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Review article

THERAPEUTIC EFFECT OF CANNABIDIOL (CBD) IN PLAQUE PSORIASIS

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Abstract

The endocannabinoid system (ECS) of the skin is a complex molecular network of receptors, endocannabinoids, and enzymes that has sparked the interest of modern dermatology since its discovery in 1988. Studies have shown that dysregulation of ECS is closely associated with various skin diseases, including psoriasis as one of the most common autoimmune skin diseases. Psoriasis has a bimodal distribution of onset and a massive socioeconomic impact in modern societies, since it affects 3% of the global population. Although our knowledge regarding the association between ECS and psoriasis is limited, modulators of ECS have paved a novel therapeutic approach to be considered when treating psoriasis patients. Cannabidiol (CBD) is a non-psychotic, lipophilic, twenty-one carbon terpenophenolic phytocannabinoid derived from *Cannabis* plant that has promising therapeutic properties. Topical or transdermal formulations containing CBD have anti-inflammatory properties via inhibition of NF-kB signaling pathway and upregulation of keratin 6 and 16 in psoriasis patients. This review article discusses the up-to-date knowledge of the endocannabinoid system in the skin, its role in the pathophysiology of psoriasis, and therapeutic potential of cannabidiol in treatment of patients with plaque psoriasis.

Keywords: endocannabinoid system, psoriasis, cannabidiol, phytocannabinoids

Introduction

Psoriasis is an autoimmune skin disorder with intertwined genetic, environmental, and immunological abnormalities contributing to its complex pathophysiology. The socioeconomic burden of psoriasis has massive consequences nowadays, since this chronic inflammatory skin disease affects merely 3% of the global population. Although it can occur at any age, it is most likely to appear between the ages of 20-30 and 50-60 years (i.e. bimodal distribution of psoriasis onset) [1].

As dermatologists, we establish a diagnosis of multiple clinical forms of psoriasis (plaque psoriasis, psoriasis unguium, psoriasis guttata, psoriasis inversa, psoriasis pustulosa, psoriasis erythrodermica, psoriasis arthropathica). However, the most common clinical form among them is plaque psoriasis characterized by its silvery-white scales on top of circumscribed, infiltrated, salmon-like in color erythematous patches.

Despite the modern understanding of psoriasis, this chronic skin disease still remains a therapeutic challenge for every dermatologist. Since 1988, when scientists Allyn Howlett and WA. Devane discovered the endocannabinoid system (ECS), this molecular system has paved a way for a novel therapeutic approach for psoriasis patients [2].

This review article unveils the ECS important role in establishing the skin homeostasis and discusses in depth the use of cannabidiol as an ECS-modifying agent in plaque psoriasis treatment.

Overview of the Endocannabinoid System in the Human Skin

The endocannabinoid system (ECS) is a complex molecular network comprising three key components: receptors with broad tissue distribution, endocannabinoids that act as ligands, and enzymes that serve as metabolic drivers, facilitating the biosynthesis and inactivation of endocannabinoids [3]. For a brief overview of this complex signaling network's components see Table 1.

Endocannabinoids, together with phytocannabinoids and synthetic cannabinoids, are the three major classes of pharmacologically active substances that can alter the function of the ECS. Unlike phytocannabinoids and synthetic cannabinoids that are plant-derived and laboratory-derived, respectively, endocannabinoids are produced within the human body itself[3]. As pleiotropic ligands, endocannabinoids can bind not only to cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R), but also to transient receptor potential receptors (TRP) and peroxisome proliferator-activated receptors (PPAR) as well [2]. Another key component is the enzymes that can serve as a synthesizing (e.g. diacylglycerol lipase isozymes α and β) or inactivating (e.g. fatty acid amide hydrolase) catalyzers [2].

Table 1. Overview of endocannabinoid system's components [2]

ECS component	Description	Examples
Classes of Receptors	1. G-protein coupled receptors	CB1R, CB2R
	2. Ligand-sensitive ion channels	TRP channels
	3. Nuclear receptors	PPAR α and γ
Endocannabinoids	Bind to multiple receptors, showcasing pleiotropic activity.	Anandamide or N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG)
Enzymes in ECS	Facilitate biosynthesis and inactivation of endocannabinoids.	Biosynthesis: Diacylglycerol lipase (DAGL-α/β)
		Inactivation: Fatty acid amide hydrolase (FAAH)

The understanding of the ECS is rooted in three groundbreaking scientific discoveries made during the 1980s and 1990s. The first breakthrough came in 1988, when Allyn Howlett's laboratory demonstrated the existence of cannabinoid receptors using a radiolabeled ligand. Later, in the 1990s, CB1 and CB2 receptors were subsequently isolated and cloned by Gérard *et al.* and Sean Munro *et al.,* respectively [4]. Initially, it was widely accepted that CB1 receptors were predominantly found in the nervous system, while CB2 receptors in the immune cells. However, further experimental studies have revealed a much broader tissue distribution, including the presence of cannabinoid receptors in the human skin.

In addition to cannabinoid receptors, all components of the ECS can be found in various cell types that make up the human skin. CB1 receptors reside within the membranes of keratinocytes from the uppermost epidermal layers, differentiated sebaceous cells, and cells of the infundibulum and inner root sheet of the hair follicle. In contrast, CB2 receptors are primarily found in basal keratinocytes, undifferentiated sebaceous cells, and undifferentiated infundibular hair follicle cells [5]. Furthermore, both cannabinoid receptors are present in the melanocytes, dermal fibroblasts, myoepithelial cells of sweat glands, and adipocytes, as well[5]. A detailed schematic presentation of ECS in the human skin is provided in Figure 1.

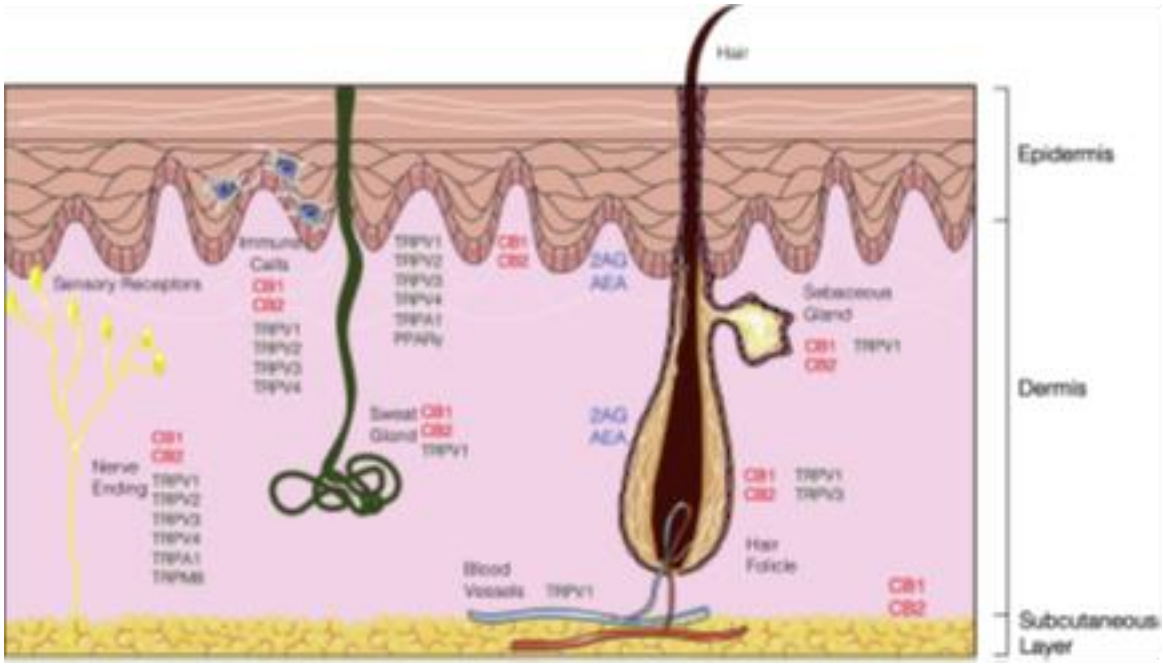

Fig. 1. Endocannabinoid system in the human skin [*Carmen Del Río et al.*][5]

Up-to-date scientific knowledge highlights the ECS's influence on pregnancy and fertility, neurocognition, and complex neurophysiological processes, including appetite, emotional behavior, etc. Moreover, scientists emphasize the ECS role in maintaining the skin homeostasis, since its dysregulation is associated with pathogenesis of acne, seborrhea, psoriasis, and other autoimmune and fibrotic skin diseases [2,3].

Cannabidiol: pharmacological aspects

Cannabidiol (CBD), along with Δ9-tetrahydrocannabinol (THC), are the most notable phytocannabinoids derived from the *Cannabis* plant [6]. As a flowering plant native to Asia, the *Cannabis* genus belongs to the *Cannabaceae* family and comprises three different species: *Cannabis sativa* (i.e. hemp), *Cannabis indica*, and *Cannabis ruderalis* [7]. The Cannabis plant has been cultivated and consumed worldwide for recreational, religious, and therapeutic purposes, as well as for practical applications in the paper and clothing industries [6,8]. The earliest known record for medical use of *Cannabis* in psoriasis treatment dates back to 2737 BC, documented in the first Chinese Pharmacopeia drafted by the emperor Shen Nung [6].

CBD and THC are hydrophobic substances, characterized by rapid metabolism, poor bioavailability, and share the same chemical formula C21H30O2 [7,9]. Although both CBD and THC have a twenty-one carbon terpenophenolic structure, CBD features an exocyclic C-atom saturated with a hydroxyl group (-OH), while THC has a cyclic ring (see Fig. 3) [9]. This structural difference ensures that non-psychotic CBD cannot be converted into psychoactive THC [9].

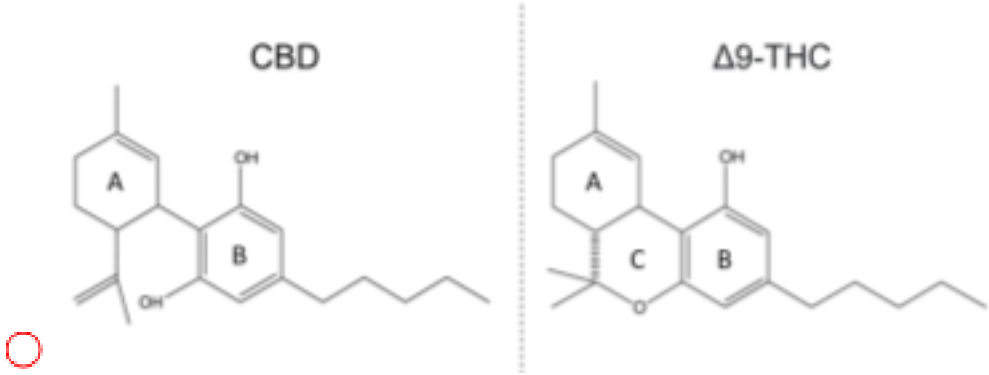

Fig. 3. Chemical structures of CBD and THC. The exocyclic C-atom saturated with –OH is marked with red circle [*Martinez Naya N et al.*] [9]

CBD has a molecular weight of 314.46Da and log P value (lipid/water partitioning) of 6.3 [8]. As a lipophilic substance, CBD can be administered via oral, oromucosal, vaporizable, sublingual, rectal, transdermal, or intravenous route [10]. Once administered, CBD binds mainly to the lipoproteins at a high rate (95%) and is distributed predominantly in lipid-rich tissues (e.g. adipose tissue, heart, brain, liver, lungs, and spleen) [9]. When administered orally, CBD bioavailability is too low due to extensive first-pass metabolism (≈ 95%) in the liver. This first-pass metabolism is primarily mediated by the CYP2C19 and CYP3A4 enzymes, which are part of the cytochrome P450 family [7]. The secondary metabolites are later eliminated through the gastrointestinal and/or urinary system [9,10].

Topical and transdermal application of CBD for the treatment of various skin diseases have attracted the interest of modern dermatology. Both routes offer significant advantages, as they bypass the extensive first-pass hepatic metabolism, resulting in higher bioavailability rate, and prolonged steady-state plasma concentrations. Additional benefits include direct application of the active substance to the affected skin area and the possibility to use higher concentrations of cannabidiol without the risk of adverse systemic effects. Furthermore, *in vitro* studies have well demonstrated the anti-inflammatory, antioxidant, anti-ageing, anti-acne, anti-UVA/UVB damage, antibacterial, and antifungal properties of CBD and phytocannabinoids in general [7]. However, a successful transdermal application requires a lower molecular weight and lower lipid/water partitioning than those of CBD. In 2003, Lodzki *et al.* overcame these inconveniences by using ethosomal carriers to successfully deliver CBD transdermally in a murine model [8]. On the other hand, for topical use, conventional topical formulations, such as creams, gels, or ointments are suitable, though factors like pH (<6), light exposure, and temperature must be optimized to maintain the stability of CBD in its active form [7].

Despite our extensive knowledge on pharmacokinetics of CBD, our understanding of its pharmacodynamics remains limited. Most of the evidence regarding the effects of CBD is based on preclinical studies, while clinical trials are still lacking. An *in vitro* study on HaCaT cells (lipopolysaccharide-inflamed human keratinocytes) by Sangiovanni *et al.* provided evidence for CBD anti-inflammatory properties through the inhibition of TNF-mediated NF-kB transcription [8]. Additionally, a recent study from 2024 by Camilla Di Mea *et al*. has further demonstrated the CBD anti-inflammatory properties on both normal and HaCaT cells. This study showed a decreased release of pro-inflammatory cytokines (IL-8, IL-12, IL-31), while the release of anti-inflammatory IL-10 was boosted. At the cellular level, CBD also enhanced the expression of cannabinoid receptor 1 (CB1) and vanilloid receptor 1 (TRPV1) [11]. However, when using topical or transdermal CBD formulations to treat psoriasis, Casares *et al*. suggest that precautions should be taken, as CBD has a proliferative effect on keratins 16 and 17 [8].

Conclusion

The *Cannabis* plant has been used for more than two millennia, yet our understanding of how cannabinoids affect the endocannabinoid system remains incomplete. For dermatological purpose, cannabinoids can be incorporated into topical or transdermal formulations, which bypass the extensive first-pass metabolism and reduce the risk of systemic adverse effects. While clinical trials on CBD-based treatments for psoriasis and other skin conditions are limited, preclinical studies suggest promising anti-inflammatory, antioxidant, antimicrobial, and anti-acne properties. Further clinical studies are crucial to fully explore the therapeutic potential of CBD therapeutic potential for psoriasis and to determinate its beneficial and potential adverse effects.

Conflict of interest statement. None declared.

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