

Review

A Review of Moisturizing Additives for Atopic Dermatitis

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Abstract: Atopic dermatitis, the most common form of eczema, is a chronic, relapsing inflammatory skin condition that occurs with dry skin, persistent itching, and scaly lesions. This debilitating condition significantly compromises the patient's quality of life due to the intractable itching and other associated factors such as disfigurement, sleeping disturbances, and social stigmatization from the visible lesions. The treatment mainstay of atopic dermatitis involves applying topical glucocorticosteroids and calcineurin inhibitors, combined with regular use of moisturizers. However, conventional treatments possess a certain degree of adverse effects, which raised concerns among the patients resulting in non-adherence to treatment. Hence, the modern use of moisturizers to improve barrier repair and function is of great value. One of the approaches includes incorporating bioactive ingredients with clinically proven therapeutic benefits into dermocosmetics emollient. The current evidence suggests that these dermocosmetics emollients aid in the improvement of the skin barrier and alleviate inflammation, pruritus and xerosis. We carried out a critical and comprehensive narrative review of the literature. Studies and trials focusing on moisturizers that include phytochemicals, natural moisturizing factors, essential fatty acids, endocannabinoids, and antioxidants were identified by searching electronic databases (PubMed and MEDLINE). We introduce the current knowledge on the roles of moisturizers in alleviating symptoms of atopic dermatitis. We then further summarize the science and rationale of the active ingredients in dermocosmetics and medical device emollients for treating atopic dermatitis. Finally, we highlight the limitations of the current evidence and future perspectives of cosmeceutical research on atopic dermatitis.

Keywords: atopic eczema; moisturizers; emollients; active ingredients; skin barrier; skin physiology



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1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease [1] that usually starts in early childhood. AD affects 15–20% of children worldwide and can extend well into adulthood at an incidence of 1–3% [2,3]. A wide variation of prevalence is reported, where AD is reported more frequently in developed nations with more than a 15% prevalence rate [3,4]. It can be diagnosed clinically following validated diagnostic criteria, such as the Hanifin and Rajka diagnostic criteria [5]. Eczematous rashes are itchy and can be acute, subacute, or chronic. Though able to affect any part of the body, eczematous rashes appear with age-related morphology and distribution. It is found to be associated with other atopic diseases. Children with atopic eczema are at risk of cutaneous infections. AD was found to be associated with poorer quality of life (QoL) [6]. The epidermal barrier plays a pivotal role in atopic eczema pathogenesis. The treatment of AD focuses on maximizing skin

barrier repair and reducing inflammation. Topical corticosteroids (TCS) are the first-line anti-inflammatory treatment for AD. However, chronic usage of topical corticosteroids may further lead to skin barrier defects by inhibiting epidermal proliferation, differentiation, and lipid production [7].

Twice daily application of moisturizer improves skin hydration, reduces AD symptoms, flares, and severity, and reduces the amount of topical anti-inflammatory medication needed [8–10]. Conventional moisturizer consists of three main ingredients: emollients, humectants, and occlusive agents [9,11]. These ingredients reduce transepidermal water loss (TEWL) via various mechanisms. Emollients lubricate and soften the skin, while occlusive agents form a hydrophobic layer on the stratum corneum (SC) and prevent water evaporation. Meanwhile, humectants increase the amount of water retained by the SC through their hydrophilic nature [8,9,11]. In recent years, medical device emollient creams (MDEC) containing active ingredients have started to become the trend in the current cosmeceutical research, owing to their ability to alleviate cutaneous inflammation while repairing skin barriers [12–14]. Studies on various active ingredients with in vivo and in vitro efficacy have been published. Some are reported to be non-inferior to low potency corticosteroids [15].

In this article, we aim to review the current understanding of the pathophysiology for atopic eczema, as well as the mechanism of action, safety, and efficacy of common active ingredients that were found to be beneficial in alleviating symptoms of atopic eczema.

2. Pathophysiology of AD

A fundamental argument on the etiology of AD is whether it is primarily induced by epidermal barrier dysfunction (outside–inside hypothesis) or primarily by an immune response to environmental triggers (inside–outside hypothesis) [16]. Nevertheless, the clinical manifestation of AD is believed to involve a multifactorial interplay among gene and epidermal barrier dysfunction, Th2 immune dysregulation, environmental triggers, and skin microbiome abnormalities [16–18]. Additionally, skin pH levels [19,20] and the deficiency of endogenous natural moisturizing factors (NMFs) [21,22] were also found to play a role.

2.1. Gene Dysfunction and Epidermal Barrier Dysfunction

FLG gene mutation was found in 20–40% of patients with atopic dermatitis. It encodes the pre-protein profilaggrin, which will then be translated to filaggrin monomer. Filaggrin is required for keratinization, moisturization, and maintenance of the stratum corneum homeostasis [23]. The lack of filaggrin will lead to disruption of barrier function. *FLG* gene expression may be further downregulated when it is cross-linked with the T-helper type 2 cells (Th2) derived cascades.

SC and tight junctions play the most critical roles in the epidermal barrier. SC is made up of corneocytes intermixed in a matrix of intercellular lipids (ceramides, cholesterol, and fatty acids) [3,23]. Environmental triggers, including irritants, pruritogens, hot and dry climate, and ultraviolet radiation, can disrupt the epidermal barrier leading to higher skin pH levels, increased TEWL, altered lipid composition, reduced level of ceramides, and higher serine protease activity [13,24]. Ceramide plays an essential structural role in forming the permeability barrier that functions as a water reservoir, holding the water molecules in the multilamellar structures. The prolonged compromised global lipid composition of SC in AD sufferers and the further deficiency in ceramide fraction eventually lead to barrier dysfunction, decreased SC hydration, *S. aureus* colonization, as well as allergen penetration. Hence, the mitigation of the barrier abnormality in AD requires topical aid that adequately delivers the key lipids that mediate barrier function, which is ideally provided in a ceramide-dominant proportion [25–27].

2.2. Th2 Mediated Immune Dysregulation and Neuroimmune Interactions

The Th2-mediated immune response is currently at the center of AD pathogenesis. The exposure of irritants and pruritogens to the disrupted epidermal barrier initiates an immunological cascade that stimulates Th2 pro-inflammatory cytokine production, such as interleukin-4 (IL-4), IL-5, and IL-13 [16,23]. Subsequently, IL-4 and IL-13 stimulate the production of IL-31, which results in pruritus, triggering excessive scratching and further aggravation of the inflammatory response (Figure 1).

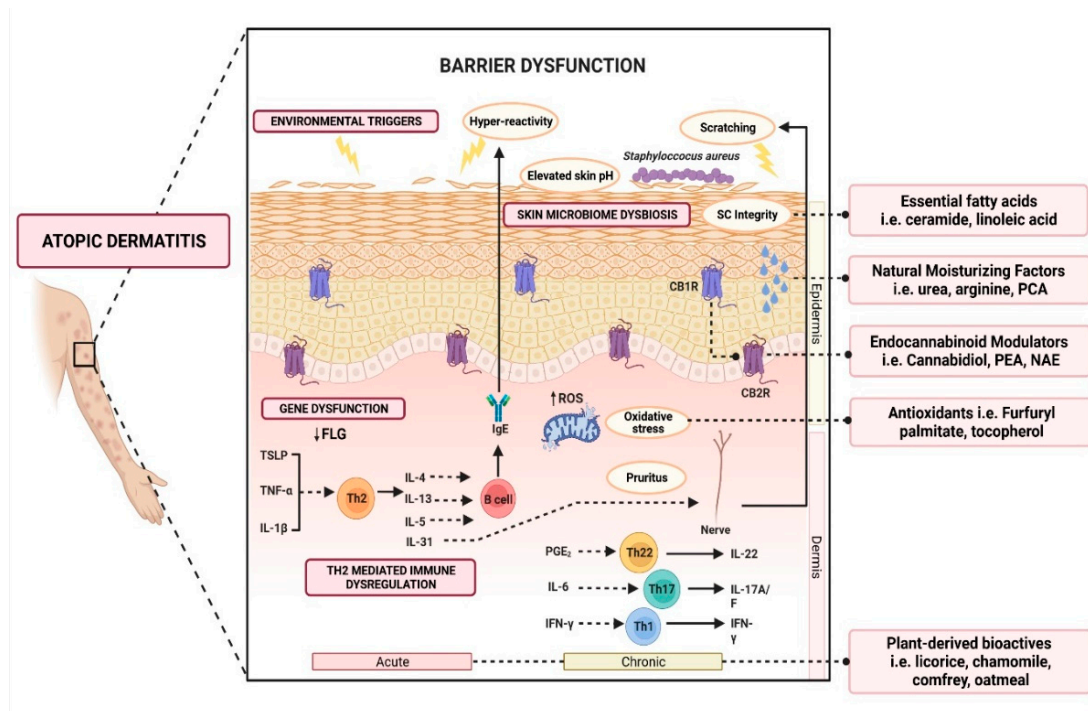


Figure 1. Schematic illustration of various active ingredients and the targeted mechanisms in alleviating atopic dermatitis.

2.3. Skin Microbiome Dysbiosis

The skin microbiome plays a pivotal role in maintaining the homeostasis of the skin, and colonization of *Staphylococcus aureus* strains in AD is thought to be associated with the clinical manifestation and pathogenesis of flares. *S. aureus* colonization was observed in up to 90% of lesional skin and 40% of non-lesional skin as opposed to being almost absent in healthy skin [28–30]. The dysbiosis contributes to the elevated pH levels that are observed throughout atopic dermatitis flares [31,32]. Furthermore, *S. aureus* colonies were found to secrete a group of virulence factors, such as superantigens (Sag), α -toxin, δ -toxin, protein A, and phenol-soluble modulins (PSM), that may exacerbate keratinocyte inflammation [28–30], release cytosolic granules (such as histamine, IL-3, and IL-13), aid in biofilm development and promote Staphylococcal colonization [30].

2.4. Other Factors Affecting Barrier Function

2.4.1. Acid Mantle in Epidermal Barrier Function

Skin pH is a vital component in maintaining the normal functions of the skin [33,34]. The film of the outermost layer of the skin, known as the acid mantle, bears a pH range of 4.0–6.0, depending on body parts [34]. Neonatal skin pH is near-neutral, where it requires several weeks of acidification processes to attain physiological skin surface pH range, making it vulnerable to external irritants during this period [35]. Dysregulation of this acidification process leads to shifts in skin pH to a mean of 6.25 in AD [33,36,37]. The disruption of the acidification mechanism alters phospholipid A2, β -glucocerebrosidase,

serine proteases, kallikrein 5, and acid sphingomyelinase activities, which are important for the maintenance of the lipid structure in SC [34,35,38]. The alteration of skin pH will impair the antimicrobial defenses of the skin [34,35,38]. Endogenous factors (such as the *FLG* gene and its amino acid breakdown, such as histidine) and exogenous factors (such as acidic and alkaline substances) have been proposed to affect the acid mantle of the skin [35,38,39].

2.4.2. Natural Moisturizing Factors

Natural moisturizing factors (NMFs) refer to endogenous, highly hygroscopic substances that play a pivotal role in the maintenance of SC hydration [40]. NMFs also contribute to the maintenance of functional hydrolytic enzymes involved in desquamation and aid in optimum SC barrier function [40]. Amino acids account for 40–50% of NMFs, followed by pyrrolidone carboxylic acid (PCA) (12%), lactic acid (12%), urea (7%), inorganic salts, sugar, glycerol, and a variety of ions [40,41]. These water-soluble substances are highly efficient humectants that comprise 20–30% of the dry weight of SC mass [41]. The deficiency or reduction in NMFs is associated with an increased risk of AD and various SC abnormalities that manifest as dry skin, scaling, flaking, and increased surface pH [21,22].

3. Role of Moisturizers in the Treatment of AD

Multiple clinical guidelines recommend the use of moisturizers for the treatment of AD [42]. This helps in reducing the frequency of AD flares (3.74 times reduced risk) [42] and the total amount of steroid use (up to 15.30 g less within six weeks, $p = 0.003$) [42]. Although a large variety of moisturizers are available in the market, not all are beneficial. Some formulations may contain allergens (e.g., fragrance, benzyl alcohol, D-limonene, *Lavandula angustifolia* oil, and *Melaleuca alternifolia* oil), leading to contact dermatitis and worsening of the inflammation [43]. Carefully designed moisturizers should be hypoallergenic, pH-balanced, and contain humectants, emollients, and active ingredients that help to reduce inflammation [43–45]. Some medical device emollient creams (MDEC) are found to be suitable for alleviating AD symptoms [46,47]. MDECs are clinically designed to not only improve hydration but also repair and protect the skin's barrier function. According to the European Commission, some MDECs are classified as class IIa medical devices due to their primary action relying on mechanical or physical means [48]. Several notable MDECs, such as Atopclair® (Menarini, Italy), Dexyane MeD® (Ducray Laboratoires Dermatologiques, France), and VEL-091604 (BSI Beauty Science Intelligence, Germany) have shown comparable clinical efficacy with corticosteroids in alleviating symptoms of moderate to severe AD, which will be discussed in the next section.

Over the last few years, emollients have been supplemented with different powerful bioactive ingredients to improve epidermal action. These additives are increasingly investigated as preventative and treatment aids for AD. Notably, these additives are categorized as compounds derived from plants, natural moisturizing factors, physiological lipids and ceramide, cannabinoid receptor modulators, and antioxidants (Figure 1). Herein, a summary of evidence-based cosmeceutical research on additives in emollients indicated for AD is presented.

4. Active Ingredients Beneficial in Alleviating Atopic Eczema Inflammation

4.1. Plant-Derived Active Ingredients

4.1.1. Licorice-Derived Bioactives

Licorice, the root of the *Glycyrrhiza* species, is known to have application in the treatment of various inflammatory skin diseases, particularly in eczematous skin disorders, supported by extraordinary evidence in clinical research [46,47,49–57]. Licorice-containing creams were found to be as effective as mild to medium-potency TCS, 1% hydrocortisone, and 1% desonide cream in treating moderate-to-severe AD [47]. Nearly 400 bioactive compounds have been isolated from *Glycyrrhiza* spp., most of which fall into the classes of flavonoids and triterpene saponins. Licorice has been used in food and herbal medicine across the world. In particular, *Glycyrrhiza glabra* L. (Fabaceae), *Glycyrrhiza uralensis* Fisch.

Ex DC., and *Glycyrrhiza inflata* Bat. are the three licorice species registered in the Chinese Pharmacopoeia 2015. Common ingredients used in dermatology are licochalcone A, glycyrrhetic acid (GA), and glycyrrhizin.

Licochalcone A is an oxygenated chalconoid phenol derived specifically from the root of Xinjiang licorice, *G. inflata*. Vast clinical trials demonstrated the positive anti-inflammatory and anti-pruritic results of topical semi-solid formulations which contain Licochalcone A [15,58–60]. On the other hand, GA, a pentacyclic triterpenoid saponin compound, is a bioactive marker of *G. glabra* and *G. uralensis*. Meanwhile, glycyrrhizin is the major water-soluble bioactive compound of *G. glabra*, found at concentrations of 1–9% at its stem [61]. The chemical structure of glycyrrhizin carries a molecule of GA with two molecules of glucuronic acid [61,62]. Both GA and glycyrrhizin have a long history in traditional medicine in ancient Indian, Egyptian and Chinese cultures [63]. It is widely reported to possess anti-allergic and anti-inflammatory properties, the effects of which are similar to those of topical corticosteroids for the treatment of skin diseases, including atopic dermatitis, contact dermatitis, and psoriasis [55,64,65].

The anti-inflammatory mode of action of Licochalcone, GA, and glycyrrhizin are directed towards the suppression of pro-inflammatory mediators, such as prostaglandin E₂ (PGE₂) from cyclooxygenase-2 (COX-2), as well as leukotriene B₄ (LTB₄), IL-1 β and IL-6 by the residential skin cells and the cells of the innate and adaptive immune system [57,63]. In addition, these bioactive compounds also exhibit antimicrobial activity against multidrug-resistant *S. aureus* [66] and have been shown to suppress of translocation of nuclear factor (NF- κ B)-regulated gene products and inhibit TNF- α induced inflammation [67]. GA and glycyrrhizin possess the ability to reduce oedema through inhibition 12-O-tetradecanoylphorbol-13-acetate-induced glucose transport, whereas the reduction in pruritus was associated with the inhibition of leukotriene B₄ (LTB₄) [53]. Additionally, glycyrrhizin was reported to bind directly to high-mobility group box 1 (HMGB1) protein, consequently inhibiting the HMGB1 signalling cascade, leading to the suppression of inflammatory cytokines [57].

Studies have demonstrated that a 0.025% Licochalcone A-containing moisturizer significantly improved AD clinical characteristics and itch intensity [66,68]. The improvement was found to be comparable to 1% hydrocortisone [15]. Furthermore, there is also a pronounced decrease in *S. aureus* colonization. These improvements can take place as soon as seven days after the initial treatment [58]. It also significantly reduces flare by 60% compared to its vehicle [59]. Similarly, thrice daily preparation of 1% GA- and 2% GA-based gels showed a significant reduction in erythema scores of 35.02% and 60.76%, respectively, followed by 56.64% and 83.76% reduction in oedema scores, as well as a reduction in pruritus scores of 44.1% and 72.53% [55]. In multiple multi-centered, randomized, vehicle-controlled studies, a cream containing GA, *Vitis vinifera* L. extract, and telmestine (Atopiclair®) demonstrated significant symptomatic relief and skin barrier improvement [49–51,54]. This allows it to be authorized in US and EU as a medical device cream for symptomatic relief in the management of AD [49]. Some adverse effects, including rash, stinging sensation, and burning sensation were observed in a small percentage of the patients, however, it is considered rare and not more frequent than the vehicle [49,51]. The evidence of GA was further demonstrated by other medical devices with GA, namely Dexyane MeD® and VEL-091604, which also demonstrated promising clinical efficacy for mild to moderate AD, either as a stand-alone treatment or in combination with TCS [46,47,56].

It is worth mentioning that the above formulas are not the sole active ingredients. These products are commonly formulated with other antioxidative or anti-inflammatory agents such as allantoin, bisabolol, and other natural extracts. Thus, the efficacy of these medical devices might be enhanced by the synergistic effects between these botanical-derived bioactive compounds and other antioxidative agents.

Certain researchers shared the concern that the utilization of GA and glycyrrhizin may lead to increased systemic glucocorticoid and mineralocorticoid toxic effects [69]. This may be attributed to its ability to inhibit 11 β -hydroxysteroid dehydrogenase, an enzyme

responsible for converting endogenous cortisol to cortisone. These indications were only reported in oral ingestion and intravenous injection of GA and glycyrrhizin combined with the prescription of hydrocortisone or prednisolone [68]. To date, no evidence of such effects due to topical GA and glycyrrhizin has been reported [70].

To conclude, these are significant results considering that the current AD treatments depend heavily on the recurrent use of topical corticosteroids for acute flare treatment and prevention, and show that various phytochemicals-formulated emollients should be included in future larger-scale clinical studies.

4.1.2. Chamomile-Derived Bioactives

Matricaria chamomilla L., generally known as chamomile, has a long-standing history in herbal medicine in the treatment of dry skin, inflammatory skin disorders, pruritic skin disorders, and various dermatoses owing to its anti-inflammatory, anti-histaminic, mild astringent, soothing, and healing potential [71,72]. Several in vitro and animal studies have reported the significant efficacy of chamomile extracts and oil in eczematous atopic models [72–74]. It modulates the type-2 inflammation response by altering the Th2 cell activation, which results in the downregulation of IL-4 production [72,73]. It also demonstrated anti-pruritic effects by suppressing IgE over-production and hindering the binding of histamine to its receptor, which eventually reduces the histamine release from mast cells [72]. In addition, chamomile oil also regulated the Th17 cell differentiation pathway, leading to a decreased level of IL-17, inhibition of NF- κ B activation, and suppression of the pro-inflammatory factors TNF- α and IL-6 which ultimately reduces inflammation in eczema [74]. Indeed, an over-the-counter chamomile extract containing a cream, Kamillosan[®] (MEDA Pharma, Germany), was found to ameliorate mild-to-moderate AD in several clinical studies. The studies demonstrated marginal superiority against 5% bufexamac and 0.75% fluocortin butyl ester and equally effective therapeutic results compared to 0.25–0.5% hydrocortisone [75,76].

Chamomile's therapeutic benefits for treating eczema are associated with its major sesquiterpene constituents, including azulene, bisabolol, and elemenes [74]. In particular, α -bisabolol, also known as levomenol, accounts for its potent anti-inflammatory effects, among others [72,74]. Moreover, α -bisabolol is known for its ability as a percutaneous penetration and absorption enhancer [77]. It was reported that α -bisabolol increased the permeability coefficient of triamcinolone acetonide by 73-fold in human skin samples with respect to untreated skin [77]. This is likely due to its effect of increasing the lipid fluidity of SC, permitting the increase in diffusion rate across the skin barrier [77,78]. Dermocosmetics containing α -bisabolol have shown soothing effects and eczema associated-inflammation reduction as observed through reduced TEWL and improvement in SCORAD, TESS, ESS, and VAS scores [79–84]. The efficacy was also found among paediatric populations [79–81,84].

In a relatively small percentage of the population, chamomile may induce allergic contact dermatitis reactions. This hypersensitive reaction, known as Compositae mix allergy, is initiated by several species of plants in the Compositae or Asteraceae family [85]. The common allergens in the Compositae family are sesquiterpene lactones, polyacetylenes, and thiophenes. Bisabolol is considered a potential cause of allergic contact dermatitis in AD patients with a history of moisturizer intolerance [86]. However, it is to be noted that the frequency of allergic reactions to chamomile and bisabolol is low even within the other Compositae allergens [85]. This was evident in the fact that allergic reactions to the mixture of Compositae extracts were observed in only 118 out of 3851 subjects [87]. Furthermore, among the allergenic subjects, chamomile elicited lesser allergic reactions (65 subjects) in comparison with feverfew (82 subjects), chrysanthemums (75 subjects), and tansy (71 subjects) [87].

Taking this evidence into account, α -bisabolol and α -bisabolol-rich oil may prove to be meaningful active ingredients in cosmeceutical and pharmaceuticals application on eczematous skin cases, though clinicians and patients should be made aware of its allergenic potential.

4.1.3. Comfrey-Derived Bioactive

Commonly known as comfrey, *Symphytum officinale* L. is a perennial herb native to the United Kingdom but also commonly found in Europe, North America, and North Asia [88]. It has been extensively utilized in European indigenous medicine as poultice or ointment to soothe irritated and inflamed tissue, promote wound healing, and reduce osteoarticular inflammation [89,90]. Though its pharmacological effects are undoubted, the oral consumption of comfrey is widely prohibited due to its hepatotoxicity from some of its pyrrolizidine alkaloids constituents, such as lasiocarpine, echimidine, symphytine [91–93]. Fortunately, external application of comfrey and its extracts have proved to be safe, with no report of major adverse effects, mainly due to poor cutaneous penetration and absorption of these alkaloids [94,95]. In fact, the therapeutic effects and clinical efficacy of topical comfrey-containing creams and ointments are supported by several clinical studies that evaluated their effects in treating pain, cutaneous wounds, and inflammation from sprains and bruises [96–98]. These anti-inflammatory and tissue healing activities are attributed to their bioactive constituents, including allantoin and rosmarinic acid [71,88,89].

Allantoin is a heterocyclic organic compound and a uric acid oxidation product [89,90], widely used in various personal care products as a skin conditioner, emollient agent, mild keratolytic agent, and soothing agent [88,90]. At the same time, allantoin has been shown to stimulate healthy cell proliferation, epithelization, and wound healing. A clinical study revealed that an emulsion with a 5% concentration of allantoin had significant wound-healing effects by promoting fibroblastic proliferation and extracellular matrix, which contribute to the accelerated re-establishment of healthy skin in comparison to the vehicle [99]. The anti-inflammatory activity of allantoin was also observed in a murine allergic model by reducing IgE levels and IL-4 and IL-5 production [100].

Allantoin-containing moisturizers were shown to positively relieve mild-to-moderate atopic dermatitis [83,101,102]. Curel® moisture cream (Kao, Japan), which contains 0.5% allantoin and pseudo-ceramide, was found to be a beneficial adjunct to topical corticosteroids in providing symptom relief and improved skin texture in adults and children with mild-to-moderate AD [102]. Its use was found to significantly improve the quality of life, mean SCORAD, and mean POEM. Twice-daily regular application also resulted in the significantly reduced frequency of flares. Furthermore, 12.5% of 40 subjects discontinued the use of TCS by the end of the four weeks of study [102]. Similar outcomes were reported in another trial [101]. Trials subjects were found to have high compliance, tolerability, and acceptability of allantoin in topical preparations with no related or severe adverse effects observed [101,102].

Rosmarinic acid is an esterified caffeic acid and 3,4-dihydroxyphenyl lactic acid [103]. It exerts a plethora of biological activities, including anti-inflammatory, antioxidant and antibacterial effects. Rosmarinic acid demonstrated an anti-inflammatory effect by inhibiting the expression of IL-1 β , IL-6, and TNF- α and downregulating the NF- κ B pathway. These anti-inflammatory effects were found in various in vitro and animal studies [104]. It was also found to hamper the infiltration of CD4⁺ helper T cells, CD8⁺ cytotoxic T cells, and mast cells to DNFB-induced skin lesions in NC/Nga mice, leading to the suppression of IFN- γ and IL-4 via activated T cells and reduced levels of total serum IgE [105]. Clinically, topical applications of 0.3% rosmarinic acid emulsion were proven to provide symptomatic relief for eczematous lesions by demonstrating a significant improvement in erythema, crusting, pruritus, SCORAD, skin thickness, and TEWL [106]. It is to be noted that the use of both systemic and topical corticosteroids was eliminated throughout the study. This indicates the possibility of introducing rosmarinic acid as a TCS-sparing agent for AD, albeit more extensive studies have to be carried out to establish firmer clinical evidence [106].

4.1.4. Colloidal Oatmeal

Colloidal oatmeal is widely known to alleviate the disease hallmarks of AD. It was found that daily application of colloidal oatmeal extracts-containing lotion showed significant clinical improvements in 50 subjects with severely dry skin in as little as three

weeks of treatment [107]. The efficacy is also demonstrated by another over-the-counter 1% colloidal oatmeal cream for pediatrics suffering from mild-to-moderate AD [108,109]. During the three weeks of the study period, significant improvements were demonstrated in clinical (EASI, IGA, and pruritus score) and objective assessment (erythema, dryness, skin hydration). This efficacy is non-inferior to a controlled prescribed cream (EpiCeram[®], Primus Pharmaceuticals, US) [108,109]. Colloidal oatmeal is thought to induce the repair of barrier damage, regulate lipid complex in SC, and enhance pH-buffering capacity, which aids in protection against irritants and normalizing cutaneous pH to its acidic range [107]. This may be associated with its ability to form a protective, occlusive barrier that retards water loss from the epidermis. In addition, the phytochemicals in oatmeal, such as saponins, may contribute to maintaining skin pH by solubilizing dirt, oil, and sebaceous secretions [108,109]. As a result of the evident pharmacological benefits, dermatologists have increasingly recommended the use of colloidal oatmeal-containing moisturizers for the treatment and prevention of AD.

4.2. Natural Moisturizing Factors

Urea is one of the first and most studied NMF compounds that has been formulated in moisturizing emollients since 1943 [110]. Urea, also known as carbamide, is an organic compound with the chemical structure of a carbonyl group attached to two amine residues. Besides acting as a humectant, urea also acts as a mild keratolytic agent when formulated at higher concentrations (>10% urea) [111]. The efficacy and safety of topical urea creams in treating AD have been proven through substantial clinical evidence. Older clinical studies mainly include the application of 10% urea cream as a stand-alone treatment [112] or in combination with 1% hydrocortisone [113–115]. These studies conclusively reported a significant improvement in SC hydration, water-binding capacity, and TEWL in atopic skin [112–115]. On top of that, the efficacy of the combination treatment was clinically superior to that of hydrocortisone alone [115]. It should be noted that a higher dose of urea might cause a certain degree of burning and stinging sensation in 8–45% of patients [113,115]. Therefore, more recent clinical studies adopted formulations with lower doses of urea from 1% [116] to 5% [117,118], combined with other ingredients such as vitamin B12, profilaggrin complex, polidicanol, glycyrrhetic acid, and high overall lipid content of >20% [116–118]. The efficacy of these multi-component urea creams was evident in the recovery of barrier dysfunction, reduced clinical severity of AD, and higher QoL of the sufferers, as observed in improved EASI, IGA, PIQoL scores [116–118].

Arginine, as one of the amino acid precursors of urea, PCA, and lactic acid, has been included in several multi-component moisturizer formulations targeted at the treatment of mild-to-moderate AD patients [119–121]. The safety and efficacy of these NMF-containing moisturizers in treating adults and paediatric AD patients were evident in multiple extensive studies [119–121]. NMFs have been used safely and effectively in large populations of patients. Hence, in particular, urea should remain a viable clinical treatment option for AD.

4.3. Ceramides and Fatty Acids Organization in Permeability Barrier Function

Regular application of semi-solid preparations with triple-physiologic lipids in a 3:1:1 molar ratio of ceramide, cholesterol, and free fatty acids, respectively, have been shown to significantly reduce the need for topical steroid application [12,122,123]. An open-label study has first revealed that substituting standard moisturizers with an over-the-counter ceramide-dominant cream (TriCeram[®], Osmotics, New York, NY, USA) in the treatment regime of severe, paediatric AD patients resulted in the dramatic improvement of SC integrity, hydration, and SCORAD assessment [25]. It was found that the physiologic lipids in the lipid-enriched moisturizers traverse both intact and disrupted SC, which is taken up by keratinocytes and enhances the nascent lamellar membrane, thereby accelerating the recovery of the permeability barrier function. Several clinical studies support the tolerability and efficacy of these ceramide-dominant moisturizers in AD patients [124,125]. Indeed, some were clinically approved by the FDA as a treatment for pruritus and in-

inflammation related to xerosis in AD [124]. Dermatologist evaluation on day 14 and day 28 showed significant improvement in disease severity, assessed as SCORAD index, as well as decreased pruritus intensity and higher sleeping quality, which is on a par with that of fluticasone, a medium-potency TCS, suggesting that it could potentially be used as an effective monotherapy or ancillary remedy for AD [123]. These results are consistent with the following study, where this ceramide-dominant cream showed clear or almost clear IGA scores in 54% of the 207 participants with mild-to-moderate AD [126]. Interestingly, the efficacy of the ceramide cream as a monotherapy was non-inferior to TCS or tacrolimus ointment [126]. In addition, significant pruritus score reductions were also reported in patients with moderate-to-severe pruritus, reflecting an average reduction of 38% from the baseline score [126]. Notably, some early studies revealed that ceramide might potentially bring about negative impacts on the barrier function when used alone [127,128]. Hence, the key physiologic lipids, particularly ceramide, free fatty acid, and cholesterol must be provided with an appropriate ratio in order to improve the barrier function following the impairment of the normal epidermal barrier [12]. This evidence indicates that physiologic lipid-based topical emulsion could be considered an effective monotherapy for patients with mild-to-moderate cases or ancillary therapy for moderate-to-severe AD, which may open up possibilities in reducing the usage of TCS in AD therapy.

4.4. Endocannabinoid System—A New Star in the Therapy of Eczema

Over the past few years, there has been an increase in interest in the endocannabinoid system (ECS)'s role in inflammatory skin diseases, including eczematous eruption [129–132]. The ECS is an endogenous metabolic system comprised of receptors with binding affinity to delta-9-tetrahydrocannabinol (THC). These receptors, including cannabinoid receptor 1 (CB1R), and cannabinoid receptor 2 (CB2R), are reportedly present on the skin [132,133]. CB1R is found at the stratum spinosum and granulosum, while CB2R is present at the basal layer [133]. The activation of these endocannabinoid receptors may increase DNA methylation via the p38 MAP kinase pathway, thereby inhibiting keratinocyte proliferation [132]. Furthermore, cutaneous ECS activation selectively reduces the secretion of thymic stromal lymphopoietin (TSLP), a pro-inflammatory mediator, and enhances the expression of anti-inflammatory and T-regulatory cytokines, including IL-10 and TGF- β [129,130]. Thus, manipulation of CB1R and CB2R is thought to be potentially able to treat a variety of dermatological conditions [131,132]. Cutaneous endocannabinoid activation is reported to reduce histamine-induced pruritus by hindering synaptic transmission in cutaneous C-fibers and the following neuropeptide release [129]. In addition, endocannabinoid bioactive compounds are also found to exhibit anti-pruritic properties via the inhibition of TRPV 1 [134].

Cannabinoids represent a class of compounds whose structures and physicochemical makeup are similar to psychoactive THC, found in *Cannabis sativa* L. Cannabinoids consist of three main classes—endocannabinoids, phytocannabinoids, and synthetic cannabinoids. The role of cannabinoids in eczematous eruption has been reported in both in vitro and in vivo animal studies [135–138]. Cannabidiol (CBD) is a phytocannabinoid from the cannabis plant whose structure differs slightly from THC and has demonstrated physiologic effects, including anti-inflammatory and anti-pruritic role in atopic skin. In a recent observational study with 14 adult participants with mild-to-moderate AD, regularly applying 1% CBD-containing gel significantly improved disease severity and pruritus [139]. These improvements were evident through a 34.5% average reduction in EASI scores ($p < 0.005$) and a 29% average decrease in the VAS scale ($p < 0.05$) in comparison to the baseline level [139]. Another clinical study was performed to assess the role of CBD-containing cream on atopic eczema, psoriasis, and scarring [140]. It was found that the CBD-containing cream increased hydration, transepidermal water loss, and elastic fibers of the skin [140]. However, SCORAD was not properly reported in the results. The potential benefits of cannabinoids in alleviating the clinical manifestations of AD are not negligible, and hence deserve recognition in its ongoing clinical research.

N-palmitoylethanolamine (PEA), also known as Palmitate MEA, belongs to the family of N-acylethanolamine (NAE). NAE is able to downregulate inflammatory response via cannabinomimetic action of CB receptor. PEA exhibits little affinity to CB receptors, but instead acts as an “entourage” to endogenous cannabinoids such as anandamide (arachinodylethanolamine) at the cannabinoid receptors, inhibiting their inactivation [134]. A cream containing PEA was found to significantly reduce the dermatological hallmarks of atopic dermatitis, including erythema, pruritus, scaliness, lichenification, and dryness by 54–66% in a global study [141]. It also reduced the need for the topical application of corticosteroids by 62% in mild-to-moderate AD patients, where 56% of the participants were able to discontinue TCS altogether [141]. The QoL of the patients was seen to be increased through 60% sleep quality improvement [141]. The efficacy was also demonstrable in alternative preparations of PEA- and NAE-containing cream [142]. These findings promise that ECS modulators containing moisturizers may potentially be utilised as TCS-sparing treatment, or adjuncts for eczematous skin conditions, though further progress in clinical research is strictly necessary.

4.5. Furfuryl Derivatives and Antioxidants

Given the compelling research on the role of oxidative stress in AD, moisturizers enriched in antioxidants, can serve as a substantial aid in the treatment of eczematous skin. Furfuryl derivatives act as antioxidants that exert remarkable quenching properties of reactive oxygen species (ROS), especially singlet oxygen ($^1\text{O}_2$) [143]. The imbalance of the highly reactive singlet oxygen induces the state of oxidative stress, which has been implicated in the pathogenesis of AD [144,145]. This state of oxidative stress is known to promote tissue inflammation through gene upregulation that leads to increased production of pro-inflammatory cytokines [144]. Pieces of evidence such as excess production of ROS during AD exacerbation and inefficient cellular antioxidant defense capacity in AD sufferers were reported in both in vitro and in vivo studies [144,145].

Furfuryl alcohol and its derivatives effectively inhibit the production of $^1\text{O}_2$ [146,147]. This inhibition ability is attributed to the presence of a conjugated diene that interacts with O_2 by either conversion to oxygen in the triplet state or sequestering the radical through a Dienes–Alders-type diene dienophile addition reaction [143]. Furfuryl palmitate is an ester derivative from furfuryl alcohol and palmitic acid, which demonstrated efficacy and high tolerability in multiple clinical studies on eczematous skin. It is noteworthy that the esterification of the furyl ring in furfuryl palmitate increases the penetration capacity, hence promoting better skin absorption [143]. Of the five clinical investigations, moisturizers containing furfuryl palmitate and another widely known antioxidant, tocopherol (vitamin E), were able to significantly contrast the signs and manifestations of mild-to-moderate AD in both paediatric and adult patients [84,148–151]. Additionally, excellent positive outcomes were reported through the reduction in erythema, pruritus scores, and disease severity, showing the clear superiority of furfuryl palmitate-based moisturizers with respect to vehicle cream [149,151], and even showing non-inferiority with respect to TCS [150]. It is worth mentioning that during these trials, no major adverse effects were reported and the results were associated with high compliance and tolerability [143]. All in all, due to its efficacy and tolerability, furfuryl derivatives-enriched emollients could be considered a valuable steroid-free treatment option for AD sufferers.

5. Limitations of Current Cosmeceutical Research on AD

Though there is an increasing amount of research involving dermocosmetics, it is imperative to note that they are currently at a low level of clinical evidence. This is attributed to the fact that most of the clinically investigated formulas involved a combination of various active agents or a mixture of extracts. The observed efficacy from these multi-component formulas might not reflect the biological effect of a single active agent, but is likely due to the synergistic effects of two or more ingredients.

The majority of the studies are conducted with small sample sizes and poor study designs. Furthermore, there is a lack of harmonization in the clinical assessment measures, affecting the systemic review of the evidence as well as the meta-analysis. Future studies should be conducted with proper randomization. A controlled arm (i.e., head-to-head, placebo-controlled) should be introduced to allow the safety and efficacy of one bioactive compound to be better demonstrated without bias [152]. The utilization of proper blinding will further improve the study quality. However, such study design requires significant resources that are notably scarce in the realm of dermocosmetics.

6. Conclusions

Our review identified active ingredients such as plant-derived ingredients (e.g., licorice, chamomile, comfrey, oatmeal, and cannabinoids), essential lipids (e.g., ceramide, linoleic acid), natural moisturizing factors (e.g., urea, arginine, PCA, lactic acid) and antioxidants (e.g., furfuryl palmitate, vitamin E) that are potentially safe and effective treatments to alleviate symptoms of atopic eczema. Notably, the efficacy of some of the active ingredients is comparable to low- to medium-potency corticosteroids. Furthermore, these actives-containing moisturizers yield high treatment compliance, tolerability, as well as reduced levels of corticosteroid use. However, current poor study designs contributed to low-level clinical evidence for the recommendation of these ingredients for clinical use. More head-to-head clinical trials, homogenization of clinical outcomes and improvement of the study designs will provide better insight into the clinical roles of active ingredients in moisturizers.

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