus), antiseptics, silver-coated textiles, topical crisaborole is recommended for mild (SCORAD <25) or transient eczema. Proactive therapy with TCI (Tacrolimus, Pimecrolimus) or TCS (class II or III), wet wraps, UV therapy (UVB 311 nm), psychosomatic counselling and climate therapy is recommended for moderate (SCORAD 25-30) or recurrent eczemas. Hospitalization, biologics such as dupilumab, tralokinumab, Janus kinase inhibitors such as abrocitinib, baricitinib, upadacitinib, cyclosporin A, methotrexate, azathioprine, mycophenolate mofetil is recommended for patients with severe (SCORAD >50) or persistent eczema [7]. The Indian guidelines also recommend the use of emollients and TCS as first-line therapy for AD.[2]

Although the efficacy of TCS has been demonstrated, they are associated with impairment of the epidermal barrier function and skin atrophy [24], limiting their use in sensitive skin areas, and preventing long-term use. In addition, patient's fears of side effects from corticosteroids (i.e., corticophobia) are common.[8,25] Emollients remain the mainstay treatment for atopic dermatitis.[2] Emollients should be recommended in sufficient quantities, and they should be used liberally and frequently, with a minimum of 250g per week for children. It is also advisable to utilize soap alternatives and emollient bath oils. In the winter, emollients with a higher lipid content are ideal. Regular use of emollient has a short- and long-term steroid-sparing effect in mild-to-moderate AD.

An induction of remission with TCS or TCI is required first.[8] Most emollients showed some beneficial effects, producing better results when used with active treatment, prolonging the time to flare, and reducing the number of flares and amount of TCS needed to achieve similar reductions in eczema severity.[26] Several non-medicated products containing putative active ingredients are used for topical treatment of AE, referred to as "emollients plus" per European guidelines. Emollients plus contain flavonoids, bacterial lysates, or synthetic derivatives of menthol.[7]

Rationale for Selected Active Ingredients in a Novel Emollient Plus

Despite an increasing range of topical medications, emollients remain a fundamental part of AD management.[27] Emollients with a variety of active ingredients to target AD pathophysiology have been developed.[28] A novel generation of Emollient Plus has been developed which could not only act as maintenance therapy for AD but would also have synergistic anti-inflammatory effect.[10] Some of the active ingredients present in a novel emollient plus are liquorice extract (anti-inflammatory and anti-pruritic), niacinamide (restoration of barrier function), sterols (restoration of barrier function), laureth-9-polydocanol (anti-pruritic), xylitol (microbiome maintenance) and galacto-oligosaccharide (GOS) (microbiome maintenance) (Fig. 2).

Inhibition against tumor necrosis factor-α production and nuclear factor-kB activation was seen in peritoneal mouse macrophages pre-treated with glycyrrhetinic acid (one of the main bioactive ingredients in liquorice) for 30 minutes, followed by lipopolysaccharide 100 ng/mL for 24 hours indicating its anti-inflammatory response.[29] In a randomized, double-blind, placebo-controlled trial in patients with mild-to-moderate AD (n=90), a 73% reduction in pruritus scores was reported in those treated with liquorice extract 2% versus baseline after 2 weeks.[30]

Topical application of niacinamide 0.5% and soy phytosterol 0.5% recovered approximately 95% of epidermal barrier integrity 8 days after tape stripping in

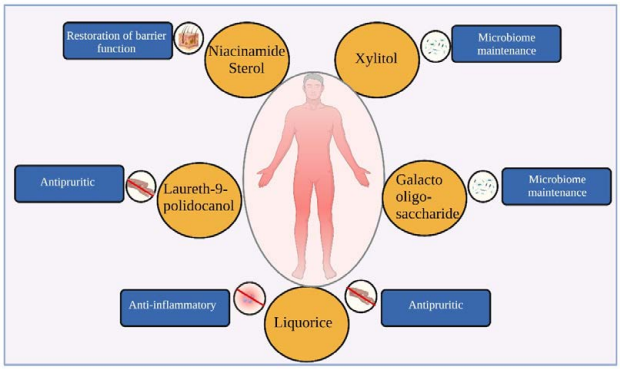

Figure 2: Components of Emollient plus

six healthy volunteers.[31] In a double-blind study involving 41 females with sun-damaged skin, niacinamide 2% twice daily significantly reduced TEWL (by up to 20%) versus control over a 24-day treatment period.[32]

In cell suspensions from a patient with AD, xylitol 5%/farnesol 0.2% cream inhibited the production of glycocalyx and dissolved fibrin fibers, synergistically inhibiting biofilm formation by *S. aureus*.[33] In a randomized, double-blind, placebo-controlled trial in 17 patients with AD, the ratio of total *S. aureus* bacteria significantly decreased with xylitol and farnesol after 7 days compared with baseline ($p=0.016$) and with placebo ($p=0.08$).[34] Polydocanol 3% and urea 5% substantially reduced itching in patients with skin disorders.[35]

Mode of Action of the Components of Emollient Plus

Liquorice extract

Liquorice contains over 400 compounds, including triterpene saponins and flavonoids [36]. The anti-inflammatory effects of liquorice extract are attributed to its flavonoids and other active compounds [36,37]. Liquorice flavonoids, such as isoliquiritigenin, mitigate inflammation by inhibiting the mitogen-activated protein kinase (MAPK) signaling pathway via suppression of ERK1/2 and p38 phosphorylation [36]. Liquorice flavonoids exhibit antioxidant activity, which can help reduce inflammation by neutralizing reactive oxygen species (ROS), potent inflammatory mediators[38]. Compounds in liquorice, such as glycyrrhizic acid (GA), liquiritin (LQ), and liquiritigenin (LG), inhibit the elevation of pro-inflammatory mediators like inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and interleukin (IL)-6 in cells[37]. Liquorice treatment can up-regulate the expression of Claudin in tight junction proteins, improving intestinal mucosal damage and exerting a therapeutic effect[39].

Niacinamide

Niacinamide plays a pivotal role in NAD^+ synthesis, contributing to redox reactions and energy production in cutaneous cells[40]. This helps restore cellular energy levels and promotes healthy skin function. Niacinamide has been shown to attenuate oxidative stress and inflammatory responses in the skin[40]. This can help reduce inflammation and promote healing, thereby restoring the skin's barrier function[40]. Niacinamide is known to improve skin barrier function and reduce trans epidermal water loss by increasing ceramide and free fatty acid levels[41]. It also increases production of epidermal proteins, including keratin, involucrin, and filaggrin[41].

Galacto-oligosaccharides (GOS)

Galacto-oligosaccharides (GOS) are oligosaccharides formed by β-galactosidase transgalactosylation[42]. They are indigestible food components that can pass through the upper gastrointestinal tract relatively intact and ferment in the colon to produce short-chain fatty acids (SCFAs) that further regulate the body's intestinal flora[42]. GOS ferments in the colon to produce SCFAs[42]. SCFAs have been shown to enhance the growth of beneficial microorganisms, which can help in alleviating symptoms of atopic dermatitis[43]. GOS performs well compared to other oligosaccharides in regulating gut microbiota[42]. This is important because a balanced gut microbiota is associated with improved immune response and reduced inflammation, both of which are crucial in managing atopic dermatitis[43]. GOS has been found to minimize the production of interleukin-10 and suppress the production of cytokines, such as interleukin 17[44]. These cytokines are involved in the inflammatory response, so their regulation can help in managing atopic dermatitis[44].

Xylitol

Xylitol is known to hydrate the skin and improve its barrier function. In addition to the skin-hydrating properties, xylitol exerts anti-irritant and anti-inflammatory effects in a dose-dependent manner[10]. This can help reduce the inflammation and irritation commonly seen in AD. Xylitol induces gene expression changes in the keratinocytes which are the primary type of cell found in the epidermis. Xylitol has been found to decrease TEWL in patients with AD after 7 days of use. Xylitol has selective antibacterial and prebiotic activity, which can help maintain the skin microbiome[45]. A balanced skin microbiome is crucial for maintaining skin health and preventing flare-ups in conditions like AD[46].

Novel Emollient Plus in the Management of AD

Several studies, both pre-clinical and clinical, have demonstrated the efficacy and safety of emollient plus in patients with AD (Table 1). In an in vitro study, skin organ cultures were subject to tape stripping (100 repeated applications and subsequent removals of adhesive tapes to the skin surface) as a model for skin barrier damage.[10] Emollient plus significantly increased epidermal thickness in organ cultures treated with 100% emollient plus solution versus those treated with diluent solution ($p<0.01$). The use of emollient plus significantly ($p<0.01$) increased epidermal thickness, increased claudin-1, caspase-4 and involucrin expression and decreased kerartin-16 expression in organ cultures.[47] Emollient plus significantly reduced pruritus in patients compared to baseline (Day 1: 42.6% reduction; Day 21: 40.7% reduction) and untreated areas. Following treatment, pruritus reduced from a mean rating of 5.4 (on a 0–10 VAS) at baseline to 3.1–4.4 across all evaluation time

Table 1: Studies with novel emollient plus

Study design	Objectives	Patients	Treatment	Evaluation	Results
Study 1. Gasparri. 2019					
Observational pilot study (n=10 AD patients); comparisons were made between treated versus non-treated areas on each patient	Investigate the efficacy of Emollient plus on skin moisture, epidermal barrier function, and AD signs and symptoms	Ten otherwise healthy Caucasian adults with clinical signs of AD	Emollient plus applied twice daily to areas of AD on one side of the body, with treated and untreated areas for comparison.	Performed at baseline, 1, and 2 days after the first application of Emollient plus, and after 7 and 21 days of twice-daily treatment	Significant reduction in pruritus was seen versus baseline (Day 1: 42.6% reduction; Day 21: 40.7% reduction) and versus untreated areas. 80% of patients were 'satisfied' or 'very satisfied' with Emollient plus
Study 2. Quadri, *et al.* 2021 – *Pre-clinical analysis*					
An in-vitro study, using a tape-stripping mediated skin barrier disruption model	Investigate the effect of Emollient plus on skin barrier recovery	N/A	After tape stripping, epidermal cells were treated with either Emollient plus or diluent (control) and cultured	Samples were analyzed at 18 hours (skin barrier integrity analysis) or up to 120 hours (lipid restoration analysis)	Emollient plus significantly increased epidermal thickness in organ cultures.
Study 3: Quadri, *et al.* 2021 – *Clinical analysis*					
Double-blind, randomized, placebo-controlled study in patients with mild-to-moderate AD in clinical remission	Evaluate the role of Emollient plus in hydration and vascularization of the skin	Male (n=10) or female (n=10) between the ages of 24 and 60 with mild- to-moderate AD in clinical remission phase	Assigned to one of two treatment groups: Group 1: n=10 (5 male), Emollient plus once daily Group 2: n=10 (5 male), placebo once daily	Performed at baseline, and after 1 and 2 months of once-daily treatment with Emollient plus or placebo	After 2 months of treatment with Emollient plus, a significant reduction in epidermal thickness was seen versus placebo
Study 4: Sparavigna, *et al.* 2019					
Single center, randomized, double-blind study in patients with mild AD	Primary objective: efficacy of Emollient plus versus vehicle on pruritus	Patients were male or female aged 24–50 years (mean age: 40 years) with mild AD (SCORAD <25)	Emollient plus (n=58 forearms) or vehicle (n=39 forearms) applied twice daily to the left or right forearm for 28 days	Performed at baseline, and after 14 and 28 days of treatment with Emollient plus or vehicle	Significant reduction of pruritus compared with baseline (T14 d: 53%, $p<0.05$; T28 d: 89%, $p<0.05$) and with vehicle (T14 d: 53% vs 23%, $p<0.05$; T28 d: 89% vs 60%, $p<0.05$, respectively)
Study 5: Gasparri, *et al.* 2021					
Monocentric, open study in subjects predisposed to AD	Evaluate the changes in skin microbiome after 28 days of treatment versus baseline in Emollient plus - treated areas	Eleven patients considered predisposed to AD: very dry skin; ≥1 episode of dermatitis during life; skin prone to irritation/ erythema; and frequent itching	Emollient plus was applied twice daily between the neck and shoulders for 28 days	To assess alpha microbiome diversity, bacterial DNA was extracted from treated areas at baseline and after 28 days of treatment	Microbial diversity improved in the majority of subjects following 28 days of treatment with Emollient plus.
Study 6: Sparavigna, *et al.* 2020					
Open-label, single-arm, interventional, multicentre study in patients previously treated with pimecrolimus	Primary objective: Evaluate the time to flare, defined as the time to next disease exacerbation	One hundred and one patients, both genders aged >12 years with mild-to-moderate AD (IGA=2 or 3), who had responded successfully to 1% pimecrolimus cream	Emollient plus was applied twice daily for 4 months	Performed at baseline, and after 14 days, then every month for 4 months	Emollient plus after 1% pimecrolimus, was able to maintain regression of flare-up to at least 4 months in 99% of the patients. Percentage of patients who had an IGA of 2 decreased over time from 17% at baseline to 2% at Month 4.

points (3.2 at Day 21). Emollient plus also significantly improved skin moisture levels at each evaluation time point versus baseline in these patients, increasing up to 111.5% at Day 21 versus baseline (mean [SEM]: 27.7 [2.5] vs 13.1 [1.0]; p<0.001).[48] In another study, the use of emollient plus significantly reduced pruritis and improved skin hydration in patients with AD.[49] Pimecrolimus followed by emollient plus is a useful treatment approach in the management of mild to moderate AD. Emollient plus after Pimecrolimus cream was able to maintain regression of flare-up to at least 4 months in almost all patients. Improvement was seen in all other clinical efficacy outcomes: IGA, erythema, xerosis, oedema, bleeding, excoriations and lichenification, VAS for dryness, itching and sleep loss and the SCORAD score, and was associated with optimal tolerability.[49] To date, no adverse events have been reported with emollient plus in patients with AD, and most patients have confirmed that it is cosmetically acceptable. Some clinical researchers were concerned that the use of GA and glycyrrhizin may lead to increased systemic glucocorticoid and mineralocorticoid toxic effects. However, there is no such evidence available till date.[50] Prebiotics like galacto-oligosaccharide can reduce AD up to 32% in children [51] although few studies have reported that use of probiotics may cause increased rate of recurrent episodes of wheezing bronchitis in AD patients.[52] An open, single center, randomized controlled trial in Slovakia was conducted with 119 patients with mild to moderate AD[11]. The primary efficacy criterion of the study was the amount of corticosteroid used. The results showed that between baseline and day 28, the mean amount of corticosteroid used was significantly lower in the emollient 'plus' group compared to the control group. The emollient 'plus' group also had fewer days of corticosteroid application and fewer applications per day[11]. The study demonstrated that the daily use of the emollient 'plus' balm resulted in significant corticosteroid-sparing effects in patients with mild to moderate AD. The emollient 'plus' balm reduced the amount of corticosteroid used, the number of days of application, and the frequency of applications per day. The treatment was well-tolerated and showed similar improvements in AD severity and quality of life compared to the control group[11].

Limitations of the Studies

Patients with AD often have increased penetration of allergens, immune dysregulation due to defective skin barrier. [53] Frequent use of emollients and topical medication predisposes the patients towards developing allergic contact dermatitis. [53] Farnesol has been reported to be a contact allergen.[54] Galacto-oligosaccharide was also reported to cause allergic reactions among atopic population in Singapore.[55] Although most of the studies done with Emollient Plus have shown positive results, these studies have the limitations such as small sample size and single center designs. Most of the studies were done in patients >12 years of age. Patch testing should also be done to check for potential allergens. Clinicians need to be aware that these promising studies may not translate into real-life benefit.

Conclusions

Emollient application should be a key component of atopic dermatitis patients' therapy regimens because there is strong evidence that it can lessen the severity of the condition and the requirement for pharmaceutical intervention. In clinical trials, a novel emollient plus improved several cardinal symptoms and processes implicated in AD, including pruritus, skin hydration and epidermal barrier function. It has also shown to improve cutaneous microbial diversity. The complementary approach with pimecrolimus 1% cream and a new emollient plus is useful in the management of mild to moderate AD. Novel Emollient plus may be a useful adjunct to pharmacological therapy in AD and as maintenance therapy, providing rapid and significant improvements in skin moisture, epidermal barrier function, and signs and symptoms of AD. It can maintain the flare-free period for a long period of time. The choice of applying a cream, ointment or lotion depends on the environmental conditions.[56]

Acknowledgements

The authors acknowledge Arghya Bhattacharya, Ph. D for medical writing support (Viatris). The figures were created with BioRender.com.

Conflict of Interest

Dr Jayesh Rajgopal and Dr Dhara Shah are employees of Viatris. All other authors have no competing interest.

Funding

The medical writing and funding were done by Viatris.

Data Availability Statement

No underlying data was collected or produced in this study.

References

1. Langan S. Dermatite atópica. *Lancet.* 2020;396(10247): 345-360.
2. Rajagopalan M, De A, Godse K, et al. Guidelines on Management of Atopic Dermatitis in India: An Evidence-Based Review and an Expert Consensus. *Indian J Dermatol.* 2019; 64(3): 166-181.
3. Urban K, Chu S, Giesey RL, et al. The global, regional, and national burden of atopic dermatitis in 195 countries and territories: An ecological study from the Global Burden of Disease Study 2017. *JAAD Int.* 2021; 2: 12-18.
4. Avena-Woods C, Mangione RA, Wu WK. Exploring the Community Pharmacist's Knowledge of Celiac Disease. *Am J Pharm Educ.* 2018; 82(2): 6353.

5. Rajagopalan M, Chitkara AJ, Dalwai S, et al. Burden of Disease, Unmet Needs in the Diagnosis and Management of Atopic Dermatitis: An Indian Expert Consensus. *Clin Cosmet Investig Dermatol.* 2021; 14: 1755-1765.

6. Drucker AM, Wang AR, Li WQ, et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017; 137(1): 26-30.

7. Wollenberg A, Kinberger M, Arents B, et al. EuroGuiDerm guideline on atopic eczema. *J Eur Acad Dermatol Venereol.* 2022.

8. Wollenberg A, Barbarot S, Bieber T, et al. European dermatology forum (EDF), the European academy of dermatology and venereology (EADV), the European academy of allergy and clinical immunology (EAACI), the European task force on atopic dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), global allergy and asthma European network (GA2LEN) and the European Union of medical specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol.* 2018; 32(6): 850-878.

9. Chalmers JR, Haines RH, Bradshaw LE, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet.* 2020; 395(10228): 962-972.

10. Araviiskaia E, Pincelli C, Sparavigna A, et al. The Role of a Novel Generation of Emollients, 'Emollients Plus', in Atopic Dermatitis. *Clin Cosmet Investig Dermatol.* 2022; 15: 2705-2719.

11. Zelenkova H, Kerob D, Salah S, et al. Impact of daily use of emollient 'plus' on corticosteroid consumption in patients with atopic dermatitis: An open, randomized controlled study. *J Eur Acad Dermatol Venereol.* 2023; 37 Suppl 5: 27-34.

12. Kim J, Kim BE, Leung DYM. Pathophysiology of atopic dermatitis: Clinical implications. *Allergy Asthma Proc.* 2019; 40(2): 84-92.

13. Matejuk A. Skin Immunity. *Arch Immunol Ther Exp (Warsz).* 2018; 66(1): 45-54.

14. Luger T, Amagai M, Dreno B, et al. Atopic dermatitis: Role of the skin barrier, environment, microbiome, and therapeutic agents. *J Dermatol Sci.* 2021; 102(3): 142-157.

15. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol.* 2014; 134(4): 769-779.

16. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol.* 2008; 121(6): 1337-1343.

17. Egawa G, Kabashima K. Barrier dysfunction in the skin allergy. *Allergol Int.* 2018; 67(1): 3-11.

18. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy.* 2014; 2014: 354250.

19. De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2011; 127(3): 773-786 e771-777.

20. Gruber R, Bornchen C, Rose K, et al. Diverse regulation of claudin-1 and claudin-4 in atopic dermatitis. *Am J Pathol.* 2015; 185(10): 2777-2789.

21. Jiang YJ, Kim P, Uchida Y, et al. Ceramides stimulate caspase-14 expression in human keratinocytes. *Exp Dermatol.* 2013; 22(2): 113-118.

22. Lessard JC, Pina-Paz S, Rotty JD, et al. Keratin 16 regulates innate immunity in response to epidermal barrier breach. *Proc Natl Acad Sci U S A.* 2013; 110(48): 19537-19542.

23. Jensen JM, Folster-Holst R, Baranowsky A, et al. Impaired sphingomyelinase activity and epidermal differentiation in atopic dermatitis. *J Invest Dermatol.* 2004; 122(6): 1423-1431.

24. Jensen J-M, Pfeiffer S, Witt M, et al. Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *Journal of allergy and clinical immunology.* 2009; 124(3): R19-R28.

25. Lee JY, Her Y, Kim CW, et al. Topical Corticosteroid Phobia among Parents of Children with Atopic Eczema in Korea. *Ann Dermatol.* 2015; 27(5): 499-506.

26. van Zuuren EJ, Fedorowicz Z, Christensen R, et al. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev.* 2017; 2(2): CD012119.

27. Hong J, Buddenkotte J, Berger TG, et al. Management of itch in atopic dermatitis. *Semin Cutan Med Surg.* 2011; 30(2): 71-86.

28. Hon KL, Kung JSC, Ng WGG, et al. Emollient treatment of atopic dermatitis: latest evidence and clinical considerations. *Drugs Context.* 2018; 7: 212530.

29. Armanini D, Nacamulli D, Francini-Pesenti F, et al. Glycyrrhetinic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. *Steroids.* 2005; 70(8): 538-542.

30. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. *J Dermatolog Treat.* 2003; 14(3): 153-157.

31. Offerta A, Bonina F, Gasparri F, et al. In vitro Percutaneous Absorption of Niacinamide and Phytosterols and in vivo Evaluation of their Effect on Skin Barrier Recovery. *Current Drug Delivery.* 2016; 13(1): 111-120.

32. Bissett D. Topical niacinamide and barrier enhancement. *Cutis.* 2002;70(6 Suppl): 8-12; discussion 21-13.

33. Katsuyama M, Kobayashi Y, Ichikawa H, et al. A novel method to control the balance of skin microflora Part 2. A study to assess the effect of a cream containing farnesol and xylitol on atopic dry skin. *J Dermatol Sci.* 2005; 38(3): 207-213.

34. Katsuyama M, Ichikawa H, Ogawa S, et al. A novel method to control the balance of skin microflora. Part 1. Attack on biofilm of Staphylococcus aureus without antibiotics. *J Dermatol Sci.* 2005; 38(3): 197-205.

35. Freitag G, Hoppner T. Results of a postmarketing drug monitoring survey with a polidocanol-urea preparation for dry, itching skin. *Curr Med Res Opin.* 1997; 13(9): 529-537.

36. Wu Y, Wang Z, Du Q, et al. Pharmacological Effects and Underlying Mechanisms of Licorice-Derived Flavonoids. *Evid Based Complement Alternat Med.* 2022; 2022: 9523071.

37. Yu JY, Ha JY, Kim KM, et al. Anti-Inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin and liquiritigenin, in BV2 cells and mice liver. *Molecules.* 2015; 20(7): 13041-13054.

38. Leite CDS, Bonafe GA, Carvalho Santos J, et al. The Anti-Inflammatory Properties of Licorice (Glycyrrhiza glabra)-Derived Compounds in Intestinal Disorders. *Int J Mol Sci.* 2022; 23(8).

39. Wang HB, Wang PY, Wang X, et al. Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein Claudin-1 transcription. *Dig Dis Sci.* 2012; 57(12): 3126-3135.

40. Marques C, Hadjab F, Porcello A, et al. Mechanistic Insights into the Multiple Functions of Niacinamide: Therapeutic Implications and Cosmeceutical Applications in Functional Skincare Products. *Antioxidants (Basel).* 2024; 13(4).

41. Yadav E. Niacinamide and Coenzyme Q10: Molecular Insights into Skin Health, Longevity, and Optimized Cosmetic Formulations. *Advance Research in Dermatology & Cosmetics (ARDC).* 2023; 2(1): 1-2.

42. Mei Z, Yuan J, Li D. Biological activity of galacto-oligosaccharides: A review. *Front Microbiol.* 2022; 13: 993052.

43. Suh MG, Bae GY, Jo K, et al. Photoprotective Effect of Dietary Galacto-Oligosaccharide (GOS) in Hairless Mice via Regulation of the MAPK Signaling Pathway. *Molecules.* 2020; 25(7).

44. Kim D-Y, Jung D-H, Song E-J, et al. D-galactose Intake Alleviates Atopic Dermatitis in Mice by Modulating Intestinal Microbiota. *Frontiers in Nutrition.* 2022; 9.

45. Bieber T. Atopic dermatitis. *N Engl J Med.* 2008; 358(14): 1483-1494.

46. Korponyai C, Szel E, Behany Z, et al. Effects of Locally Applied Glycerol and Xylitol on the Hydration, Barrier Function and Morphological Parameters of the Skin. *Acta Derm Venereol.* 2017; 97(2): 182-187.

47. Quadri M, Lotti R, Bonzano L, et al. A Novel Multi-Action Emollient Plus Cream Improves Skin Barrier Function in Patients with Atopic Dermatitis: In vitro and Clinical Evidence. *Skin Pharmacol Physiol.* 2021; 34(1): 8-18.

48. Gasparri F. Effects of a novel emollient cream on skin moisture, epidermal barrier function and atopic dermatitis signs and symptoms: Results from a clinical study. *24th World Congress of Dermatology, Milan, Italy.* 2019; June 10-15.

49. Sparavigna A, Tenconi B, La Penna L. Efficacy of a novel emollient plus cream in atopic dermatitis: a randomised, vehicle-controlled, double-blind study. *J Plast Pathol Dermatol.* 2019; 15(2): 85-93.

50. Sigurjonsdottir HA, Franzson L, Manhem K, et al. Liquorice-induced rise in blood pressure: a linear dose-response relationship. *J Hum Hypertens.* 2001; 15(8): 549-552.

51. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev.* 2013(3): CD006474.

52. Kopp MV, Hennemuth I, Heinzmann A, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Probiotics for Primary Prevention: No Clinical Effects of Lactobacillus GG Supplementation. *Pediatrics.* 2008; 121(4): e850-e856.

53. Owen JL, Vakharia PP, Silverberg JI. The Role and Diagnosis of Allergic Contact Dermatitis in Patients with Atopic Dermatitis. *Am J Clin Dermatol.* 2018; 19(3): 293-302.

54. Nardelli A, Carbonez A, Ottoy W, et al. Frequency of and trends in fragrance allergy over a 15-year period. *Contact Dermatitis.* 2008; 58(3): 134-141.

55. Soh JY, Huang CH, Chiang WC, et al. Anaphylaxis to galacto-oligosaccharides--an evaluation in an atopic population in Singapore. *Allergy.* 2015; 70(8): 1020-1023.

56. Magnolo N, Jaenicke T, Tsianakas A, et al. Comparison of different skin care regimens in patients with moderate to severe atopic dermatitis receiving systemic treatment: A randomized controlled trial. *J Eur Acad Dermatol Venereol.* 2023; 37 Suppl 5: 18-26.