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Cannabidiol and the endocannabinoidome in atopic dermatitis

Canabidiol e o endocanabinoidoma na dermatite atópica

Cannabidiol y el endocanabinoidoma en la dermatitis atópica

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ABSTRACT

Objective: To analyze the main pathophysiological mechanisms of atopic dermatitis from a neuroimmune perspective, emphasizing the integration of epidermal barrier dysfunction, chronic inflammation mediated by Th2 immune axes, and neurogenic pruritus pathways, while also discussing the regulatory role of the endocannabinoidome and the mechanistic basis of modulation by cannabidiol. **Literature review:** Atopic dermatitis results from the interplay between skin barrier dysfunction, immunological hyper-reactivity, and neuroimmune alterations that perpetuate chronic pruritus. Cytokines such as IL-4, IL-13, and IL-31 compromise the epidermal barrier and intensify inflammation, whereas neurogenic mediators amplify peripheral and central sensitization. The endocannabinoidome constitutes a regulatory axis comprising lipid mediators, metabolic enzymes, and multiple canonical and non-canonical receptors—including TRP, PPARγ, and GPR55—that participate in modulating inflammation, epidermal differentiation, and pruritogenic signaling. Cannabidiol indirectly regulates the endocannabinoidome through mechanisms such as negative allosteric modulation of CB1, functional interaction with CB2, and partial inhibition of FAAH, thereby positively influencing the inflammatory and neuroimmune processes involved in the disease. **Final considerations:** The endocannabinoidome is emerging as a relevant conceptual framework for understanding the integration of inflammation, the epidermal barrier, and pruritus. Cannabidiol demonstrates promising modulatory potential, although this is currently limited by scientific gaps requiring further rigorous investigation.

Keywords: Atopic dermatitis, Endocannabinoidome, Cannabidiol, Cutaneous neuroimmunology, Pruritus.

RESUMO

Objetivo: Analisar, sob perspectiva neuroimune, os principais mecanismos fisiopatológicos da dermatite atópica, enfatizando a integração entre disfunção da barreira epidérmica, inflamação crônica mediada por eixos imunes do tipo Th2 e vias neurogênicas do prurido, além de discutir o papel regulatório do endocanabinoidoma e os fundamentos mecanísticos da modulação por canabidiol. **Revisão bibliográfica:** A dermatite atópica resulta da interação entre disfunção da barreira cutânea, hiper-reatividade imunológica e alterações neuroimunes que perpetuam o prurido crônico. Citocinas como IL-4, IL-13 e IL-31 comprometem a barreira epidérmica e intensificam a inflamação, enquanto mediadores neurogênicos ampliam a sensibilização periférica e central. O endocanabinoidoma configura um eixo regulatório composto por mediadores lipídicos, enzimas metabólicas e múltiplos receptores canônicos e não canônicos, incluindo TRP, PPARγ e GPR55 que participa da modulação da inflamação, diferenciação epidérmica e sinalização

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pruritogênica. O canabidiol regula indiretamente o endocanabinoidoma por mecanismos como modulação alostérica negativa do CB1, interação funcional com CB2 e inibição parcial da FAAH, repercutindo positivamente nos processos inflamatórios e neuroimunes envolvidos na doença. **Considerações finais:** O endocanabinoidoma consolida-se como eixo conceitual relevante para compreender a integração entre inflamação, barreira epidérmica e prurido. O canabidiol demonstra potencial modulador promissor, embora ainda limitado por lacunas científicas que requerem investigação adicional rigorosa.

Palavras-chave: Dermatite atópica, Endocanabinoidoma, Canabidiol, Neuroimunologia cutânea, Prurido.

RESUMEN

Objetivo: Analizar los principales mecanismos fisiopatológicos de la dermatitis atópica desde una perspectiva neuroinmune, enfatizando la interacción entre disfunción de la barrera epidérmica, inflamación crónica mediada por respuestas Th2 y vías del prurito neurógeno, además del papel regulador del endocannabinoidoma y la modulación por cannabidiol. **Revisión de la literatura:** La dermatitis atópica resulta de la disfunción de la barrera cutánea, la hiperreactividad inmunológica y alteraciones neuroinmunes que perpetúan el prurito crónico. Citocinas como IL-4, IL-13 e IL-31 comprometen la barrera epidérmica e intensifican la inflamación, mientras mediadores neurógenos amplifican la sensibilización periférica y central. El endocannabinoidoma es un sistema regulador formado por mediadores lipídicos, enzimas y receptores, incluidos TRP, PPARγ y GPR55, que modulan inflamación, diferenciación epidérmica y señalización pruritogénica. El cannabidiol regula indirectamente este sistema mediante modulación de CB1, interacción con CB2 e inhibición parcial de FAAH, favoreciendo el control de procesos inflamatorios y neuroinmunes. **Consideraciones finales:** El endocannabinoidoma constituye un marco relevante para comprender la relación entre inflamación, barrera epidérmica y prurito. El cannabidiol presenta potencial terapéutico prometedor, aunque aún existen lagunas científicas que exigen investigaciones más rigurosas.

Palabras clave: Dermatitis atópica, Endocannabinoidoma, Cannabidiol, Neuroinmunología cutánea, Prurito.

INTRODUCTION

Atopic dermatitis is a highly prevalent chronic inflammatory skin disease characterized by a recurrent course, clinical heterogeneity, and a significant impact on quality of life. In recent decades, advancements in understanding its pathogenesis have demonstrated that the disease is not attributable to a single pathological axis but rather arises from the dynamic interplay among epidermal barrier dysfunction, immune dysregulation, and neuroimmune alterations associated with persistent pruritus (LEUNG DYM and BIEBER T, 2003; LEUNG DYM and GUTTMAN-YASSKY E, 2014; KIM J J, et al., 2019).

Beyond its cutaneous manifestations, atopic dermatitis imposes a substantial functional, emotional, and social burden. Persistent pruritus, sleep disturbance, psychological distress, impaired daily activities, and reduced work or school performance significantly compromise patients' quality of life. This broad clinical impact reinforces the need for integrative therapeutic approaches capable of simultaneously addressing inflammation, neural dysregulation, and skin barrier dysfunction, highlighting the relevance of cutaneous neuroimmunology as a comprehensive framework for understanding disease mechanisms and identifying novel therapeutic targets.

Cutaneous barrier dysfunction facilitates the penetration of allergens, irritants, and microorganisms, thereby triggering sustained inflammatory responses. Concurrently, the predominant activation of the Th2-type response, with the production of cytokines such as IL-4, IL-13, and IL-31, contributes to the maintenance of chronic inflammation, exacerbates epidermal barrier impairment, and establishes a direct link with pruritus, a central symptom of the disease (D'AVINO P, et al., 2025; GUTTMAN-YASSKY E, et al., 2018; KIM J, et al., 2019). These processes are modulated by complex neuroimmune interactions involving keratinocytes, immune cells, and sensory nerve fibers, consequently characterizing atopic dermatitis as a neuroimmuno-cutaneous disease.

In this context, therapeutic strategies excessively focused on isolated molecular targets exhibit clear limitations, particularly in the integrated control of inflammation, pruritus, and the restoration of cutaneous homeostasis. Consequently, there is growing interest in endogenous regulatory systems capable of acting pleiotropically and integratively. The cutaneous endocannabinoid system has emerged as such a central regulatory axis, participating in the modulation of inflammation, immune response, epidermal differentiation, and neurogenic signaling (BÍRÓ T, et al., 2009; TÓTH BI et al., 2011; TÓTH BI et al., 2019).

The expansion of this concept to the **endocannabinoidome** describes a more comprehensive functional network, encompassing endogenous lipid mediators, metabolic enzymes, and multiple additional molecular targets, including classical and non-canonical cannabinoid receptors, transient receptor potential ion channels, and nuclear receptors involved in the regulation of inflammation and cellular signaling (DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA and DI MARZO V, 2021).

Analyzing atopic dermatitis considering this expanded regulatory system provides a robust conceptual framework for integrating cutaneous inflammation, pruritus, and neuroimmunology, as well as for discussing the role of endocannabinoidome modulators, such as cannabidiol, within a critical mechanistic context.

LITERATURE REVIEW

Cutaneous barrier dysfunction and neuroimmune interactions in atopic dermatitis

The pathophysiology of atopic dermatitis is underpinned by continuous, bidirectional interactions among epidermal barrier dysfunction, dysregulated immune activation, and alterations in cutaneous innervation, forming an integrated pathogenic system that perpetuates chronic inflammation and persistent pruritus (CRIADO PR et al., 2024; KIM J, et al., 2019; LEUNG DYM and GUTTMAN-YASSKY E, 2014). These axes do not act linearly but rather exhibit positive feedback loops, contributing to the chronicity and clinical variability of the disease.

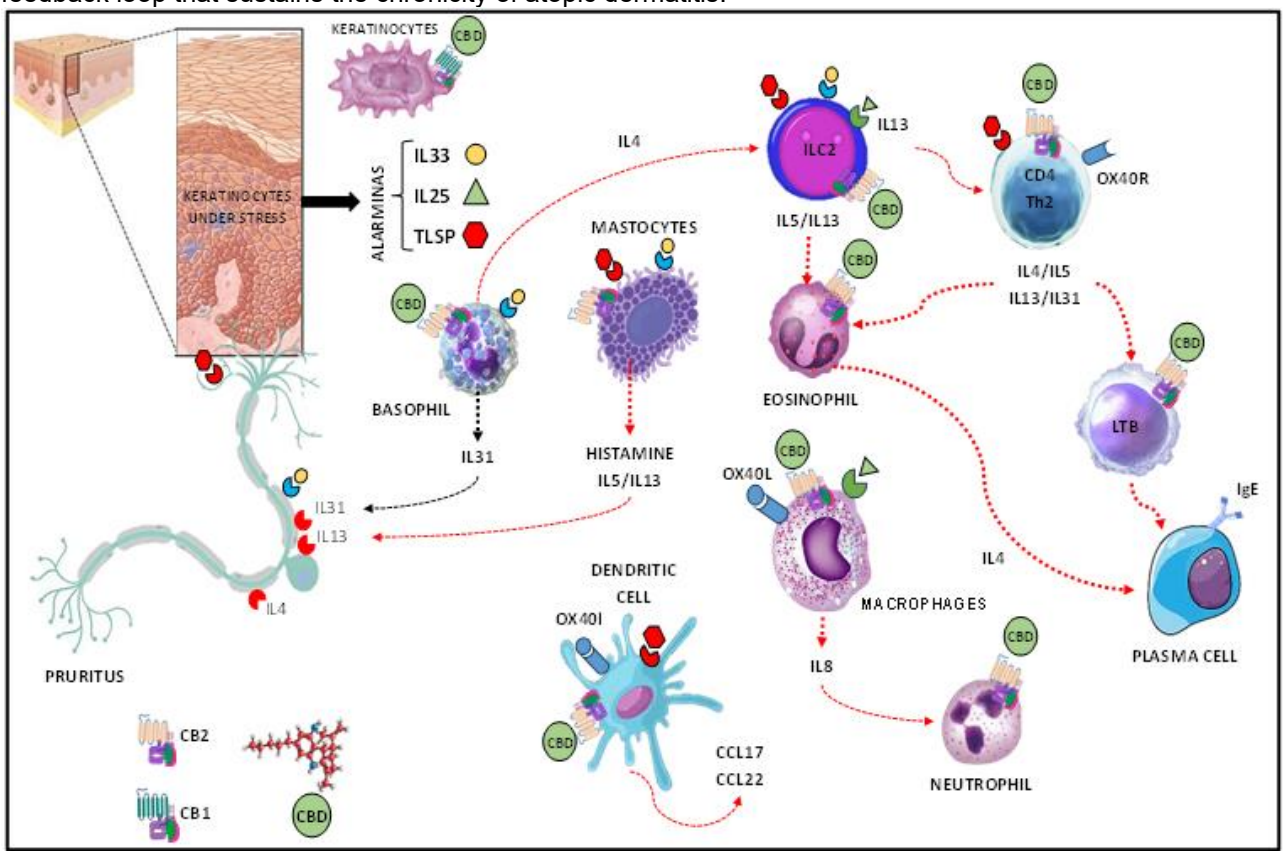
Structural alterations of the stratum corneum, including reduced filaggrin expression, impaired intercellular junctions, and an imbalance in epidermal lipid content, result in increased transepidermal water loss and greater skin permeability. These changes facilitate the penetration of allergens, irritants, and microorganisms, even in clinically unaffected skin areas, establishing a state of persistent subclinical inflammation (ELIAS PM and STEINHOFF U M, 2008; ELIAS PM, 2014; KIM J, et al., 2019; SHIMADA Y, et al., 2009).

Epidermal barrier impairment activates keratinocytes as immunological sentinel cells, leading to the release of epithelial alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These molecules promote innate immune activation and direct the adaptive response toward a predominantly Th2-type profile, through the activation of dendritic cells, mast cells, and type 2 innate lymphoid cells (BRANDT EB and SIVAPRASAD U, 2011; CRIADO PR, et al., 2024; GUTTMAN-YASSKY E, et al., 2018).

Th2-axis cytokines, especially IL-4, IL-13, and IL-31, play a central role in amplifying cutaneous inflammation. These cytokines inhibit the expression of epidermal structural proteins such as filaggrin, loricrin, and involucrin, and reduce the production of antimicrobial peptides, favoring recurrent skin infections and microbial dysbiosis (HOWELL MD, et al., 2008; KIM J, et al., 2019; LEUNG DYM, et al., 2021). IL-31, in turn, acts directly on cutaneous sensory neurons, establishing a critical link between inflammatory reaction and pruritus (**Figure 1**).

With disease progression, other immunological pathways begin to contribute to the inflammatory picture, including Th22 and Th17 responses, associated with epidermal hyperplasia, skin thickening, and lichenification of lesions. The coexistence of these diverse immunological profiles reflects the plasticity of the immune response in atopic dermatitis and contributes to the phenotypic diversity observed throughout the disease course (CRIADO PR, et al., 2024; KIM J, et al., 2019; NOGRALES KE, et al., 2009).

Figure 1 - Immune reaction in atopic dermatitis and the participation of cannabidiol (CBD) and cannabinoid receptors (CB1; CB2) in epidermis cells, resident and non-resident antigen-presenting cells, cells of the TH2-like reaction. Epidermal barrier dysfunction, influenced by genetic predisposition and exposome factors, leads to the release of epithelial alarmins such as TSLP and IL-33, which promote Th2-type inflammation. Pruritogenic cytokines, especially IL-31, act directly on sensory nerve fibers, inducing neurogenic pruritus and neural sensitization. Scratching intensifies barrier damage and inflammation, establishing a neuroimmune feedback loop that sustains the chronicity of atopic dermatitis.



Source: Araujo AKL, et al., 2026. Adapted from Ständer S and Luger TA, 2010.

The neuroimmune dimension represents an essential component of pathophysiology. Chronic pruritus in atopic dermatitis is predominantly mediated by non-histaminergic mechanisms, involving the direct activation of sensory nerve fibers by cytokines, epithelial alarmins, and neurogenic mediators such as substance P and calcitonin gene-related peptide (CGRP). These stimuli promote an increase in the density and excitability of cutaneous nerve fibers, as well as peripheral and central sensitization, intensifying the perception of pruritus (IKOMA A et al., 2006; KIM J, et al., 2019; STÄNDER S and LUNGER TA, 2010).

Repetitive scratching behavior mechanically aggravates epidermal barrier dysfunction, intensifies local inflammation, and stimulates the continuous release of inflammatory and neurogenic mediators, thereby establishing the itch-scratch cycle, considered one of the primary mechanisms for maintaining disease activity (IKOMA A et al., 2006; KIM J, et al., 2019). Furthermore, alterations in the cutaneous microbiota play a relevant role in the pathogenesis of atopic dermatitis. Reduced microbial diversity, associated with the predominant colonization by *Staphylococcus* species, contributes to the continuous activation of cutaneous immunity through the production of superantigens and bacterial toxins, intensifying inflammation and pruritus (CRIADO PR, et al., 2024; KONG HH, et al., 2012; NAKATSUJI T, et al., 2017).

Pruritus and neuroimmunology in atopic dermatitis

Chronic pruritus in atopic dermatitis results from the sustained activation of peripheral and central neuroimmune pathways, being predominantly mediated by non-histaminergic mechanisms. Unlike acute pruritus, this symptom emerges from the direct interaction among inflammatory cytokines, keratinocytes, and

sensory nerve fibers, configuring an essential pathogenic axis for the maintenance of chronic cutaneous inflammation (IKOMA A et al., 2006; KIM J, et al., 2019; STÄNDER S and LUNGER TA, 2010).

Among the cytokines involved, IL-31 holds a central position as a pruritogenic mediator. Primarily produced by Th2 lymphocytes, IL-31 acts directly on cutaneous sensory neurons through its specific receptors, promoting increased neuronal excitability and intensification of the pruritic signal transmission. This mechanism establishes a direct link between immune inflammation and sensory perception, independent of histamine release (KIM J et al., 2019; STÄNDER S and LUNGER TA, 2010; SONKOLY E; et al., 2006).

In addition to IL-31, other Th2-associated cytokines, such as IL-4 and IL-13, exert direct effects on sensory neurons, modulating their excitability and amplifying the pruritogenic response, thereby reinforcing the neuroimmune nature of the symptom in atopic dermatitis (KIM J, et al., 2019; OETJEN LK et al., 2017).

Keratinocytes play an active role in this process by releasing epithelial alarmins, such as TSLP, IL-25, and IL-33, in response to barrier dysfunction and inflammatory stress. These molecules, beyond modulating the immune response, interact directly with cutaneous nerve endings. TSLP has been described as capable of directly activating sensory neurons, contributing to the initiation and perpetuation of pruritus independently of the initial involvement of classical immune cells (**Figure 1**) (KIM J, et al., 2019; WILSON SR, et al., 2013).

Chronic cutaneous inflammation also induces structural and functional alterations in skin innervation. Patients with atopic dermatitis exhibit an increased density of intraepidermal nerve fibers and greater proximity between nerve endings and immune cells, such as mast cells and dendritic cells. This neuroanatomical rearrangement favors the amplification of neuroimmune interactions and contributes to peripheral sensitization, intensifying the perception of pruritus (KIM J, et al., 2019; TOMINAGA M and TAKAMORI K, 2014).

Concurrently, neurogenic mediators released by activated nerve fibers, such as substance P and calcitonin gene-related peptide (CGRP), provide positive feedback to cutaneous inflammation by inducing vasodilation, vascular extravasation, and activation of resident immune cells. This process of neurogenic inflammation reinforces the bidirectional nature of communication between the nervous system and the immune system in atopic dermatitis. Furthermore, the neurogenic inflammation mediator endothelin-1 causes human skin barrier disruption in atopic dermatitis via an ETAR/TRPA1-Axis (IKOMA A, et al., 2006; STEINHOFF U, et al., 2006; LEO R, et al., 2025).

Beyond peripheral sensitization, evidence suggests central mechanisms are involved in the perpetuation of chronic pruritus. Repetitive stimulation of sensory pathways can lead to central sensitization, characterized by amplification of neuronal response in the central nervous system and persistence of the pruritic sensation even in the absence of intense peripheral stimuli, contributing to the dissociation between cutaneous inflammatory activity and symptom intensity in some patients (IKOMA A, et al., 2006; STÄNDER S and LUNGER TA, 2010).

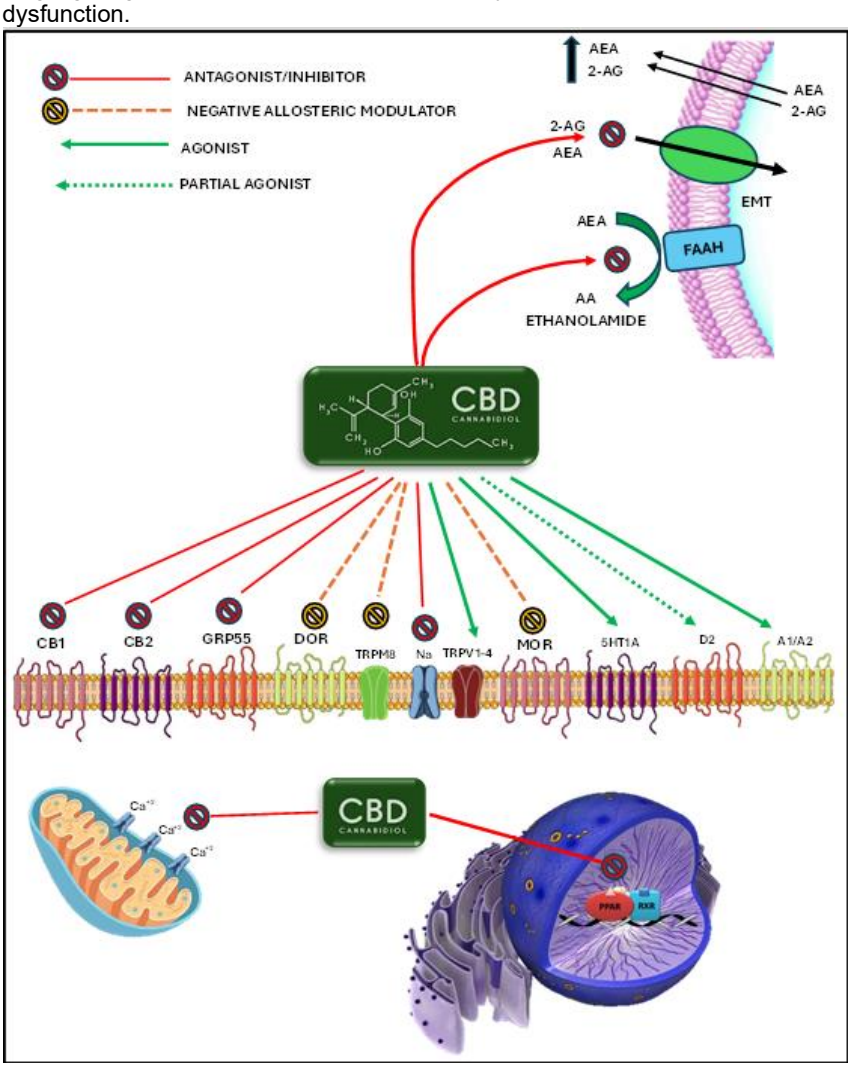
Cutaneous endocannabinoid system and endocannabinoidome

The endocannabinoid system constitutes a highly conserved lipid regulatory axis involved in maintaining tissue homeostasis across various organs. Classically, this system is composed of cannabinoid receptors type 1 (CB1) and type 2 (CB2), the main endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and enzymes responsible for their synthesis and degradation, such as N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL) (BÍRÓ T et al., 2009; DI MARZO V, et al., 1998; PIOMELLI D and TAGNE AM, 2022).

In the skin, components of the endocannabinoid system are widely expressed in keratinocytes, melanocytes, fibroblasts, endothelial cells, resident immune cells, and sensory nerve endings, underscoring its direct involvement in regulating cell proliferation, epidermal differentiation, inflammatory responses, and neurogenic signaling. This broad cellular distribution reinforces the role of the ECS as a local regulatory system capable of integrating metabolic, immunological, and neural signals within the cutaneous microenvironment (BÍRÓ T, et al., 2009; TÓTH BI, et al., 2011; TÓTH BI, et al., 2019).

Conceptual advancements have expanded the classical definition of the endocannabinoid system to the concept of the endocannabinoidome, which describes a more comprehensive functional network. This network is composed not only of classical endocannabinoids and their receptors but also a diversity of structurally related lipid mediators, redundant metabolic enzymes, and multiple additional molecular targets (DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA e DI MARZO V, 2021). These mediators include N-acylethanolamides, monoacylglycerols, and other polyunsaturated fatty acid derivatives, all capable of modulating various cellular pathways. Its high complexity and functional redundancy distinguish the endocannabinoidome. In addition to CB1 and CB2 receptors, this network involves non-canonical receptors, such as transient receptor potential ion channels (particularly TRPV1, TRPA1, and TRPM8), as well as peroxisome proliferator-activated nuclear receptors (PPAR-α and PPAR-γ) and G protein-coupled orphan receptors, such as GPR55. This diversity of targets confers a pleiotropic character to the endocannabinoidome, enabling the coordinated modulation of inflammatory, metabolic, and neurogenic processes (DI MARZO V and PISCITELLI F, 2015; MACCARRONE U, et al., 2023) (**Figure 2**).

Figure 2 - Indirect modulation of endocannabinoidome by cannabidiol (CBD). Cannabidiol has a low direct agonist affinity for CB1 and CB2, acting predominantly by indirect mechanisms. The negative allosteric modulation of CB1, the indirect functional interaction with CB2 and the partial inhibition of FAAH, with increased endocannabinoid tone, stand out. In addition, CBD interacts with non-canonical targets such as GPR55, TRP channels (e.g., TRPV1), and PPARγ, modulating neurogenic and inflammatory pathways. "Highlighting the activation of inflammatory cells and epidermal barrier dysfunction.



Source: Araujo AKL, et al., 2026. Adapted from Maccarrone U, et al. (2023).

Cannabidiol and endocannabinoidome modulation in atopic dermatitis

Cannabidiol (CBD), a non-psychotropic phytocannabinoid derived from *Cannabis sativa,* is distinguished by exerting its biological effects predominantly through indirect modulation of the endocannabinoidome, exhibiting low direct agonist affinity for classical cannabinoid receptors CB1 and CB2. In contrast to Δ⁹-tetrahydrocannabinol (THC), CBD interacts with multiple molecular targets involved in the regulation of inflammation, immune response, and neurogenic signaling, configuring a pharmacological profile compatible with integrative and multifunctional regulatory systems (DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA e DI MARZO V, 2021).

Considering the pathophysiology of atopic dermatitis, marked by the convergence of epidermal barrier dysfunction, chronic inflammation, and persistent pruritus mediated by neuroimmune pathways, CBD's action on the endocannabinoidome presents a consistent conceptual basis. Instead of acting on a single molecular target, CBD simultaneously influences different components of this regulatory network, enabling the coordinated modulation of interdependent cellular and molecular processes, consistent with the multifactorial nature of the disease (BÍRÓ T, et al., 2009; DI MARZO V and PISCITELLI F, 2015; TÓTH BI, et al., 2011).

CBD's interaction with cannabinoid receptors and allosteric modulation

Although CBD exhibits low direct agonist affinity for CB1 and CB2 receptors, studies show that it acts as a negative allosteric modulator of the CB1 receptor, reducing the efficacy and potency of endogenous and exogenous agonists. This mechanism allows for attenuation of excessive activation of pathways associated with neuronal excitability, while preserving the physiological endocannabinoid signaling necessary for maintaining homeostasis (CHUNG H, et al., 2019; DI MARZO V and PISCITELLI F, 2015; YANG X, et al., 2015).

In the cutaneous context, CB1 modulation can influence processes related to keratinocyte proliferation and differentiation, as well as neurogenic signaling associated with pruritus. Moreover, CBD's indirect interaction with CB2, a receptor ubiquitously expressed in immune cells, contributes to modulating inflammatory responses in conditions marked by chronic immune activation, thus strengthening the interplay between skin inflammation and neuroimmunology (BÍRÓ T, et al., 2009; KLEIN TW, 2005; MACCARRONE U, et al., 2015).

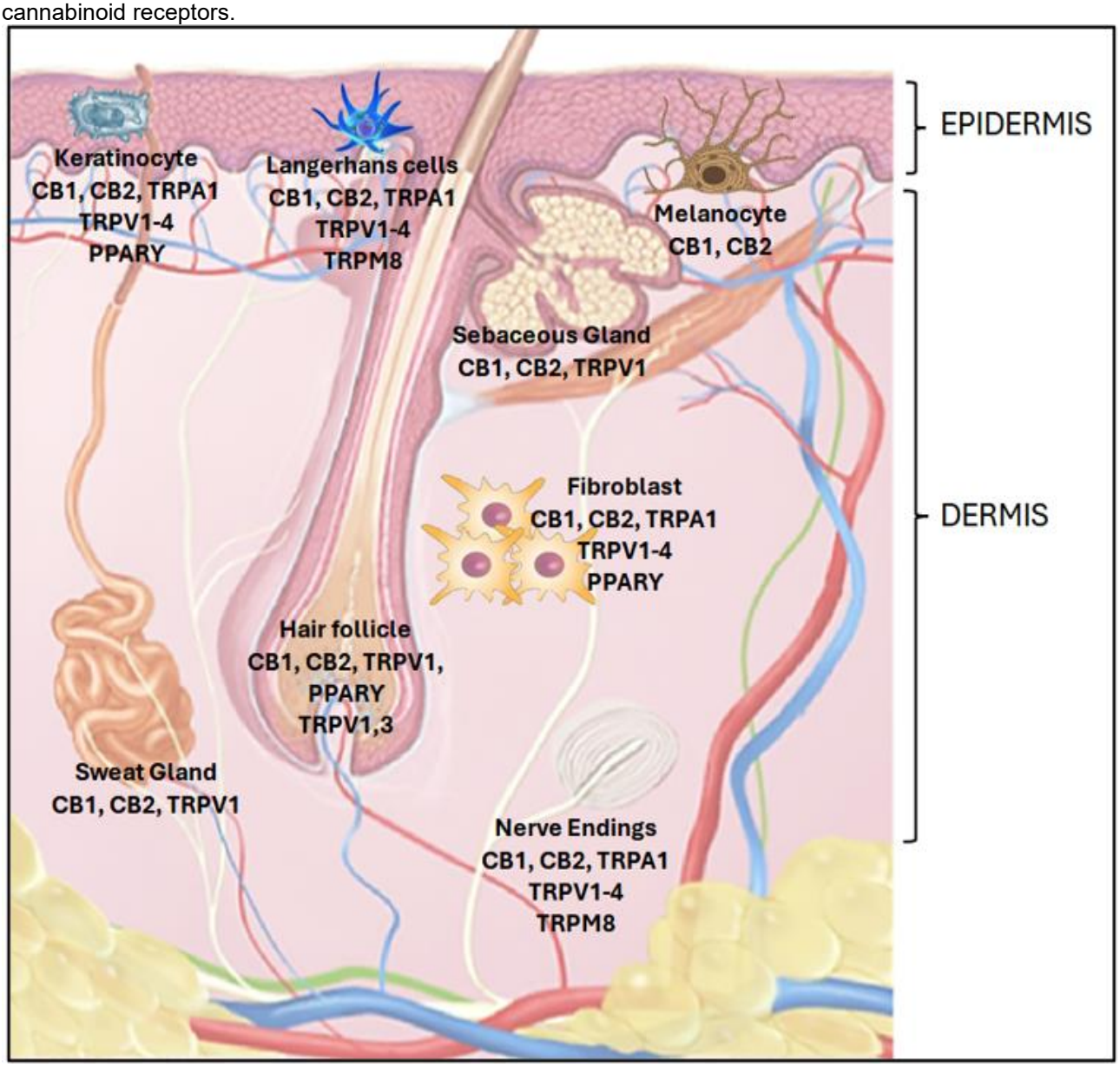
Non-Canonical Targets of CBD in the endocannabinoidome

One of the most relevant aspects of CBD's pharmacological profile is its interaction with non-canonical targets of the endocannabinoidome. Among these, the transient receptor potential (TRP) family channels, notably TRPV1, stand out. CBD acts as a functional agonist of this channel, promoting initial activation followed by desensitization, a mechanism linked to reduced neuronal excitability and the release of neuropeptides involved in neurogenic inflammation (IANNOTTI FA and DI MARZO V, 2021). Considering that chronic pruritus in atopic dermatitis is predominantly mediated by non-histaminergic pathways and involves the direct activation of sensory nerve fibers by pruritogenic cytokines, TRPV1 modulation by CBD offers a robust molecular rationale for interfering with the neuroimmune mechanisms previously described (EICHENFIELD LF, et al., 2014, EICHENFIELD LF, et al., 2017; STÄNDER S and LUNGER TA, 2010).

In addition to TRP channels, CBD interacts with peroxisome proliferator-activated nuclear receptors, especially PPAR-γ, whose activation is associated with negative regulation of inflammatory pathways, modulation of lipid metabolism, and cellular differentiation—processes directly related to epidermal barrier integrity and chronic cutaneous inflammation (O'SULLIVAN, 2016; DI MARZO V and PISCITELLI F, 2015). Another relevant target is the G protein-coupled orphan receptor GPR55, often described as a non-classical cannabinoid receptor, on which CBD acts as a functional antagonist, interfering with pro-inflammatory and pro-nociceptive pathways (DE PETROCELLIS L, et al., 2010; RYBERG E, et al., 2007).

The **Figure 3** presents the key non-canonical targets of cannabidiol (CBD) within the cutaneous endocannabinoidome. Notable among these are TRP channels—particularly TRPV1—as well as the nuclear receptor PPARγ and the orphan receptor GPR55. CBD's interaction with these targets contributes to the modulation of cutaneous inflammation, neuroimmune signaling, and the excitability of nerve fibers associated with pruritus. These mechanisms reinforce CBD's potential as a modulator of the inflammatory and pruritogenic processes involved in atopic dermatitis.

Figure 3 - Non-canonical targets of cannabidiol (CBD) in cutaneous endocannabinoidome. Cannabidiol interacts with non-canonical endocannabinoidome targets, including TRP channels (especially TRPV1), PPARγ, and the orphan receptor GPR55, modulating cutaneous inflammation, neuroimmune signaling, and excitability of nerve fibers associated with pruritus, without predominant direct activation of classical cannabinoid receptors.



Source: Araujo AKL, et al., 2026. Adapted from Di Marzo V and Piscitelli F, 2015.

Modulation of endocannabinoid metabolism by CBD

Beyond direct interaction with receptors and channels, CBD exerts relevant effects on endocannabinoid metabolism. Evidence shows that CBD can partially inhibit the activity of fatty acid amide hydrolase (FAAH), an enzyme responsible for the degradation of anandamide and other N-acylethanolamides, resulting in an indirect increase in endocannabinoid tone and potentiation of signaling mediated by endogenous ligands (BISOGNO T, et al., 2001; DI MARZO V and PISCITELLI F, 2015).

In a highly redundant and interconnected system like the endocannabinoidome, this metabolic modulation can simultaneously impact multiple lipid mediators involved in the regulation of inflammation, immune response, and neurogenic signaling, thereby reinforcing the integrative nature of CBD's action in the context of atopic dermatitis (DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA e DI MARZO V, 2021).

Molecular and translational implications of endocannabinoidome modulation in atopic dermatitis

The endocannabinoidome modulation mechanisms described earlier highlight the relevance of this system as an integrative regulatory axis in the pathophysiology of atopic dermatitis. The coordinated action of the endocannabinoidome on keratinocytes, immune cells, and sensory nerve fibers positions it as a system capable of interconnecting central disease processes, including chronic cutaneous inflammation, epidermal barrier dysfunction, and persistent pruritus (DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA e DI MARZO, 2021).

The pathophysiological complexity of atopic dermatitis imposes limitations on therapeutic approaches excessively targeting isolated molecular components, given that the disease results from the convergence of multiple interdependent pathogenic axes. In this regard, endogenous regulatory systems capable of simultaneously modulating different biological pathways become particularly relevant, providing a conceptual basis for integrative strategies to control cutaneous inflammation and neuroimmune signaling associated with pruritus (LEUNG DYM and GUTTMAN-YASSKY E, 2014; LEUNG DYM et al., 2021).

The modulation of the endocannabinoidome by cannabidiol presents specific interest as it reflects this integrative model. By interfering in parallel with inflammatory, immunological, and neurogenic pathways, through indirect interactions with classical cannabinoid receptors, non-canonical targets, and endocannabinoid metabolic enzymes, CBD exhibits a pharmacological profile compatible with the multifactorial nature of atopic dermatitis, without characterizing a classical immunosuppressive action (DE PETROCELLIS L and DI MARZO V 2010; DI MARZO V and PISCITELLI F, 2015; IANNOTTI FA and DI MARZO V, 2021).

Despite the strong mechanistic rationale supporting cannabidiol as a potential therapeutic approach for atopic dermatitis, the current evidence remains heterogeneous and is still predominantly derived from mechanistic, preclinical, and translational investigations. Most studies have focused on molecular pathways involved in inflammation, epidermal barrier regulation, and neuroimmune signaling, whereas high-quality clinical evidence remains limited.

The relatively small number of randomized controlled trials, together with variations in study design, formulations, dosing regimens, and outcome measures, hinders definitive conclusions regarding clinical efficacy and long-term safety. Therefore, translating these promising experimental findings into evidence-based therapeutic recommendations requires further well-designed clinical studies.

In addition to the current limitations of clinical evidence, several challenges must be addressed before cannabidiol can be routinely incorporated into the management of atopic dermatitis. These include the lack of standardized topical formulations, uncertainties regarding optimal dose, route of administration, and treatment duration, as well as the need to establish long-term safety, identify the patient populations most likely to benefit, and validate these findings through adequately powered randomized controlled clinical trials.

From a molecular perspective, CBD's influence on resident immune cells can contribute to the modulation of cytokine production associated with Th2-type inflammation, while preserving essential cutaneous defense mechanisms. This characteristic is particularly relevant in a condition where chronic inflammation and epidermal barrier dysfunction coexist with increased susceptibility to skin infections (KLEIN TW, 2005; MACCARRONE U, et al., 2015).

Furthermore, CBD's interaction with endocannabinoidome components involved in neuronal excitability and neurogenic inflammation provides a consistent biological rationale for its conceptual relevance in modulating chronic pruritus.

Together, these molecular and translational implications support the relevance of the endocannabinoidome as a conceptual platform for the integrated understanding of atopic dermatitis. The critical analysis of this system's modulation by cannabidiol contributes to broadening the understanding of the regulatory mechanisms involved in chronic cutaneous inflammation and persistent pruritus, while acknowledging the current limits of scientific evidence and reinforcing the need for future investigations conducted with methodological rigor.

FINAL CONSIDERATIONS

Atopic dermatitis is a chronic inflammatory skin disease driven by interactions among epidermal barrier dysfunction, immune dysregulation, and neuroimmune mechanisms related to pruritus. The cutaneous endocannabinoid system, framed within the broader concept of the endocannabinoidome, plays a key role in regulating skin homeostasis by modulating inflammation, barrier integrity, and neurogenic signaling. Cannabidiol may stands out for its multifocal pharmacological profile, indirectly modulating the endocannabinoidome and interacting with multiple non-canonical targets, aligning with the multifactorial nature of the disease. Although the mechanistic rationale for cannabidiol in atopic dermatitis is biologically plausible, clinical translation remains limited by the scarcity of controlled human studies, heterogeneity of formulations, uncertain dosing parameters, and the need to evaluate long-term safety in different patient populations. Future research should clarify the connections between inflammation, barrier dysfunction, and neuroimmune pathways, as well as better characterize CBD's diverse molecular interactions, to support more integrative and therapeutic approaches that require clinical validation.

REFERENCES

1. BÍRÓ T, et al. Endocannabinoids and the skin. Trends in Pharmacological Sciences, 2009; 30, 411–420.
2. BISOGNO T, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. British Journal of Pharmacology, 2001,134, n. 4,845–852.
3. BRANDT EB, SIVAPRASAD U. Th2 cytokines and atopic disease. Journal of Clinical & Cellular Immunology, 2011; 2, 110–118.
4. CHUNG H, et al. Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study PloS one 2019,14.7: e0220025.
5. CRIADO PR. Dermatite atópica: atualização em imunopatogênese. Anais Brasileiros de Dermatologia, 2024; 99,1,1–15.
6. D'AVINO P, et al. Distinct Roles of IL-4, IL-13, and IL-22 in Human Skin Barrier Dysfunction and Atopic Dermatitis. Allergy, 2025.
7. DE PETROCELLIS L, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. British Journal of Pharmacology, 2012; 161: 1494–1504.
8. DI MARZO V, PISCITELLI F. The endocannabinoid system and its modulation by phytocannabinoids. Neurotherapeutics, 2015; 12, n. 4, 692-698.
9. EICHENFIELD LF, et al. Atopic dermatitis: epidemiology and pathogenesis. Journal of the American Academy of Dermatology, 2014; 70, 338–351.
10. EICHENFIELD LF, et al. IL-31 and pruritus. Journal of Allergy and Clinical Immunology, 2017;140, 605–614.
11. ELIAS PM. Lipid abnormalities and lipid-based repair strategies in atopic dermatitis. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 2014; 1841, n.3, 323-330.
12. ELIAS PM, STEINHOFF M. Outside-to-inside (and now back to "outside") pathogenic mechanisms in atopic dermatitis. Journal of Investigative Dermatology, 2008, 128 n.5, 1067-1070.
13. GUTTMAN-YASSKY E, et al. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. Experimental dermatology, 2018, 27 n.4, 409-417.
14. HOWELL MD, et al. Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. Journal of Investigative Dermatology, 2008; 128 n.9, 2248-2258.
15. IANNOTTI FA, DI MARZO V. The gut microbiome, endocannabinoids and metabolic disorders. Journal of Endocrinology, 2021;248, 2, R83-R97.
16. IKOMA A, et al. The neurobiology of itch. Nature reviews neuroscience, 2006, 7 n.7, 535-547.
17. KIM J, et al. Skin barrier dysfunction. Experimental Dermatology, 2019; 28, 123–131.

18. KLEIN TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nature Reviews Immunology, 2005; 5.5: 400-411.
19. KONG HH, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome research, 2012, 22.5: 850-859.
20. LEO R, et al. The Neurogenic Inflammation Mediator Endothelin-1 Causes Human Skin Barrier Disruption in Atopic Dermatitis via an ETAR/TRPA1-Axis. Allergy (2025).
21. LEUNG DYM, BIEBER T. Atopic dermatitis. The Lancet, 2003; 361,151–160.
22. LEUNG DYM, GUTTMAN-YASSKY E. Deciphering atopic dermatitis. Journal of Allergy and Clinical Immunology, 2014; 134, 769–779.
23. LEUNG DYM. et al. Skin barrier dysfunction. Journal of Allergy and Clinical Immunology, 2021; 148, 1–8.
24. MACCARRONE M, et al. Endocannabinoid signaling at the periphery: 50 years after THC. Trends in pharmacological sciences, 2015; 36, n.5, 277-296.
25. MACCARRONE M, et al. Goods and bads of the endocannabinoid system as a therapeutic target: lessons learned after 30 years. Pharmacological reviews, 2023, 75, n 5: 885-958.
26. NAKATSUJI T, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. Science translational medicine, 2017; 9.378 eaah4680.
27. NOGRALES KE, et al. IL-22–producing “T22” T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17–producing TH17 T cells. Journal of Allergy and Clinical Immunology, 2009; 123, n.6, 1244-1252.
28. O’SULLIVAN SE. An update on PPAR activation by cannabinoids. British Journal of Pharmacology, 2016; 173, 12, 1899–1910.
29. OETJEN LK, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell, 2017; 171(1): 217-228.
30. PIOMELLI D, TAGNE AM. Endocannabinoid-based therapies. Annual Review of Pharmacology and Toxicology, 2022, 62: 483-507.
31. RYBERG E, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. British Journal of Pharmacology, 2007, 152(7): 1092–1101.
32. SONKOLY E, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. Journal of Allergy and Clinical Immunology, 2006; 117.2: 411-417.
33. STÄNDER S, LUGER TA. Itch in atopic dermatitis—pathophysiology and treatment. Acta Dermatovenerologica Croatica, 2010,18 n.4.
34. SHIMADA Y, et al. Transepidermal water loss. Skin Research and Technology, 2009;15, 305–310.
35. STEINHOFF M, et al. Role of vasculature in atopic dermatitis. Journal of allergy and clinical immunology, 2006; 118.1: 190-197.
36. TOMINAGA M, TAKAMORI K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. The Journal of dermatology, 2014, 41.3: 205-212.
37. TÓTH BI et al. Endocannabinoid signaling in skin. Trends in Pharmacological Sciences,2011; 32, 554–563.
38. TÓTH BI, et al. Cannabinoid receptors in skin homeostasis. Experimental Dermatology, 2019; 28, 1–9.
39. WILSON SR, et al. TSLP and itch. Cell, 2013;155, 285–295.
40. YANG X et al. Molecular mechanism of allosteric modulation for the cannabinoid receptor CB1.Nature Chemical Biology, 2022, 18 n 8: 831-840.