

The Endocannabinoid System and Its Role in Eczematous Dermatoses

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The skin serves as the foremost barrier between the internal body and the external world, providing crucial protection against pathogens and chemical, mechanical, and ultraviolet damages. The skin is a central player in the intricate network of immune, neurologic, and endocrine systems. The endocannabinoid system (ECS) includes an extensive network of bioactive lipid mediators and their receptors, functions to modulate appetite, pain, mood, and memory, and has recently been implicated in skin homeostasis. Disruption of ECS homeostasis is implicated in the pathogenesis of several prevalent skin conditions. In this review, we highlight the role of endocannabinoids in maintaining skin health and homeostasis and discuss evidence on the role of ECS in several eczematous dermatoses including atopic dermatitis, asteatotic eczema, irritant contact dermatitis, allergic contact dermatitis, and chronic pruritus. The compilation of evidence may spark directions for future investigations on how the ECS may be a therapeutic target for dermatologic conditions.

The skin serves as the foremost barrier between the internal body and the external world. Besides serving as a protective barrier, the skin is composed of an intricate network of immune, neurologic, and endocrine systems. Recent research has demonstrated that the skin and its associated pilosebaceous units function as neuroimmunoendocrine organs operating through a multicellular communication network via external stimuli, neuropeptides, and mediators released by neighboring cells.¹ This delicate orchestra is essential in maintaining skin homeostasis through regulating cell growth, survival, and death and modulating immune responses.²

Endocannabinoids, phytocannabinoids, and synthetic cannabinoids belong to a class of ligands called “cannabinoids” that act on cannabinoid receptors and inhibit neurotransmitter release in central and peripheral neural tissues. Phytocannabinoids, such as tetrahydrocannabinol (THC), are produced in plants such as *Cannabis sativa*. Examples of synthetic cannabinoids include HU-210, nabilone, and dronabinol. Dronabinol was approved by Food and Drug Administration in 1985 to treat nausea and vomiting induced by cancer treatment³ and in 1992 as an appetite stimulant for patients with acquired immunodeficiency syndrome.⁴ Nabilone is approved to treat nausea in patients with cancer⁵ and is being studied for treating fibromyalgia.⁶ A synthetic endocannabinoid antagonist called rimonabant can decrease appetite in obese patients but is associated with suicidal thoughts.⁷

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R.K.S. has served as a consultant for Valent Pharmaceutical North America. The other authors have no funding and conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000257

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THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) includes an extensive network of bioactive lipid mediators and their receptors that function to modulate appetite, pain, mood, and memory and have been implicated in skin homeostasis.⁸ Examples of endogenously produced endocannabinoids include 2-arachidonyl-glycerol (2-AG), anandamide (AEA), and *N*-palmitoylethanolamine (PEA). CB₁ and CB₂ are G protein-coupled cannabinoid receptors.⁹ CB₁ is concentrated in the brain and central nervous system, whereas CB₂ is found in peripheral neural tissue and is especially involved in modulating the immune system. CB₁ activation heightens psychoactivity, increases inflammation, and is associated with risk for metabolic syndrome. Conversely, CB₂ overactivation decreases immune activation and impedes wound healing. Therefore, a delicate balance between CB₁ and CB₂ signaling and the overall endocannabinoid tone are essential for physiologic homeostasis (Fig. 1).

Both CB₁ and CB₂ activities have been characterized in dermal nerve cells, keratinocytes, hair follicular epithelial cells, and sebocytes (Fig. 2).^{10–13} Endocannabinoids are also ligands for nonselective ion channels called transient receptor potential cation channel subfamily V member 1 (TRPV1), which are expressed in immune cells, keratinocytes, and neurons supplying sensation to the skin.¹⁴ TRPV-1 mediates cutaneous pain sensation to chemicals and temperature.¹⁵ Human keratinocytes express TRPV-1, and endocannabinoid binding to TRPV-1 is suggested to play an important role in pain perception and inflammation in response to epidermal insult.¹⁶

REGULATION OF ENDOCANNABINOID SIGNALING

After neurotransmitters bind their receptors, the activated post-synaptic neurons synthesize membrane-bound endocannabinoid precursors that are cleaved to form endocannabinoids in response

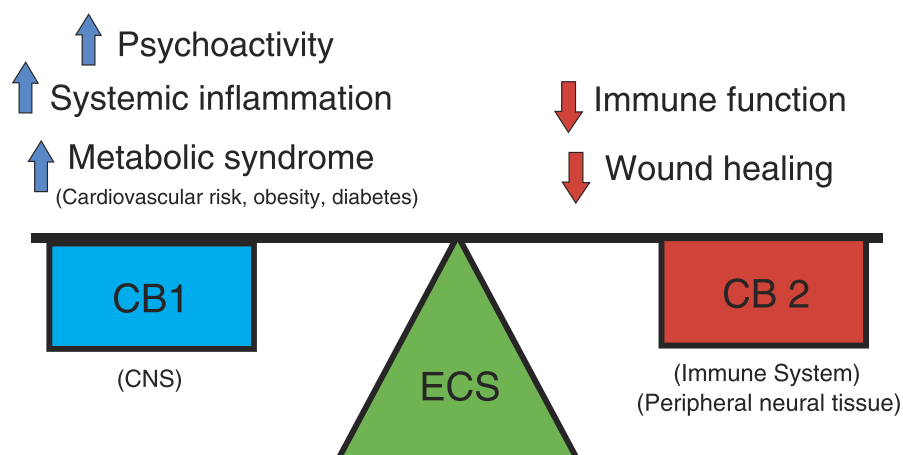


Figure 1. CB₁ and CB₂ homeostasis. CB₁ and CB₂ activation leads to different end-effector functions. A finely-tuned balance in CB₁/CB₂ signaling is crucial to physiologic homeostasis.

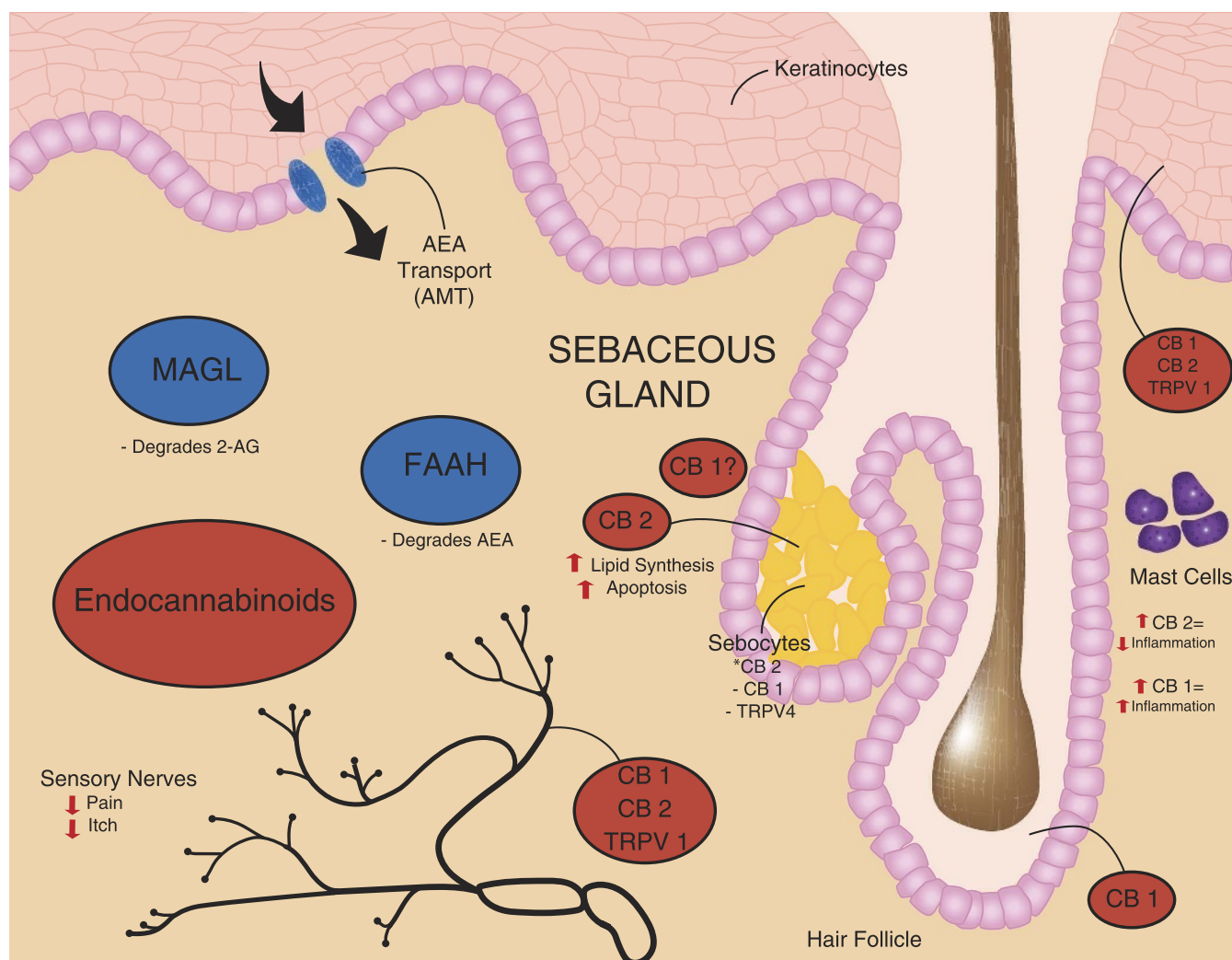


Figure 2. The cutaneous ECS. Endogenous endocannabinoids, such as AEA and 2-AG, are produced in the epidermis and pilosebaceous unit. These endocannabinoids bind CB₁, CB₂, and TRPV receptors present on keratinocytes, sebocytes, neurons, and hair follicular cells to maintain proper function and homeostasis within the skin and its appendages.

to an increase in free Ca^{2+} in the cytosol. Endocannabinoids then act in a retrograde manner and bind to presynaptic CB_1 , leading to inhibition of Ca^{2+} influx, thereby blocking future neurotransmitter release (Fig. 3).¹⁷

N-Palmitoylethanolamine has a weaker affinity for the CB_1 and CB_2 receptors than 2-AG and AEA and may have an “entourage” effect, by augmenting the effects of other endocannabinoids on TRPV-1 receptors.¹⁸ It may do this by increasing the TRPV-1-mediated Ca^{2+} entry in response to AEA, acting as an endogenous enhancer of AEA actions via TRPV-1.¹⁹

Degradation of AEA is primarily mediated by fatty acid amide hydrolase (FAAH),²⁰ and 2-AG is degraded by monoacylglycerol lipase (MAGL).²¹ *N*-Palmitoylethanolamine is hydrolyzed by *N*-acyl ethanolamine hydrolyzing acid amidase (NAAA) and FAAH-2.^{22–24} Anandamide membrane transporter controls AEA levels by decreasing extracellular AEA.²⁵ The ECS may be modulated by inhibiting degradation enzymes, such as FAAH, resulting in longer lasting or robust effects on the endocannabinoid receptors.

ENDOCANNABINOID IMPLICATIONS IN ECZEMATOUS DERMATOSES

Endocannabinoids are produced naturally in many cell types.⁹ Dysregulation of endocannabinoid homeostasis may contribute to skin pathology such as impaired skin barrier function in atopic dermatitis (AD).²⁶ In this review, we discuss the role of endocannabinoid signaling on the skin cell growth, regulation, proliferation, apoptosis, and communication and how perturbation of ECS homeostasis contributes to dermatologic diseases such as asteatotic eczema (AE), AD, irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and chronic pruritus (Table 1). Finally, we highlight emerging treatments for dermatologic conditions via ECS modulation.

Asteatotic Eczema

Asteatotic eczema is characterized by dry, scaly, and itchy skin that is often exacerbated during dry and cold weather. It commonly affects the older people and is associated with skin exposure to environmental irritants, such as water, soap, and shaving.³⁵

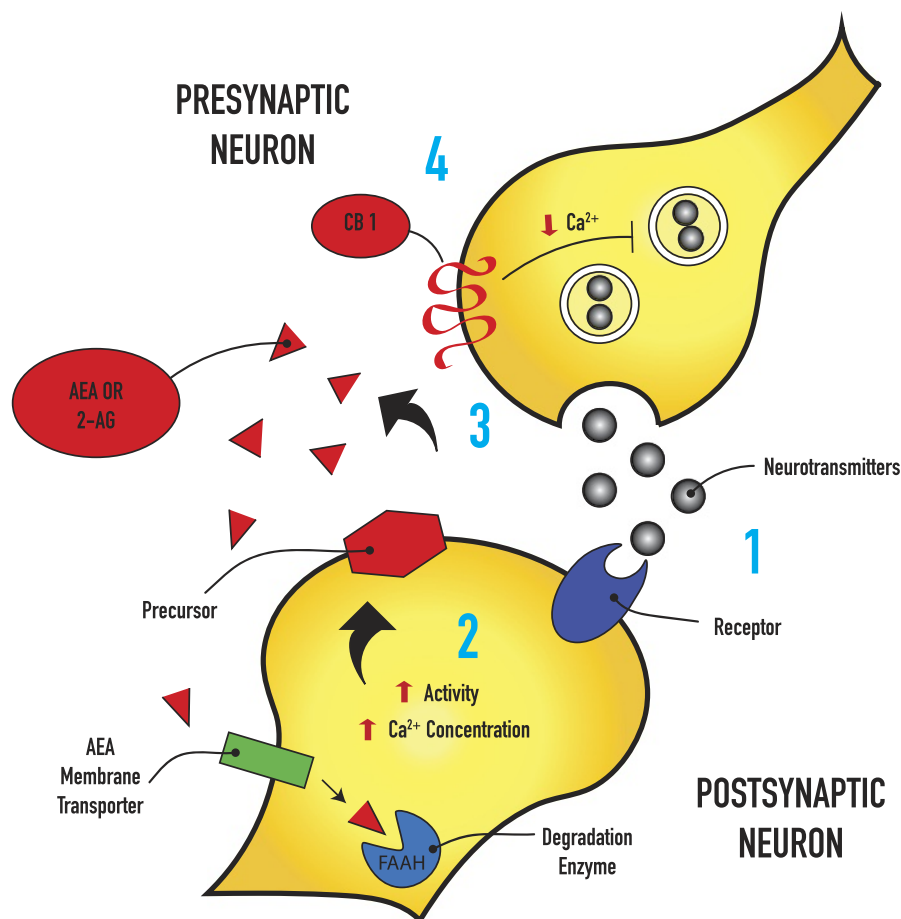


Figure 3. Endocannabinoid signaling and degradation. 1, Neurotransmitters released from the presynaptic neuron bind their receptors on the postsynaptic neuron. 2, Activation of the postsynaptic neuron causes an intracellular increase in free calcium, which induces the synthesis of membrane-bound endocannabinoid precursors. 3, Endocannabinoid precursors are cleaved and endocannabinoids (eg, AEA and 2-AG) are released into the synaptic cleft. Endocannabinoids act in a retrograde manner to bind presynaptic cannabinoid receptors. This results in inhibition of calcium movement into the cell, leading to blocked neurotransmitter release.

TABLE 1. Human, Animal, and In Vitro Studies of Endocannabinoid Therapeutics Human In Vivo and Human In Vitro Studies

Disease Assessed	Study	Pharmacological Tools Used	Study Design and Duration	Subjects or Experimental System	Control or Placebo	Major Outcome Measures	Major Results
Human In Vivo and Human In Vitro Studies							
AE	Yuan et al, 2014 ²⁷	Emollient PEA/AEA cream (0.3% PEA, 0.21% AEA): "product P"	4-wk, monocentric, randomized, double-blind, comparative trial	60 women with mild or moderate eczema, all 40–60 y	Emollient devoid of PEA/AEA: "product A"	(1) Eczema Area and Severity Index (Erythema, skin integrity, scaling, itching, dryness) (2) CPT with 5-Hz stimulus (3) Barrier function of stratum corneum, assessed by skin surface hydration (Corneometer) and TEWL	(1) Product P was better at improving dryness, scaling, and itching than product A ($P < 0.05$). (2) Product P had higher 5-Hz CPT current stimuli than product A after 14 d ($P < 0.10$). (3) Significant correlation between CPT and skin surface hydration for "P" group ($P < 0.0$). (4) There was a statistically significant increase in skin hydration in both groups ($P < 0.05$), with greater increase in product P than product A. (5) TEWL decreased significantly in both groups ($P < 0.05$), but there was no statistically significant difference between the 2 groups.
AD	Del Rosso, 2007 ²⁸	Combination treatment: PEA-containing nonsteroidal cream + clocortolone pivalate 0.1% cream	6 wk, investigator-blinded, split-body, randomized trial	43 (25 children aged 4–15 y and 18 adults aged 19–41 y) all with moderate AD	Moisturizer cream + clocortolone pivalate 0.1% cream	(1) Time to clearance of symptoms (2) Time to next flare (3) Patient preference (4) Adverse events	(1) All subjects in both groups were totally clear of symptoms by week 6. (2) Mean time to flare in PEA group is 79.2 d for children and 72.4 d for adults; mean time to flare in control group is 50 d for children and 44.2 d for adults. (3) 73% of patients preferred the PEA-containing cream and 27% preferred the control moisturizer treatment. (4) Four occasions of mild, transient stinging using the PEA cream. (1) Significant improvement of symptoms with an average reduction of 58.6% for the entire population (2) Patients reported an overall significant reduction in pruritus ($P < 0.001$ each). (3) Significant improvement in sleep quality during study period. (4) Average weekly application rate of topical corticosteroids decreased by 62% ($P < 0.001$). (5) 253 adverse effects in 187 patients (pruritusx11, burningsx10, erythemax9, miscellaneousx14)
AD	Eberlein et al, 2008 ²⁶	Physiogel AI cream (Stiefel Labs): PEA-containing cream 0.3% (applied twice daily)	6-wk, multicenter, observational, noncontrolled, prospective cohort study.	2456 (age, 2–70 y)		(1) Doctor assessment (erythema, pruritus, excoriation, scaling, ichenification, dryness) 4-point scale: 0 = absent, 3 = severe (2) Patient questionnaires (3) Adverse effects	(1) Combo treatment (Mimyx cream + control ointment) increased median time to relapse by 48% ($P = 0.003$) compared with the side of the body treated with control ointment only. (2) Risk of relapse decreased by 20% in combo treatment (Mimyx cream + control) vs control alone ($P = 0.051$).
AD	Laumann, et al, 2006 ⁵⁵	Mimyx cream (Stiefel Labs): PEA-containing cream 3% in combination with control ointment	43-d investigator blinded, randomized bilateral study	74	Control ointment applied to other half of the body	(1) Median time to relapse of symptoms (2) Risk of relapse	

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TABLE 1. (Continued)

Disease Assessed	Study	Pharmacological Tools Used	Study Design and Duration	Subjects or Experimental System	Control or Placebo	Major Outcome Measures	Major Results
AD	Pulvirenti et al, 2007 ²⁹	Adelmidrol 2% in topical emulsion containing hyaluronic acid, phytylphosphatidylcholine, sodium pyroglutamate, and trans 2 dodecenol dioic acid (applied twice daily)	4-wk pilot study	20 pediatric subjects with mild AD (11 males and 9 females; age, 3–16 y)	Untreated lesions (6 areas in 6 subjects)	(1) Efficacy of topical adelmidrol 2% emulsion assessed by IGA score (2) Safety of topical adelmidrol 2% emulsion	(1) 16 patients (80%) had complete resolution of symptoms (2) Control subjects had no improvement. (3) No adverse effects reported.
AD and MC activation	Sugawara, et al, 2012 ⁵⁶	1. AEA 2. CB ₁ agonist: ACEA 3. CB ₁ antagonist: AM251	In vitro study	414 human scalp samples from 8 healthy patients aged 49–72 y		(1) MC detection with Toluidine blue (2) Quantitative immunohistochemistry to measure kit, CB ₁ , tryptase (3) Electron microscopy to detect MC degranulation	(1) 75.5% of kit + MCs express CB ₁ . (2) Treatment with AEA and CB ₁ agonist ACEA did not alter levels of MCs. (3) CB ₁ antagonist AM251 significantly increased the number of mature MCs. (4) AM751-treated MCs showed degranulation and maturation.
Contact irritant dermatitis (SLS and UVR induced)	Kendall et al, 2016 ⁵⁷	2 doses of UVR or doses of SLS to produce comparable erythema to UVR-treated samples	In vitro study	Buttock skin of 10 healthy volunteers (age, 20–49 y; 7 females and 3 males)	Untreated skin	(1) Dermal and epidermal skin lipids (prostanoids, hydroxyl fatty acids, endocannabinoids, sphingolipids) quantified using liquid chromatography and tandem mass spectrometry	(1) Increased epidermal NAE and hydroxyl fatty acids in response to SLS, but not to UVR-induced inflammation. (2) After SLS treatment, 3.7-fold increase in palmitoyl ethanolamide ($P = 0.025$) and 3-fold increase in stearoyl ethanolamide expression ($P = 0.009$). (3) 1.9-fold increase in chemoattractant 12-HETE hydroxyicosatetraenoic acid (HETE) after SRS treatment ($P = 0.017$). (4) No significant change in 2-AG expression in response to either SLS or UVR exposure.
Pruritus (experimentally induced)	Dvorak et al, 2003 ³⁰	Camabindol receptor agonist: HU210 4-wk, open-label (1) Skin patch (50 mM) (2) Dermal microdialysis (5 mM) Histamine: (1) Iontophoresis 50 μ g (2) Dermal microdialysis (5 μ m)	noncomparative trial	(1) Iontophoresis, 12 healthy males (2) Microdialysis, 3 males and 3 females	Ethanol-pretreated skin site	(1) Skin blood flow measured by laser doppler (2) Widespread flare reaction evaluated planimetrically (3) Extravasation of plasma proteins measured in the dialysate (4) Perceived itch measured using VAS	(1) Experimentally induced pruritus was significantly reduced with HU210 ($P < 0.05$) for 1.5 minutes. However, with ongoing monitoring, there was no significant difference. (2) Skin blood flow ($P < 0.003$) and flare responses ($P < 0.03$) were significantly reduced in the HU210 24-h patch group compared with the ethanol pretreated group. (3) Protein extravasation due to histamine was enhanced with use of HU210. (1) 14 of 22 patients felt less itchy, with 63.6% reporting significant reduction in itch, and average reduction in itch was 66.4%. (2) No adverse effects reported.
Chronic pruritus	Stander et al, 2006 ³¹	PEA-containing emollient		22 patients all with chronic pruritus (prurigo, lichen simplex, refractory pruritus)		(1) Subject perception of itch (2) Adverse effects	

Uremic pruritus	Szepielowski et al, 2005 ³²	DMS cream containing endocannabinoid AEA and Physogel AI cream containing PEA (applied twice daily for 3 wk)	3-wk, nonrandomized, nonblinded, open observational study	21 patients on maintenance hemodialysis (10 females and 11 males; age, 31–81 y)	(1) Pruritus assessed by VAS (2) Patient questionnaire	(1) After 3 wk, pruritus completely eliminated in 8 patients (38.1%). 2. Significant reduction in pruritus scores based on VAS and questionnaire ($P < 0.0001$). 3. Complete reduction in xerosis in 17 patients (81%). (1) CB ₁ and CB ₂ receptors present in scalp skin samples and SZ95 sebocytes. However, CB ₂ expression was greater than CB ₁ expression in sebocytes. RT-PCR demonstrated transcription of CB ₂ gene but not the CB ₁ gene in sebocytes. (2) Sebocytes synthesize AEA (66.7 [10] fmol/mg) and 2-AG (6.2 [1] pmol/mg). (3) Both AEA and 2-AG treatment lead to significant ($P < 0.05$) and dose-dependent increase in lipid accumulation in sebocytes. (4) AEA and 2-AG significantly increased cell death, primarily via apoptosis. ($P < 0.05$). (5) Lipid synthesis was enhanced, and cell death was induced in the presence of CB ₂ agonist. The effects of AEA were prevented by CB ₂ antagonist. (6) CB ₂ signaling involves the MAPK pathway: PD098059 significantly antagonized the effects of AEA ($P < 0.05$). (7) AEA and 2-AG significantly upregulated the expression of PPAR α and PPAR γ ($P < 0.05$).
Sebum production	Dobrosi et al, 2008 ¹³	ECs: AEA, 2-AG ACEA: CB ₁ agonist AM-251: CB ₂ antagonist TWH-015: CB ₂ agonist AM630-CB ₂ antagonist PD098059—MAPK inhibitor GW9662—PPAR γ inhibitor	In vitro study	Human immortalized SZ95 sebocytes	(1) CB ₁ and CB ₂ receptor expression assessed with immunocytochemistry, Western blot, and RT-PCR (2) EC production assessed with mass spectroscopy (3) Oil Red O and quantitative Nile Red fluorescence assay (4) Sebocyte viability (5) AEA action on CB ₁ R vs CB ₂ R in presence of CB ₂ agonist JNH-015 and CB ₂ antagonist AM 630	(1) No change in lipid synthesis after 24 and 48 h with CBD treatment. CBD inhibited the lipogenic actions of AEA in a dose-dependent manner. CBD normalized the AA-induced pathologic lipogenesis of SZ95 sebocytes (2) SZ95 proliferation significantly decreased at 1–10 μ M of CBD, but not below the starting cell count: 50 μ M of CBD evoked cell death (3) CBD prevented TNF- α expression after treatment with lipopolysaccharide and LPA.
Sebum production	Olah et al, 2024 ⁵⁴	CBD 1–10 μ M	In vitro	Human immortalized SZ95 sebocytes Human scalp and arm skin samples from 4 women	(1) Basal lipid synthesis of SZ95 sebocytes assessed by Oil Red O and Nile Red. (2) Antiproliferative activity of CBD assessed by sebocytes cell counts. (3) Anti-inflammatory activity measured by TNF- α expression after treatment with LPS and LTA.	(1) No change in lipid synthesis after 24 and 48 h with CBD treatment. CBD inhibited the lipogenic actions of AEA in a dose-dependent manner. CBD normalized the AA-induced pathologic lipogenesis of SZ95 sebocytes (2) SZ95 proliferation significantly decreased at 1–10 μ M of CBD, but not below the starting cell count: 50 μ M of CBD evoked cell death (3) CBD prevented TNF- α expression after treatment with lipopolysaccharide and LPA.
Animal in vivo and in vitro studies	Petrosino et al, 2010 ³³	DNFB-induced allergic dermatitis Intrapertoneal PEA	In vitro study	9 per group CB ₁ /CB ₂ ^{+/+} DKO mice Immortalized human keratinocytes: HaCaT cells	(1) PEA levels (2) TRPV1 expression	(1) DNFB increased ear skin PEA more in DKO mice (97.8 [4.9] pmol/mL) vs WT mice (36.5 [5.4] pmol/mL). (2) DNFB upregulated TRPV1, PPAR α , and PEA-synthesizing enzymes. (3) Intrapertoneal PEA inhibited DNFB-induced ear inflammation

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TABLE 1. (Continued)

Disease Assessed	Study	Pharmacological Tools Used	Study Design and Duration	Subjects or Experimental System	Control or Placebo	Major Outcome Measures	Major Results
Allergic dermatitis	Petrosino et al, 2016 ⁶³	Adelmidrol (PEA analogue)	In vitro study	Canine keratinocytes and human keratinocytes (HaCaT) Human embryonic cells (HEK-293); WT or with NAAA.	Azelic acid	(1) Concentration of AEA, 2-AG, and PEA after treatment with adelmidrol (2) FAAH and NAAA (hydrolyzing enzymes) activity after adelmidrol treatment	(1) Adelmidrol increased PEA concentration in canine cells. (2) Adelmidrol did not inhibit activity of PEA catabolism enzymes (FAAH and NAAA).
Allergic dermatitis	Karsak et al, 2007 ¹¹	CB ₁ receptor antagonist: SR-141716A CB ₂ antagonist: SR-144528 THC injection DNFB-known allergen	In vitro study	CB ₁ /CB ₂ ^{-/-} DKO mice FAAH-knockout mice	WT mice—CB ₁ /CB ₂ ^{+/+}	(1) Ear swelling after treatment with CB ₁ and CB ₂ antagonists (2) AEA and 2-AG levels after DNFB treatment (3) Ear swelling and granulocyte recruitment after THC injection (4) Effect of DNFB on FAAH-knockout mice	(1) Ear swelling significantly increased after CB ₁ /CB ₂ receptor antagonism. (2) Increase in AEA and 2-AG in DNFB-treated ear, with greater increase in DKO mice compared to WT mice. (3) Significantly reduce ear swelling and granulocyte recruitment in THC-treated mice. (4) FAAH-knockout mice had significantly decreased allergic response to DNFB challenge.
AD	Nam, 2016 ⁶⁸	CB ₁ receptor agonists: AEA HU-308 Oxazolone—known skin irritant	In vitro study	Rat leukemic cell line: RBL-2H3 Bone-marrow derived mouse MCs Oxazolone-induced AD mice model		(1) Cell viability (MTT assay) (2) MC proliferation (3) MC recruitment in the epidermis after oxazolone treatment (4) Histamine levels in the blood after oxazolone treatment	(1) CB ₁ receptor agonists inhibited release of inflammatory mediators without causing cytotoxicity. (2) There was a dose-dependent decrease in MC proliferation with 43% reduction at 24 h with CB ₁ R agonists. (3) Topical CB ₁ receptor agonist decreased MC recruitment into the skin and reduced levels of histamine in the blood in oxazolone-induced AD.
AD	Abramo et al, 2014 ⁶⁹	None	Prospective study	10 (5 healthy dogs, 5 dogs with AD)	Skin of healthy dogs without AD	(1) Amount of lipid reported as percent of biopsy tissue weight, assessed by LC-APCI-MS. (2) AEA, OEA, and 2-AG concentrations calculated by isotope dilution (pmol/g tissue) (3) MC count and distribution, assessed by Toluidine blue (4) Immunohistochemistry of MS	(1) Significant decrease in lipids in skin of AD dogs compared with that of healthy dogs ($P < 0.05$; 6-fold lower amount of lipids in AD skin vs healthy canine skin). (2) Lipid mediators significantly increased in AD skin compared with control, with PEA being the highest at 30-fold higher ($P < 0.05$), and there was a 6-fold higher amount of AEA in AD skin. (3) MCs were significantly increased in subepidermal and perfollicular spaces of AD skin vs control ($P < 0.01$).
Contact irritant dermatitis	Oka et al, 2006 ³⁴	Oxazolone to induce dermatitis CB ₂ receptor antagonist: SR144528 CB ₁ receptor antagonist: AM251	In vitro study	Rats with oxazolone-induced AD	Skin of normal rats	(1) Amount of 2-AG in mouse ear after repeat challenge with oxazolone (2) Ear thickness after oxazolone challenge	(1) Amount of 2-AG in mouse ear increased after challenge with oxazolone (increase of 1.4 [1.7], 5.9 [1.4], and 9.3 [1.7] at 0, 12, and 24 h, respectively). (2) Treatment with CB ₂ antagonist SR144528 reduced recruitment of eosinophils and ear swelling by 18%. (3) AM251 did not markedly suppress ear swelling.

CBD indicates cannabidiol; CPT, current perception threshold; DKO, double-knockout; EC, endocannabinoid; HETE, hydroxyeicosatetraenoic acid; IGA, Investigator's Global Assessment; MAPK, mitogen-activated protein kinase; MC, mast cell; LC-APCI-MS, light chromatography atmospheric pressure chemical ionisation mass spectrometry; LPA, lysophosphatidic acid; RT-PCR, reverse transcription polymerase chain reaction; TEWL, transepidermal water loss; UVR, ultraviolet radiation; VAS, visual analogue scale; WT, wild-type.

Prevention is key to controlling itch and irritation, and patients are counseled to avoid harsh cleansers, opt for short lukewarm water showers, and use daily emollients.³⁶ Severe cases may require topical corticosteroid treatment.³⁷ A meshwork of corneocytes, cholesterol, free fatty acids, and ceramides contributes to the skin barrier, and the epidermal and sebaceous lipids are essential in providing moisture and a permeability barrier.³⁸ Symptoms seen in AE and other forms of xerotic dermatitis are partially due to impaired skin barrier repair.

Endocannabinoids have been identified within the stratum granulosum, and abnormally low levels of endocannabinoids may lead to xerosis. Cutaneous ECS responds to xerosis by increasing lipid synthesis within the stratum granulosum.²⁷ Topical endocannabinoid treatment has been studied in xerotic skin.³⁹ In a 4-week clinical trial, 60 patients with AE were randomized to receive either an emollient containing PEA and AEA or a standard emollient devoid of endocannabinoids. Subjects who received the PEA/AEA cream had significant improvement in itching and skin hydration, as well as decrease in erythema, scaling, and dryness. Because naturally occurring endocannabinoids in the skin may augment skin barrier function by increasing epidermal lipid production, the authors hypothesized that a topical formulation containing PEA and AEA stimulates lipid synthesis for skin barrier repair, thereby reducing symptoms of itchy and flaky skin. Other authors have suggested that a topical formulation inhibiting local endocannabinoid degradation, in the form of FAAH or monoacylglycerol lipase inhibitors, may also improve dry skin and itch by augmenting the barrier repair benefits of endocannabinoids.⁸ The current evidence suggests that cutaneous endocannabinoid system modulation may be a promising therapeutic approach for asteatosis.

Atopic Dermatitis

Atopic dermatitis is a chronic relapsing-remitting itchy inflammatory skin condition characterized by weepy red plaques in the acute stage and lichenified thick plaques in the chronic stage. Atopic dermatitis affects up to 20% of children and adolescents and up to 5% of the population in developed countries.⁴⁰ Although the pathogenesis of AD is not completely elucidated, it is believed to be due to a constellation of factors, including immune dysregulation, epidermal and sebaceous barrier disruption, altered sensation to itch stimuli, and impaired microbial defense. The mainstay of AD treatment focuses on anti-inflammation using topical steroids and calcineurin-inhibitors, barrier repair using moisturizers, and reducing microbial colonization. Several clinical studies have demonstrated the therapeutic benefit of topical preparations containing endocannabinoid receptor agonists or degradation inhibitors in AD. In a randomized controlled study involving children and adults with AD, the cohort that used PEA-containing cream in combination with a class IV topical steroid cream (0.1% clocortolone pivalate) had a prolonged time to AD flare-up compared to the cohort that used topical steroid cream alone.²⁸ Another study involving 2000 patients with AD reported that subjects using a PEA-containing cream had a

statistically significant improvement in itch and reduction of weekly topical steroid use by 62%.²⁶ Furthermore, in a pilot study of 20 pediatric patients with mild AD, subjects who used a 2% adelmidrol (PEA analogue)-containing product had 80% resolution of symptoms, on the basis of the physician's Investigator's Global Assessment score.²⁹

Allergic Contact Dermatitis

Allergic contact dermatitis affects approximately 11% of women and 5% of men in industrialized countries and is one of the leading causes of occupational diseases.¹¹ When the skin is first exposed to an allergenic molecule, dendritic cells present the foreign molecule to naive T cells, which then mount an inflammatory response upon repeat contact with the same allergen, termed a *delayed hypersensitivity reaction*.¹¹ The current treatment for ACD surrounds trigger avoidance, topical corticosteroids and calcineurin inhibitors, and systemic immunosuppressive agents in severe cases.⁴¹ Therapeutic modulation of the ECS may offer an important avenue of investigation.⁴² Although human studies are lacking, mouse studies shed light on the therapeutic potential of endocannabinoids for ACD.

Petrosino et al³³ demonstrated that cutaneous PEA levels in mice can be increased after cutaneous exposure to 2,4-dinitrofluorbenzene (DNFB). When PEA was injected into the peritoneum of mice, the DNFB-induced ear allergic dermatitis was inhibited. These findings suggest that endogenous production and exogenous administration of PEA may be protective against ACD development; however, human studies are needed to demonstrate clinical safety and usefulness.

In a study by Karsak et al,¹¹ double-knockout mice lacking both CB₁ and CB₂ developed allergic reaction to nickel ear tags, characterized by intense scratching and skin ulcerations. On the other hand, wild-type mice and single knockouts deficient in either CB₁ or CB₂ did not develop signs of allergy to the nickel ear tags. In addition, when a contact allergen, DNFB, was applied onto the skin, single-knockout mice had a significantly more severe allergic reaction compared with the wild-type mice.¹¹ The authors hypothesized that a functional ECS may offer protection against developing ACD. The mice also demonstrated increased ear swelling and inflammation after injection of a CB₂ antagonist, SR144528. This experiment was extrapolated by treating the mice with injected and topical THC; both treatments significantly decreased ear swelling. Lastly, FAAH-knockout mice exposed to DNFB had a significantly lower ACD rate, suggesting that in the absence of AEA degradation, higher levels of AEA may prevent ACD.¹¹ These findings shed light on the use of FAAH inhibitors as potential therapy for ACD.

Irritant Contact Dermatitis

Irritant contact dermatitis is a prevalent problem in dermatology and occupational health worldwide, especially in people who do "wet work," such as hairdressers, cleaners, health care workers, and workers handling chemicals.⁴³ It is estimated that between 7% and 11.8% of the general population will be affected with ICD during their lifetime,⁴⁴ and ICD is estimated to be the cause of 95% of occupational skin conditions.⁴⁵ The role of the ECS in ICD was

examined by exposing human skin of 10 healthy volunteers to sodium lauryl sulfate (SLS), a known irritant.⁴⁶ Lipid analysis revealed increased levels of epidermal *N*-acyl ethanolamides (NAE), PEA, and hydroxyl fatty acids but no significant change in 2-AG level. This study suggests that NAE and PEA, but not 2-AG, may be involved in skin barrier repair after irritant exposure. In a separate study, oxazolone was applied onto the skin of mice to induce ICD.³⁴ Twenty-four hours after oxazolone challenge, 2-AG level in the ear was increased by 9.3 (1.7) pmol and ear swelling increased 2.7 fold. Subsequent exposure to a CB₂ antagonist (SR144528) led to decreased ear swelling by 18% and significant reduction in eosinophils recruitment. Conversely, treatment with a CB₁ antagonist (AM251) did not significantly decrease oxazolone-induced ear swelling. These findings suggest that 2-AG expression increases in response to topical irritant challenge, perhaps acting as a protective mechanism, and that CB₂, but perhaps not CB₁, is involved in the anti-inflammatory response in ICD.

Pruritus

Pruritus is an uncomfortable localized or widespread sensation that triggers the intense urge to scratch.⁴⁷ Pruritus is a common symptom in dermatologic conditions and as a dermatologic manifestation of systemic diseases. In a study of nearly 2500 subjects with AD, application of a PEA-containing cream resulted in a 38.3% resolution and 41% reduction in pruritus.²⁶ In a 4-week clinical study of healthy volunteers, pruritus was experimentally induced with histamine via dermal microdialysis.³⁰ The subjects were randomized to receive either a skin patch containing HU210 (a synthetic endocannabinoid and CB₁/CB₂ agonist) or ethanol before histamine. The subjects who received HU210 experienced significantly less pruritus for approximately 1.5 minutes after histamine treatment; however, ongoing recordings revealed no difference in itch between HU210- and ethanol-treated skin. In addition, histamine-induced skin blood flow and axonal flare responses were both significantly decreased in the HU210 patch group compared with the ethanol-treated control group. These findings suggest that ECS activation may reduce vasodilation and suppress the early phase of histamine-induced itch.

In patients with lichen simplex chronicus and prurigo nodules secondary to chronic pruritus, a topical PEA-containing emollient provided an average of an 86% reduction in subjective pruritus.³¹ In a 3-week open-label study involving 21 patients with uremic pruritus, application of AEA- and PEA-containing cream twice a day for 3 weeks resulted in total elimination of pruritus in more than 38% of the subjects and another 52% reported significantly reduced pruritus.³² Because no control group was included in these studies, it is unclear how much improvement in pruritus would be obtained from applying the emollient vehicle alone. Nevertheless, topical preparations containing endocannabinoids may provide relief from pruritus by down-regulating mast cell degranulation,⁴⁸ inhibiting inflammatory cytokines,⁴⁹ decreasing tumor necrosis factor α (TNF- α) during inflammation,⁵⁰ or providing an analgesic effect on their own.⁵¹

CONCLUSIONS

A well-balanced ECS plays an important role in maintaining skin health. An ECS imbalance has been reported in several dermatologic conditions. In this review, we discussed recent advances in understanding the role of ECS in the pathogenesis and therapeutic potential of common eczematous dermatoses. Among the reviewed studies, there is significant evidence for using endocannabinoid modulators to improve the skin barrier function, regulate the immune response in skin inflammation, and modulate histamine-induced inflammatory and neuroendocrine responses in eczematous skin conditions. In addition, endocannabinoids have been demonstrated to modulate sebocyte lipid production, which poses a novel approach to treating inflammatory skin diseases with known sebaceous dysfunction including acne, AD, seborrheic dermatitis, rosacea, and psoriasis.⁵² The cutaneous ECS seems to communicate with the immune, neurological, and endocrine systems in a delicate harmony that is important for skin health and function. Pathological alterations in the homeostasis of the ECS have been shown to contribute to the development of skin diseases, including eczematous skin conditions. Several early studies have demonstrated the therapeutic potential of ECS modulators for use in eczematous dermatoses, including endocannabinoid analogues, cannabinoid receptor antagonists and agonists, and degradation enzyme inhibitors. Further studies are needed to better elucidate the role of cutaneous ECS and its potential as a therapeutic target in dermatologic disorders.

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